28 November 2019
EMA/CHMP/596054/2019
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Toujeo

International non-proprietary name: insulin glargine

Procedure No. EMEA/H/C/000309/II/0108

Note

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

Table of contents

List of abbreviations

ADA	American Diabetes Association
AE	adverse event
AESIs	adverse events of special interest
AIA	anti-insulin antibodies
ALT	alanine aminotransferase
ATC	anatomical therapeutic chemical
BMI	body mass index
CI	confidence interval
DKA	diabetic ketoacidosis
eGFR	estimated glomular filtration rate
EMA	European Medicines Agency
EU	European Union
FDA	Food and Drug Administration
FPG	fasting plasma glucose
HbA1c	glycated haemoglobin A1c
HLT	high level term
IMP	investigational medicinal product
ISPAD	International Society for Paediatric and Adolescent Diabetes
ITT	intent-to-treat
LS	least squares
NIMP	non-investigational medicinal product
NPH	neutral protamine Hagedorn
OAD	oral anti-diabetic drugs
PCSA	potentially clinically significant abnormality
PD	pharmacodynamics
PK	pharmacokinetics
PPSR	Proposed Paediatric Study Request
PT	preferred term
QD	once daily
SAE	serious adverse event
SAP	Statistical Analysis Plan
SC	subcutaneous
SD	standard deviation
SMPG	self-monitored plasma glucose
SOC	system organ class
T1DM	type 1 diabetes mellitus
T2DM	type 2 diabetes mellitus
TEAEs	treatment-emergent adverse events
US	United States

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Sanofi-Aventis Deutschland GmbH submitted to the European Medicines Agency on 13 March 2019 an application for a variation.

The following variation was requested:

Variation requested		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of Indication to include new population for Toujeo (i.e. adolescents and children from the age of 6 years). As a consequence, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance.

The requested variation proposed amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

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 application included a critical report addressing the possible similarity with the authorised orphan medicinal product.

Scientific advice

On November 02, 2018 the applicant informed the EMA about the proposed submission plan. The applicant sought EMA's agreement that the initial Type II variation of Toujeo be submitted with the 6-months on-treatment data (primary endpoint assessment at week 26). In addition, the applicant requested EMA's agreement with the plan to rely on children/adolescent T1DM data and leverage adult T2DM data to expand the indication to the treatment of diabetes mellitus in adolescents and children aged 6 years and above.

Written Pre-submission Advice was received from EMA on December 21, 2018, indicating that EMA considered the applicant's proposal to extrapolate data from adult (insulin-naïve) patients with T2DM to the paediatric population with T1DM and advised that these data should be incorporated into a comprehensive extrapolation plan in line with the EMA guideline.

EMA indicated that submission of the Type II variation with 52 weeks of data (including the 26 week extension arm) would be the preferred approach, however it is the applicant's position that 26 weeks of data are sufficient to evaluate the efficacy and the safety profile in the paediatric population as Toujeo was well tolerated and had a general safety profile similar to the well-established safety profile of Lantus during the

26-weeks treatment period of study EFC13957. No safety concerns had been identified from the preliminary results of the 6-months safety extension which will be submitted during the review period.

1.2. Steps taken for the assessment of the product

The Rapporteur appointed by the CHMP was:

Rapporteur: Johann Lodewijk Hillege

Timetable	Actual dates
Submission date	13 March 2019
Start of procedure:	30 March 2019
CHMP Rapporteur's preliminary assessment report circulated on:	23 May 2019
PRAC Rapporteur's preliminary assessment report circulated on:	23 May 2019
PRAC members comments	7 June 2019
PRAC Outcome	14 June 2019
CHMP members comments	n/a
Joint Rapporteur's updated assessment report circulated on:	20 June 2019
Request for supplementary information and extension of timetable adopted by the CHMP on:	27 June 2019
MAH's responses submitted to the CHMP on:	6 August 2019
CHMP Rapporteur's preliminary assessment report on the MAH's responses circulated on:	17 September 2019
PRAC Rapporteur's preliminary assessment report on the MAH's responses circulated on:	18 September 2019
PRAC RMP advice and assessment overview adopted by PRAC	3 October 2019
CHMP members comments	n/a
Joint Rapporteur's updated assessment report on the MAH's responses circulated on:	10 October 2019
CHMP opinion:	17 October 2019
The CHMP adopted a report on similarity of Toujeo with Amglidia on (Appendix 1)	17 October 2019

2. Scientific discussion

2.1. Introduction

Type 1 diabetes mellitus (T1DM) occurs at any age but the majority of patients diagnosed are children and adolescents, with peaks in disease presentation at 5 to 7 years of age and around puberty.

Globally, the incidence of T1DM continues to rise by 2 to 5% each year. The prevalence of T1DM varies considerably from country to country. In the US, the estimated prevalence of T1DM is 1 in 300 by 18 years of age.

Patients with T1DM require insulin replacement therapy, which is designed to approximate physiologic basal and postprandial insulin release, thereby avoiding hyperglycaemia and hypoglycaemia. To achieve this, basal-bolus insulin regimens that approximate continuous 24-hour blood-glucose control are typically used: a basal insulin analogue is given to provide stable blood glucose lowering over the 24-hour day, including during the overnight fast, and a rapid-acting insulin analogue is given before each meal to provide postprandial control.

Currently approved basal insulin aimed at providing 24-hour glucose control is Lantus. Insulin glargine (insulin glargine 100 U/mL, Lantus) is a recombinant analogue of human insulin. Lantus is approved in EU in the treatment of diabetes mellitus in adults, adolescents and children 2 years and above. Lantus provides a 24-hour basal insulin supply after single-dose subcutaneous (SC) injection. Lantus has been registered in the US and Europe since 2000 and is considered to be a standard-of-care basal insulin.

Toujeo is another insulin glargine 300 U/mL long-acting human insulin analogue, produced by recombinant DNA technology in *E. coli* (K12), but is only approved for use in adults. It has the same composition as insulin glargine 100 U/mL (Lantus) but is a more concentrated formulation that contains 3 times the amount of active pharmaceutical ingredient (insulin glargine). Toujeo has a glucose-lowering activity of >24 hours after single-dose SC injection. Toujeo is approved for the treatment of adults with diabetes mellitus in the EU by centralized procedure on 24 April 2015, as a line extension to Toujeo 100 U/mL (previously called Optisulin) approved in the EU since June 2000.

The current variation concerns an extension of the indication of Toujeo with the paediatric population with diabetes mellitus from the age of 6 years:

Proposed indication

"Treatment of diabetes mellitus in adults, adolescents and children from the age of 6 years.".

Proposed posology

Toujeo is a basal insulin for once daily administration at any time of the day, preferably at the same time every day.

Paediatric population:

Toujeo can be used in adolescents and children from the age of 6 years (see section 5.1). When switching basal insulin to Toujeo, dose reduction of basal and bolus insulin needs to be considered on an individual basis, in order to minimize the risk of hypoglycaemia (see section 4.4).

Contents of the dossier

Paediatric indication for T1DM:

The applicant submitted an application for an indication extension application to support the safety and efficacy of Toujeo in paediatric patients aged 6 years and older with diabetes mellitus. It focuses primarily on the results from a phase 3b clinical study EFC13957 (EDITION JUNIOR) conducted in paediatric patients with type 1 diabetes mellitus (T1DM) treated with insulin glargine 300 U/mL

Paediatric indication for T2DM:

The application also included selected efficacy and safety data from 3 of the 4 Phase 3 studies in adult patients included in the initial submission dossier of Toujeo (EFC12456 in T1DM, and EFC12347 and EFC11628 in type 2 diabetes mellitus [T2DM]) to support by extrapolation the extension of the indication to include children and adolescents with T2DM.

2.2. Non-clinical aspects

No new non-clinical data have been submitted in this application, which was considered acceptable by the CHMP.

2.2.1. Ecotoxicity/environmental risk assessment

Being natural proteins, analogues such as insulin glargine, are not excreted unchanged and do not give rise to metabolites with potential biological activity. In view of this, guidance on the environmental risk assessment of medicinal products for human use (EMEA/CHMP/SWP/4447/00) especially exempt amino acids, peptides and proteins from the need for a complete environmental assessment and therefore, no assessment of the ERA for Toujeo is needed.

2.2.2. Conclusion on the non-clinical aspects

No new non-clinical data have been submitted which is considered acceptable by the CHMP.

2.3. Clinical aspects

2.3.1. Introduction

GCP

The Clinical trial is 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.

2.3.2. Pharmacokinetics

Toujeo PK in paediatric Study EFC13957

In paediatric study EFC13957 (see section 2.4.2.1 for description of the study), blood samples were taken after the end of the titration phase during the period from Week 20 to Week 26. The mean daily basal insulin dose at Week 26 was slightly higher in the HOE901-U300 group (0.615 [0.232] U/kg) compared to the Lantus group (0.567 [0.237] U/kg).

From patients who administered their dose in the evening on the day before the date of the visit, 12 h, 16 h and 20 h post-dose samples were taken. From patients who administered their dose in the morning on the day of the visit, pre-dose, 4 h and 8 h post-dose samples were taken. Descriptive statistics are provided based on the nominal times with time windows of within 1h before dosing for the pre-dose samples and +1 h for the post-dose samples. Following administration of insulin glargine either as Toujeo (300 U/mL) or as Lantus (100 U/mL), the major molecular entity in the circulation is the insulin glargine metabolite M1.

Therefore, descriptive statistics was focused on the concentrations of insulin glargine M1. The arithmetic mean and median concentrations of insulin glargine M1 were slightly lower in the Toujeo treatment arm than in the Lantus treatment arm at all time points of the evening and of the morning groups, respectively (Table 1 and Table 2).

Table 1. Summary statistics of plasma concentrations of insulin glargine M1 following Toujeo treatment in Study EFC13957

	Plasma concentration of insulin glargine M1 (ng/mL) over Nominal Time (hr) (N=87)		
Patients IMP dose administered in the morning			
	Pre-dose	4h post-dose	8h post-dose
Number	14	15	18
Mean	0.40	0.78	0.67
SD	0.40	0.79	0.79
SEM	0.107	0.204	0.186
Min	0.0	0.0	0.0
Median	0.30	0.58	0.54
Max	1.3	3.0	3.6
CV%	99.597	101.456	117.797
Patients IMP dose administered in the evening			
	12h post-dose	16h post-dose	20h post-dose
Number	57	57	52
Mean	0.40	0.43	0.55
SD	0.35	0.36	0.49
SEM	0.046	0.048	0.067
Min	0.0	0.0	0.0
Median	0.37	0.35	0.45
Max	1.4	1.4	2.4
CV%	87.434	83.928	88.178

Note: Samples with deviation from protocol time of +/-1 h are excluded from the analyses. For pre-dose sampling for injections done in the morning, the deviation protocol time is before 1h time of dosing.
Values below Lower Limit of Quantification (LLOQ) are replaced by 0 in the analyses

Table 2. Summary statistics of plasma concentrations of insulin glargine M1 following Lantus treatment in Study EFC13957

	Plasma concentration of insulin glargine M1 (ng/mL) over Nominal Time (hr) (N=93)		
Patients IMP dose administered in the morning			
	Pre-dose	4h post-dose	8h post-dose
Number	19	22	22
Mean	0.54	1.14	0.87
SD	0.43	1.02	0.82
SEM	0.098	0.218	0.175
Min	0.0	0.2	0.0
Median	0.49	0.95	0.62
Max	1.8	4.1	3.6
CV%	78.539	89.970	94.341
Patients IMP dose administered in the evening			
	12h post-dose	16h post-dose	20h post-dose
Number	60	59	59
Mean	0.61	0.62	0.60
SD	1.34	0.74	0.83
SEM	0.173	0.096	0.108
Min	0.0	0.0	0.0
Median	0.43	0.44	0.47
Max	10.5	4.6	5.5
CV%	218.401	119.033	137.252

Note: Samples with deviation from protocol time of +/-1 h are excluded from the analyses. For pre-dose sampling for injections done in the morning, the deviation protocol time is before 1h time of dosing.

PK results obtained in children 6-<18 years of age in Study EFC13957 indicate a somewhat lower exposure to insulin glargine M1 metabolite following administration of Toujeo versus Lantus. These results are in line with the results from the bioequivalence study PKD10086 in adults, which showed a lower AUC0-24, and a lower Cmax of about one-third for the Toujeo versus Lantus formulation, administered at the same dose of 0.4 U/kg body weight.

Population pharmacokinetic analysis (Analysis POH0663)

To support this application, a population-PK analysis aimed to describe the PK of HOE901-U300 in children and adolescents and to compare it with the PK of HOE901-U300 in adults. The first step of the model building was to develop a population-PK model using data from adults (Lantus study 1008) and study TDR11626 in

patient PD and PK/PD study reports. In a second step, the adult model was used as prior knowledge for the analysis using data from children and adolescents (study EFC13957). In total 3 different procedures were investigated: (i) a Bayesian analysis using the model parameters from adults for estimation of individual parameters in children and adolescents; (ii) a common fit for data in adults, adolescents and children; and (iii) a procedure using a $PRIOR function based on the parameters from the model in adults for fitting the data in children and adolescents. Then, the best procedure was used to compare individually estimated exposures in children, adolescents and adults. The PK of HOE901-U300 was based on concentration data of its main metabolite M1.

The following was concluded:

- A one-compartment model with first-order absorption and elimination was developed. The first order absorption is described as the sum of a constant and a linear time dependent parameter. The model was developed under rich data conditions for adults and served as prior information for the model development in children and adolescents under the sparse data conditions in study EFC13957. The model adequately described the pharmacokinetics of Toujeo in children and in adults.
- Age-dependent changes were fully explained by a body weight-based allometric equation with a fixed exponent of 0.75 for clearance and of 1 for volume of distribution. No age-dependent changes were observed for the absorption parameters.
- In agreement with the allometric scaling principles, a slightly higher median weight-based dose in children led to similar Toujeo exposures in adults and children. The reason could be attributed to different dependencies of clearance and dose on weight. Theoretically, for a child weighing 20 kg, a 1.4-fold higher weight-based dose is expected to lead to similar Toujeo exposures as in an adult weighing 75 kg. Accordingly, the same weight-based dose will lead to lower exposure in children compared to adults.
- Estimating the starting dose for children in the same way as for adults is considered a suitable and safe approach. Afterwards, the maintenance dose of Toujeo will be adjusted individually depending on the therapeutic effects observed.

Based on the goodness-of-fit plots, PK for the pivotal metabolite M1 in adults and children was adequately described in the final model. Comparison of the exposure to M1 by means of this popPK model demonstrated that the slightly higher dose applied in the paediatric study EFC13957 as compared to adults yielded comparable exposure. This may be due to somewhat increased clearance in children. Based on this outcome, when applying the same dose, exposure in children 6-<18 years of age will be somewhat lower than in adults. Therefore starting treatment of children applying the same starting dose as adults, with adjustment of the dose afterwards to achieve an adequate therapeutic response, appears a suitable and safe approach.

With respect to the SmPC, in section 4.2 it is indicated that, like in adults, also in children a higher dose of Toujeo (10-18%) might be necessary when shifting from insulin glargine 100 IE/ml to Toujeo.

Furthermore, the conclusion of the population PK analysis (POH0663), indicating that the same weight-based dose will lead to a lower exposure in children compared to adults, is reflected in the SmPC sections 5.1 and 5.2.

2.3.3. Pharmacodynamics

Insulin glargine is a recombinant analogue of human insulin. 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 blood glucose 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.

2.4. Clinical efficacy

2.4.1. Dose response studies

The following dose-response analysis was performed (**Analysis POH0706**):

The dose-response analysis aimed to describe the pharmacodynamics of Toujeo in children and adolescents aged 6-17 years diagnosed with T1DM with respect to HbA1c and to identify age-, weight- or other factor-dependent changes in HbA1c. This analysis was based on steady-state data from Phase 3 studies in children and adolescents (study EFC13957) and in adults (EFC12456) and was conducted in 2 steps: (i) an exploratory analysis using individually reported steady-state doses and; (ii) a regression analysis using individually reported changes in HbA1c and possible covariates influencing it. A longitudinal analysis was initially planned but omitted since practically no data were collected to describe the time-dependent changes in HbA1c. An exposure-response analysis was precluded by the lack of PK measurements in study EFC12456.

Results:

The individually reported steady-state doses per body weight were invariant to age, BMI and body weight for non-obese (BMI ≤30 kg/m2) patients. The average reported doses per body weight were higher for the paediatric population compared to the adult population.

The scatter plots of various pairwise comparison of covariate factors with a change of HbA1c from baseline indicated, that there was no relevant correlation, even when the co-operation of multiple covariate factors was tested in the regression analysis. As no relevant correlation between the relationship of HbA1c to the baseline at steady state was identifiable for the paediatric and adult populations, the estimated dose-dependent parameter could not be reliably identified. The change of HbA1c from baseline was independent from the dose per body weight.

Conclusions:

- Within the paediatric population (EFC13957) the individually reported doses per body weight at steady state were independent from body weight. The same was observed for the non-obese (BMI ≤30 kg/m2) adult population (EFC12456).
- The average reported doses per body weight were higher for the paediatric population (EFC13957) compared to the non-obese adult population (EFC12456).
- No correlation between the change of HbA1c from baseline at steady state and the individual dose at steady state per body weight could be detected.
- No differences between the paediatric population (EFC13957) and the adult population (EFC12456) could be identified with respect to the relationship of HbA1c to baseline at steady state.
- No relevant correlations between the investigated covariates and the relationship of HbA1c to baseline were observed.

These data support that a dose adaptation in the paediatric population is not needed.

2.4.2. Main studies

2.4.2.1. *T1DM: Clinical efficacy Study EFC13957 (children with T1DM)*

The clinical evidence for the efficacy and safety of Toujeo in the treatment of diabetes mellitus in paediatric population is based on a single phase 3b study lasting 12 months in which Toujeo was compared to Lantus in children and adolescent patients (aged 6 years to 17 years).

The efficacy results are based on the main 6-months randomized period of this study. The 6 months safety extension is performed and submitted. An integrated analysis of efficacy data from more than one study was not performed as there are no other clinical studies in paediatric patients treated with Toujeo.

Table 3 Summary of Studies Pertinent to the Claimed Indication T1DM

- Study identifier **- Coordinating Investigator (and centre)** **- Number of centres**	**- Objective(s) of study** **- Study design and type of control**	**Test product(s):** **- Formulation** **- Dosage regimen** **- Route of administration** **Reference therapy:** **- Formulation** **- Dosage regimen** **- Route of administration**	**Number of subjects** **- Total[a, b, c]** **- Gendera (M/F) - Race[a] (W/B/A/M)** **- Age[a] mean ± SD (range)** **- Treatment group[a]**	**diagnosis of patients** **Duration of treatment** **Study status** **Type of report**
EFC13957 - 105 active centres	- The primary objective was to compare the efficacy of a new formulation of insulin glargine (Toujeo) to Lantus for change of HbA1c from baseline to Month 6 in children and adolescents with T1DM. The secondary objectives were to compare Toujeo and Lantus in terms of percentage of patients reaching target HbA1c (<7.5%) and target FPG value (≤130 mg/dL [7.2 mmol/L]) at Month 6 overall and without any episode of severe and/or documented hypoglycaemia during last 3 months of the main 6-months randomized period; change from baseline to Month 6 in FPG; and change in mean SMPG (8-point SMPG profiles, glucose, variability of 24-hour mean plasma glucose) from baseline to Month 6. The safety of Toujeo was also assessed (including analysis of events of hypoglycaemia, hyperglycaemia with ketosis and development of anti-insulin antibody's [AIAs]) and the extent of accumulation and metabolism of Toujeo versus Lantus. - Randomized, open-label, 2-arm parallel-group, multicentre study	Toujeo (insulin glargine 300 U/mL solution) - Once-daily injection, in combination with a mealtime fast-acting insulin. Dosage titrated to a fasting (preprandial) SMPG target from 90 to 130 mg/dL (5.0 to 7.2 mmol/L), inclusive, while avoiding hypoglycaemia - SC using a Toujeo SoloSTAR pen - Lantus (insulin glargine 100 U/mL solution) - Once-daily injection in combination with a mealtime fast-acting insulin. Dosage titrated to a fasting (preprandial) SMPG target from 90 to 130 mg/dL (5.0 to 7.2 mmol/L), inclusive, while avoiding hypoglycaemia - SC using a Lantus SoloSTAR pen	- 463/461/441d - 237/226 - 422/14/17/4 - 12.9 ± 2.9 (6 - 17 years) - Toujeo: 233 / Lantus: 230	Children and adolescents with T1DM -Main 6-months on-treatment period + 6-months treatment extension period Main 6-months on-treatment period: complete / Full report 6-months treatment extension period

a Randomized, b Treated, c Completed study drug according to Investigator (end-of-treatment form), d Completed study drug for the main 6-months period. M: male, F: female, W: White, B: Black or african american, A: Asian, M: Multiple, SD: standard deviation, T1DM: type 1 diabetes mellitus, HbA1c: glycated haemoglobin A1c, FPG: fasting plasma glucose, SMPG: self-monitored plasma glucose, AIA: anti-insulin antibody, SC: subcutaneous.

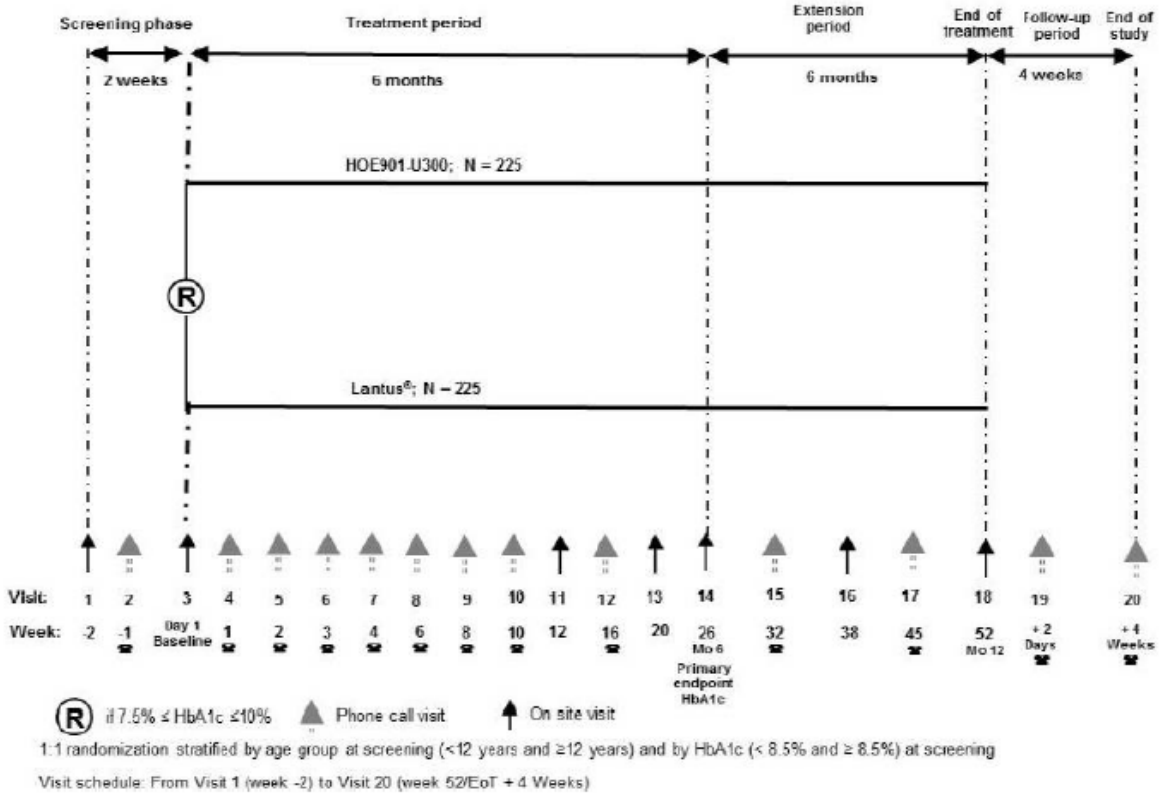
Choice for patients from the age of 6 years and not from the age of 2 years, as is the case for Lantus, was due to the unavailability of a half unit injection device for Toujeo, which would have been necessary for the younger age-group.

Methods

Study design

The study consisted of a 2-weeks screening period, a 6-months comparative efficacy and safety treatment period, a 6-months comparative safety extension period, and a 4-weeks post-treatment follow up period.

Figure 1– Study design (EFC13957)



HOE901-U300= Toujeo

Screening period;

The screening phase lasted 2 weeks to randomization.

Main 6-months open-label treatment period

During the main 6-months treatment period, the doses of Toujeo and Lantus were optimally titrated to fasting (pre-prandial) self-monitored plasma glucose (SMPG) targets of between 90 and 130 mg/dL (5.0 and 7.2 mmol/L), inclusive, while avoiding hypoglycaemia. Toujeo was administered in combination with fast-acting mealtime insulin analogue (i.e., glulisine, aspart, or lispro), administered and titrated (dose and timing) according to individual response and the product label.

Study participants

Key features of the patient population and study are summarized in the table below:

Table 4 Key features of Study EFC13957 participants

Population	Children and adolescents aged 6 years to 17 years T1DM for at least 1 year confirmed by typical symptoms at diagnosis and/or by

	antibody testing and/or clinical features. HbA1c of ≥7.5% to ≤11% on a basal plus fast-acting insulin regimen. Without hospitalization for DKA or history of severe hypoglycaemia during the previous 3 months.
Region	Worldwide
Comparator	Lantus (insulin glargine 100 U/mL)
Treatment and randomization	Toujeo: Lantus; 1:1
Stratification	HbA1c at screening (<8.5, ≥8.5%) Age group (<12 and ≥12 years)
Route	Once daily SC injection (either in the morning or in the evening)
Injection device	A pre-filled disposable pen injection device
Duration of study treatment	52 weeks
Duration of study treatment for efficacy analysis	26 weeks/6 months
Number of patients randomized	233 to Toujeo and 230 to Lantus

Treatments

Objectives

Objectives and endpoints

The primary objective of Study EFC13957 was to compare the efficacy of a more concentrated formulation of insulin glargine (Toujeo) to Lantus in terms of change in glycated haemoglobin A1c (HbA1c) from baseline to endpoint (Month 6/Week 26) in children and adolescents with T1DM.

Key efficacy endpoints evaluated in this study are presented in Table 5:

Table 5 - Efficacy endpoints in Study EFC13957

Primary efficacy endpoint	Change in HbA1c from baseline to Month 6/Week 26
Secondary efficacy endpoints	Percentage of patients with HbA1c values of <7.5% at Week 26 overall and without any episode of severe and/or documented (SMPG <54 mg/dL; 3.0 mmol/L) hypoglycaemia during the last 3 months of the main 6-months randomized period Change in fasting plasma glucose (FPG) from baseline to Week 26 Percentage of patients with FPG ≤130 mg/dL (7.2 mmol/L) at Week 26 overall and without any episode of severe and/or documented (SMPG <54 mg/dL; 3.0 mmol/L) hypoglycaemia during the last 3 months of the main 6-months randomized period Change in mean plasma glucose based on 8-point SMPG profiles from baseline to Week 26 Anti-insulin antibodies in relation to efficacy endpoint (HbA1c)

The primary and secondary efficacy endpoints and safety endpoints to evaluate the efficacy of 300 IU vs 100 IU of insulin glargine in children and adolescents with T1DM by the change in HbA1c are in line with the Guideline CPMP/EWP/1080/00 Rev. 2 (draft). The 26-weeks data were submitted to evaluate the efficacy and the safety profile in the paediatric population and data from the 26-weeks safety extension arm.

Outcomes/endpoints

Sample size

The sample size calculation was based on the primary efficacy variable of HbA1c change from baseline to Month 6/Week 26.

A sample size of 450 randomized patients (225 for Toujeo and 225 for Lantus) was ensured so that the upper bound of the two-sided 95% confidence interval (CI) for the adjusted mean difference between Toujeo and Lantus would not exceed a non-inferiority margin of 0.3% HbA1c with 92% power. This calculation assumed a common standard deviation of 0.95%, with a one-sided test at the 2.5% significant level and a true difference of zero in HbA1c between the treatment groups.

Randomisation

Eligible patients were randomized 1:1 to receive either Toujeo or Lantus once daily in an open-label manner during the 6-months treatment period and 6-months on-treatment extension period. Randomization was stratified by age group (<12 and ≥12 years) and by HbA1c (<8.5% and ≥8.5%) at screening.

Blinding (masking)

The study was open label, with an independent blinded external endpoint assessment committee for determination of relationship between increased AIA titer and impaired efficacy.

Statistical methods

Efficacy assessments were performed on the main 6-months randomized period.

The analysis population for efficacy was the intent-to-treat (ITT) population, which included all randomized patients regardless of whether a treatment kit was used and analyzed according to the treatment group allocated by randomization (ITT estimand).

The primary efficacy variable (change in HbA1c from baseline to Week 26) was analyzed for non-inferiority assessment in the ITT population using all post-baseline HbA1c data available on the main 6-months randomized period (ie, ITT estimand). The non-inferiority of Toujeo versus Lantus was considered as demonstrated if this upper bound of the 2-sided 95% confidence interval (CI) for the difference in the mean change in HbA1c between Toujeo and Lantus was <0.3%. The test for this primary endpoint was performed one-sided at level $\alpha = 0.025$. Multiple imputation was performed for two subsets of the analysis population. Missing data in patients who prematurely discontinued IMP was imputed based on available week 26 data from discontinuers using a regression model. Missing data for patients who completed the 6-months treatment period, was imputed based on available baseline, week 12 and week 24 data from completers using the MCMC method followed by regression. The change in HbA1c from baseline to Week 26 was then compared between treatment arms using an analysis of covariance (ANCOVA) model, including the fixed categorical effects of the treatment group, the randomization stratum of age group at screening visit (<12 years and ≥12 years), as well as the continuous fixed covariates of the baseline HbA1c value. The method assumes data is missing within patient strata based on treatment status, sensitivity to this assumption was tested in tipping point analysis. Furthermore, the primary analysis was repeated in a per protocol set and in a supportive on-treatment analysis.

A supportive analysis of the primary efficacy analysis was performed on the change in HbA1c from baseline to Week 26 in the ITT population during the main 6-months on-treatment period (on-treatment estimand). The supportive analysis used on-treatment HbA1c values only, first for missing data imputation then for analysis.

As sensitivity analyses to assess the impact of missing data, a tipping point analysis based on pattern mixture model approach using all HbA1c values available during the main 6-months randomized period was performed in the ITT population.

A post-hoc per protocol (PP) population, defined as a subset of the ITT population, includes all randomized and exposed patients who did not permanently discontinue the IMP allocated by randomization during the

main 6-months treatment period, who performed Week 26 and had an available value for HbA1c change from baseline at Week 26, and who did not present any major or critical protocol deviations potentially impacting analysis of the primary efficacy endpoint during the main 6-months period.

Efficacy endpoint (change in HbA1c) was analyzed in relation to anti-insulin antibodies (AIA) based on the safety population, for the main 6-months on-treatment period.

Results

Participant flow

Patient disposition

In the study, a total of 616 patients were screened in 105 study centres across 24 countries worldwide. Of these, 463 patients were randomized 1:1; 233 patients to Toujeo and 230 patients to Lantus.

The most common reasons for screen failures were primarily attributed to:

- exclusion criterion of HbA1c <7.5% or >10% at screening, or
- HbA1c <7.5% or >11% at screening (following protocol amendment 2).

A high and comparable proportion of patients (Toujeo: 96.6%; Lantus: 93.9%) completed the 6-months treatment period. Treatment discontinuations due to AEs and lack of efficacy were low (≤0.4% for each reason) in both treatment groups. The most common reason for treatment discontinuation was "other" reasons (Toujeo: 1.7%; Lantus: 3.5%) related to the patient's personal situation (i.e., "patient too busy to complete study diary", "patient moved" or "patient never started treatment") and not safety-related (Table 6). Data review and monitoring confirmed that the "other" category did not include discontinuation due to any of the pre-specified reasons, including AEs, hypoglycaemia or lack of efficacy. One patient in the Toujeo group who permanently discontinued the study during the main 6-months period, died during the study (PT: Completed suicide). The patient disposition is given below:

Table 6 - Patient disposition during the main 6-months period - Randomized population

N (%)	Toujeo (N=233)	Lantus (N=230)	All (N=463)
Randomized but not treated[a]	**0**	**2 (0.9)**	**2 (0.4)**
Randomized and treated	**233 (100)**	**228 (99.1)**	**461 (99.6)**
Completed the main 6-months treatment period	**225 (96.6)**	**216 (93.9)**	**441 (95.2)**
Permanently discontinued the treatment during the main 6-months period	8 (3.4)	12 (5.2)	20 (4.3)
Reason for treatment discontinuation during the main 6-months period			
Adverse event	1 (0.4)	1 (0.4)	2 (0.4)
Lack of efficacy	1 (0.4)	0	1 (0.2)
Poor compliance to protocol	2 (0.9)	3 (1.3)	5 (1.1)
Hypoglycaemia	0	0	0
Other	4 (1.7)	8 (3.5)	12 (2.6)
Patient's decision for treatment discontinuation during the main 6-months period	6 (2.6)	11 (4.8)	17 (3.7)
Completed the main 6-months study period	**229 (98.3)**	**225 (97.8)**	**454 (98.1)**
Permanently discontinued the study during the main	**4 (1.7)**	**5 (2.2)**	**9 (1.9)**

N (%)	Toujeo (N=233)	Lantus (N=230)	All (N=463)
6-months period			
Reason for study discontinuation during the main 6-months period			
Adverse event	2 (0.9)	0	2 (0.4)
Poor compliance to protocol	1 (0.4)	0	1 (0.2)
Withdrawal by parent/guardian	0	2 (0.9)	2 (0.4)
Withdrawal by subject	1 (0.4)	3 (1.3)	4 (0.9)
Status at last study contact of patients who permanently discontinued the study during the main 6-months period			
Alive	3 (1.3)	5 (2.2)	8 (1.7)
Death	1 (0.4)	0	1 (0.2)

[a] Patients randomized and not treated are considered as patients who permanently discontinued the treatment in randomized population, for the efficacy analyses.
Note: Percentages are calculated using the number of patients randomized as denominator.

During protocol amendment 2, in order to facilitate the recruitment of patients, the upper limit of the HbA1c range was lifted from 10% to 11%, so that patients with an HbA1c of 10.1% to 11.0% at screening are not considered screening failures due to their HbA1c.

The percentage of patients completing the 6-months study treatment was relatively high (95%), just as the percentage of patients completing the 6-months study period (98%). The randomised population in the two treatment groups was comparable with regard to patient disposition.

Data sets analysed

Table 7 Analysis populations - Randomized population

N (%)	Toujeo (N=233)	Lantus (N=230)	All (N=463)
Randomized population	233 (100)	230 (100)	463 (100)
Intent-to-Treat (ITT)	233 (100)	230 (100)	463 (100)
PK population	91	94	185
Safety population	233	228	461

Note: The safety and PK population patients are tabulated according to treatment actually received (as treated); For the other populations, patients are tabulated according to their randomized treatment

The primary analysis was performed also on the PP analysis set.

A post-hoc per protocol (PP) population, defined as a subset of the ITT population, includes all randomized and exposed patients who did not permanently discontinue the IMP allocated by randomization during the main 6-months treatment period, who performed Week 26 and had an available value for HbA1c change from baseline at Week 26, and who did not present any major or critical protocol deviations potentially impacting analysis of the primary efficacy endpoint during the main 6-months period.

Among all major or critical deviations presented in Table 7 of the 6-months CSR of Study EFc13957, the following deviations were considered as potentially impacting the efficacy and therefore were used to exclude patients from the post-hoc defined PP population:

- No baseline HbA1c value (included in the "Assessments/Procedures" category of the CSR table)
- Any major or critical deviations related to randomization procedures
- Any critical or major deviations related to prohibited medications

- Any critical or major protocol deviations related to the Eligibility criteria impacting HbA1c:
    - I01 - Children and adolescents without T1DM for at least 1 year confirmed by typical symptoms at diagnosis and/or by antibody testing and/or clinical features (e.g., history of ketoacidosis)
    - E01 - Age <6 and ≥18 years at V1 (screening)
    - E08 - HbA1c <7.5% or >10% (or >11% following protocol amendment N°2) at screening
- Any critical or major protocol deviations leading to an insulin dose titration not done according to the Protocol (included in the "Assessments/Procedures" category of the CSR table).

In addition to these major or critical protocol deviations, patients randomized and not treated and/or without on-treatment HbA1c value at Week 26 (i.e. missing primary endpoint) were also excluded from the post-hoc defined PP population due to the potential impact on efficacy analysis.

Table 8 summarizes per treatment group the number of patients included in the post-hoc defined PP population and the reasons of patients' exclusion from this population. In study EFC13957, more than 85% of the randomized population was included in the post-hoc defined PP population (91% of the randomized patients in the HOE901-U300 group and 88.3% of the randomized patients in the Lantus group). The main reason for exclusion from this population is the absence of an HbA1c value at Week 26 during the main 6-months treatment period.

Table 8: Summary of Post-hoc defined Per Protocol population - Randomized population

	HOE901-U300 (N=233)	**Lantus (N=230)**
Patient included in the Post-hoc Per Protocol population	212 (91.0)	203 (88.3)
Patient excluded from the Post-hoc Per Protocol population	21 (9.0)	27 (11.7)
Important deviations resulting in exclusion of the patient from Per Protocol population:		
Patient randomized and not treated	0	2 (0.9)
No baseline HbA1c value	1 (0.4)	0
No on-treatment HbA1c value at week26	12 (5.2)	18 (7.8)
Critical or major protocol deviations related to Randomization procedures	5 (2.1)	2 (0.9)
Prohibited medication	0	0
Critical or major protocol deviations related to the Eligibility criteria impacting HbA1c	2 (0.9)	1 (0.4)
Critical or major protocol deviations related to the titration	4 (1.7)	7 (3.0)

The analysis of the primary endpoint in the post-hoc defined PP population using changes in HbA1c from baseline to Week 26 available during the main 6-months treatment period (on-treatment estimand) is provided in Table 9, using the same ANCOVA model as for the analysis of the primary endpoint done in the ITT population.

Conclusion:

Efficacy results of the primary endpoint analysis in the post-hoc defined PP population (on-treatment estimand [Table 9]) are consistent with those of the main primary endpoint analysis in the ITT population

(ITT estimand) and support the demonstration of non-inferiority of HOE901-U300 to Lantus at the 0.3% HbA1c margin.

Table 9: Summary of mean change HbA1c (%) from baseline to Week 26 endpoint using ANCOVA – Post-hoc per-protocol population

HbA1c (%)	HOE901-U300 (N=212)	Lantus (N=203)
Baseline		
Number	212	203
Mean (SD)	8.65 (0.89)	8.63 (0.86)
Median	8.50	8.50
Min ; Max	7.0 ; 13.1	6.9 ; 11.3
Week 26		
Number	212	203
Mean (SD)	8.26 (1.13)	8.19 (1.21)
Median	8.05	7.90
Min ; Max	6.2 ; 11.5	5.9 ; 13.8
Change from baseline to Week 26		
Number	212	203
Mean (SD)	-0.39 (1.00)	-0.45 (1.00)
Median	-0.40	-0.50
Min ; Max	-3.8 ; 3.3	-3.8 ; 3.6
LS Mean (SE)	-0.390 (0.067)	-0.449 (0.068)
95% CI	(-0.521 to -0.259)	(-0.583 to -0.315)
LS Mean difference (SE) vs. Lantus	0.059 (0.095)	
95% CI	(-0.129 to 0.246)	

HbA1c samples performed from Day 152 and until Day 212 are considered in the week 26 analysis window.

ANCOVA model includes the fixed categorical effect of treatment group, the randomization stratum of age at screening (<12 years, =12 years), as well as, the continuous fixed covariates of the baseline HbA1c value.

Table 10: Summary of mean change in HbA1c (%) from baseline to Week 26 endpoint using multiple imputation analysis followed by ANCOVA (ITT estimand) - ITT population

Hba1c (%)	HOE901-U300 (N=233)	Lantus (N=230)
Baseline		
Number	232	230
Mean (SD)	8.65 (0.88)	8.61 (0.87)
Median	8.55	8.50
Min ; Max	7.0 ; 13.1	6.9 ; 11.3
Change from baseline to Week 26[a]		
Combined LS Mean (SE)	-0.399 (0.063)	-0.402 (0.064)
95% CI	(-0.522 to -0.275)	(-0.527 to -0.278)

Hba1c (%)	HOE901-U300 (N=233)	Lantus (N=230)
Combined LS Mean difference (SE) vs. Lantus	0.004 (0.090)	
95% CI	(-0.172 to 0.179)	
P-value[b]	0.965	

[a] HbA1c samples performed from Day 152 and until Day 212 are considered in the week 26 analysis window.

[b] P-value displayed only for the superiority test

Note: Multiple imputation method (1000 imputations) is used to address missing values in the ITT population

Combined estimate for least-square (LS) means and standard errors (SE) are obtained by combining LS means and SE from analysis of covariance (ANCOVA) of the different imputed data sets, using Rubin's formulae

The ANCOVA models include the fixed categorical effect of treatment group, the randomization stratum of age group at screening visit (<12 years and ≥12 years), as well as the continuous fixed covariates of the baseline HbA1c value

The results were consistent with the primary analysis and support the conclusion of non-inferiority.

In the primary model, the final analysis (using an ANCOVA model) is done using only HbA1c change at week 26, either observed during the trial or imputed; in this approach, intermediate HbA1c values (i.e. at week 12) have been used in the imputation model only in a sub-set of patients from the ITT population.

The primary efficacy variable was analyzed using a multiple imputation approach to handle missing changes in HbA1c from baseline to week 26 (primary endpoint) during the main 6-months randomized period (i.e. regardless of treatment discontinuation).

The approach consisted of performing multiple imputations separately for two independent sub-sets of patients according to whether patients permanently discontinued the treatment during the main 6-months period or not:

- In multiple imputation model for patients who did not permanently discontinue the IMP during the main 6-months period, all available post-baseline HbA1c values (including Week 12) were used to handle missing HbA1c changes from baseline to week 26.

Whereas, for patients who permanently discontinued the IMP during the main 6-months period, a basic imputation model has been build, including only the treatment group as predictor.

The primary efficacy variable, i.e. change in HbA1c from baseline to Week 26, was analyzed in the ITT population during the main 6-months randomized period, i.e. regardless of treatment discontinuation (ITT estimand).

Since the change from baseline at week 26 of HbA1c has not been observed for all patients included in the ITT population, a multiple imputation approach to handle these missing values has been used as further described below:

The main concept of this multiple imputation was to differentiate among patients with no available HbA1c change from baseline to Week 26: those who permanently discontinued the treatment during the main 6-months period versus the ones who completed the main 6-months treatment period. The underlying idea

of differentiating the imputation between these 2 subsets of patients is that the behavior of missing data for those patients who are off-treatment during the main 6-months period may not be the same as that of observed data for those patients who are on-treatment in the same treatment arm.

As a result, the multiple imputation approach consisted of performing 1,000 imputations separately for the two independent sub-sets of the ITT population according to whether patients permanently discontinued the treatment during the main 6-months period or not.

- Imputation part A: Imputation for missing data in patients who have never been treated or who prematurely discontinued IMP during the main 6-months period

Missing primary endpoint in patients who prematurely discontinued IMP during the main 6-months period was imputed using a model estimated solely from the change in HbA1c from baseline to Week 26 observed in other patients in the same treatment group who prematurely discontinue IMP during the main 6-months period and have the change in HbA1c available at Week 26. Due to the small number of these latter patients, a basic imputation model was built, including only the treatment group as predictor. Missing data was imputed using the regression method.

Missing data were imputed 1,000 times.

- Imputation part B: Imputation for missing data in patients who did not permanently discontinue the IMP during the main 6-months period

It should be noted that only few patients who did not discontinue the treatment, have missing primary endpoint, i.e. change in HbA1c at Week 26 (N=4 in each treatment group). Missing primary endpoint in patients who completed the main 6-months treatment period was imputed using a model estimated from baseline HbA1c and all available post-baseline on-treatment HbA1c during the main 6-months period (i.e. changes in HbA1c from baseline to Week 12 and Week 26) observed in any patients in the same treatment group who completed the main 6-months treatment period.

Since in general, the missing pattern will not be monotone, a two-step approach was used:

- Step 1: the Markov Chain Monte Carlo (MCMC) method was used in conjunction with the IMPUTE=MONOTONE option to create an imputed data set with a monotone missing pattern (i.e. by patient, imputation of all missing HbA1c values before the last available HbA1c value during the main 6-months treatment period). The imputation model included the continuous fixed covariates of the baseline HbA1c value as well as the changes from baseline in HbA1c at Week 12 and Week 26.

Missing data were imputed 1,000 times.

- Step 2: using the monotone data set from step 1, remaining missing data during the main 6-months treatment period was imputed for each of the 1,000 imputations using the regression method. The imputation model included the fixed categorical effects of the treatment group, the randomization stratum of age group at screening visit (<12 years and ≥12 years), as well as the continuous fixed covariates of the baseline HbA1c value and the changes from baseline in HbA1c at Week 12 and Week 26.

Only one imputation was performed in this step 2 for each imputation from step 1.

After having performed separately the imputations in the two independent sub-sets of patients, the two completed datasets with observed and imputed primary endpoints (1,000 imputations each) were gathered to obtain a single and complete dataset of the overall ITT population with 1,000 imputations (DataMI).

For each imputation of the DataMI dataset, the change from baseline to Week 26 in HbA1c (i.e. primary endpoint) was then analyzed in the ITT population using an analysis of covariance (ANCOVA), including the

fixed categorical effects of the treatment group, the randomization stratum of age group at screening visit (<12 years and ≥12 years), as well as the continuous fixed covariates of the baseline HbA1c value. The model provided baseline adjusted least squares (LS) means estimates at Week 26 for both treatment groups (using adequate contrasts at Week 26, based on the observed proportions of patients in the randomization age stratum and the observed baseline mean HbA1c in the ITT population), as well as the differences of these estimates with their corresponding SEs and 95% CIs.

The final results were then obtained by combining the LS means and LS mean differences from these 1,000 analyses, using Rubin's formula.

Baseline data

Demographic and other baseline characteristics

The demographic and other baseline characteristics including Tanner puberty stage distribution were well balanced between the two treatment groups and were considered to be representative of the general paediatric population with T1DM.

The mean age of patients was 12.9 years with 30.9% patients aged <12 years and 69.1% patients aged ≥12 years. Overall, 51.2% of patients were male, 30.2% of patients were Hispanic or Latino, and 92.1% were White. By Tanner stages, the majority of patients were adolescents (48.6%) while 26.5% were pre-pubertal and 24.9% were adults. At baseline, 62.4% of patients were within a healthy body mass index (BMI) range (5th-<85th percentile) while 17.1% of patients were obese (BMI ≥95th percentile).

At study entry, the following patient characteristics applied to the randomized population:

Table 11: Demographics and patient characteristics at baseline (abbreviated)

	Toujeo (N=233)	**Lantus (N=230)**
Age (years) Mean (SD)	12.9 (2.9)	12.9 (2.9)
Age < 12 years	73 (31.3)	70 (30.4)
Age ≥ 12 years	160 (68.7)	160 (69.6)
HbA1c (%) at screening [n(%)]		
HbA1c <8.5%	93 (39.9)	90 (39.1)
HbA1c ≥8.5%	140 (60.1)	140 (60.9)
Sex [n(%)] Male	128 (54.9)	109 (47.4)
Race [n(%)]		
White	211 (90.9)	211 (93.4)
Black	8 (3.4)	6 (2.7)
Asian	11 (4.7)	6 (2.7)
Multiple	2 (0.9)	2 (0.9)
Region [n(%)]		
Northern America	30 (12.9)	26 (11.3)
South/Latin America	60 (25.8)	70 (30.4)
Western Europe	35 (15.0)	26 (11.3)
Eastern Europe	73 (31.3)	79 (34.3)
Rest of the world (ROW)	35 (15.0)	29 (12.6)
Baseline BMI percentile - Mean (SD)	67.52 (26.62)	69.13 (26.64)
Bas. estimated GFR (mL/min/1.73m2) - Mean (SD)	116.71 (23.46)	119.32 (21.58)
Baseline Tanner puberty stage evaluation [n(%)]		

	Toujeo (N=233)	Lantus (N=230)
Pre-pubertal stage	56 (24.1)	66 (28.8)
Adolescent stage	121 (52.2)	103 (45.0)
Adult stage	55 (23.7)	60 (26.2)

Baseline disease characteristics

The baseline disease characteristics and previous daily basal and mealtime insulin daily dose were comparable between the treatment groups. By Tanner puberty stages, the previous daily basal and mealtime insulin daily dose were slightly higher in adolescents compared to pre-pubertal or adult patients.

Table 12 - Summary of disease characteristics at baseline according to baseline Tanner stage (abbreviated)

	Pre-pubertal stage (N=122)		Adolescent stage (N=224)		Adult stage (N=115)	
	Toujeo (N=56)	Lantus (N=66)	Toujeo (N=56)	Lantus (N=66)	Toujeo (N=56)	Lantus (N=66)
Duration of T1D (years) - Mean (SD)	4.1 (2.4)	4.4 (2.6)	5.7 (3.2)	5.9 (3.3)	7.3 (3.8)	6.5 (3.1)
Previous basal insulin daily dose (U/kg) - Mean (SD)	0.467 (0.189)	0.517 (0.274)	0.486 (0.192)	0.515 (0.207)	0.462 (0.171)	0.453 (0.175)
Previous mealtime insulin daily dosed (U/kg) - Mean (SD)	0.411 (0.190)	0.437 (0.266)	0.514 (0.239)	0.500 (0.235)	0.508 (0.226)	0.483 (0.203)
Previous mealtime insulin analogue type - [n (%)]						
Insulin aspart	21 (43.8)	29 (49.2)	67 (61.5)	46 (47.9)	27 (55.1)	30 (62.5)
Insulin glulisine	6 (12.5)	5 (8.5)	11 (10.1)	11 (11.5)	9 (18.4)	8 (16.7)
Insulin lispro	21 (43.8)	25 (42.4)	31 (28.4)	39 (40.6)	13 (26.5)	10 (20.8)

Conduct of the study

The mean duration of T1DM at study entry was approximately 6 years. The majority of patients had T1DM duration of ≥5 years (Toujeo: 52.8%; Lantus: 49.6%).

A total of 461 patients (Toujeo: 233; Lantus: 228) were exposed to study treatment and were included in the safety population for analysis of exposure. The cumulative duration of treatment exposure during the main 6-months on-treatment period was 113.02 patient-years in Toujeo and 111.38 patient-years in Lantus. The mean duration of exposure to study treatment was similar in both treatment groups (180 days [26 weeks] in Toujeo and 179 days [26 weeks] in Lantus). The majority of patients continued treatment beyond 25 weeks, 92.7% for Toujeo and 93.4% for Lantus.

Study EFC13957 allowed entry of a broad population of paediatric patients in terms of their baseline HbA1c as well as age and countries the study was conducted globally in 24 participating countries (including 13 EU countries as well as Serbia and North Macedonia). The patients from Europe represented 46% of the randomized population.

Therefore, the study population represents the intended target patient population. The study protocol was configured to ensure at least 30% of participants in the age range below 12 years which was achieved in order to ensure sufficient number of trial participants in the younger age group.

Although there are differences in glycaemic control across countries as well as paediatric diabetes centres, the mean HbA1c observed in the Study ECF13957 of 8.63% is corroborated by mean HbA1c reported from several large European clinical registries: the mean HbA1c in the Hvidore study of 2,873 T1D children from 18 countries in Europe was 8.6%, the mean HbA1c observed among 37,539 paediatric T1D patients treated between 1995 and 2012 in Germany and Austria was 8.3%, and the mean HbA1c ranged from 7.7 to 8.6% in a paediatric population with T1DM in 4 Nordic countries. In addition, the mean HbA1c among different age group patients included in a recent insulin study in paediatric population with T1DM ranged between 8.0-8.3%.

In order to assess the impact of the proportion of age strata and the baseline mean HbA1c used in the model on the estimation of the means HbA1c change from baseline to Week 26 by treatment group, sensitivity analyses have been performed by varying these values (proportion of age stratum and mean HbA1c value) over a range of plausible values:

- Figure 2 illustrates the estimated means of HbA1c changes from baseline to Week 26 by treatment group based on the observed baseline mean HbA1c in the overall ITT population (i.e. 8.63%) and by varying the hypothetical proportions of age strata in the target population (from 15% to 45% of the patients below 12 years old).
- Figure 3 illustrates the estimated mean HbA1c change from baseline to Week 26 by treatment group based on the observed proportions of age strata in the overall ITT population (<12 years: 30.9%; ≥12 years: 69.1%) and by varying the hypothetical value of baseline mean HbA1c in the target population (from 7.8% to 9.2%).

These sensitivity analyses showed that:

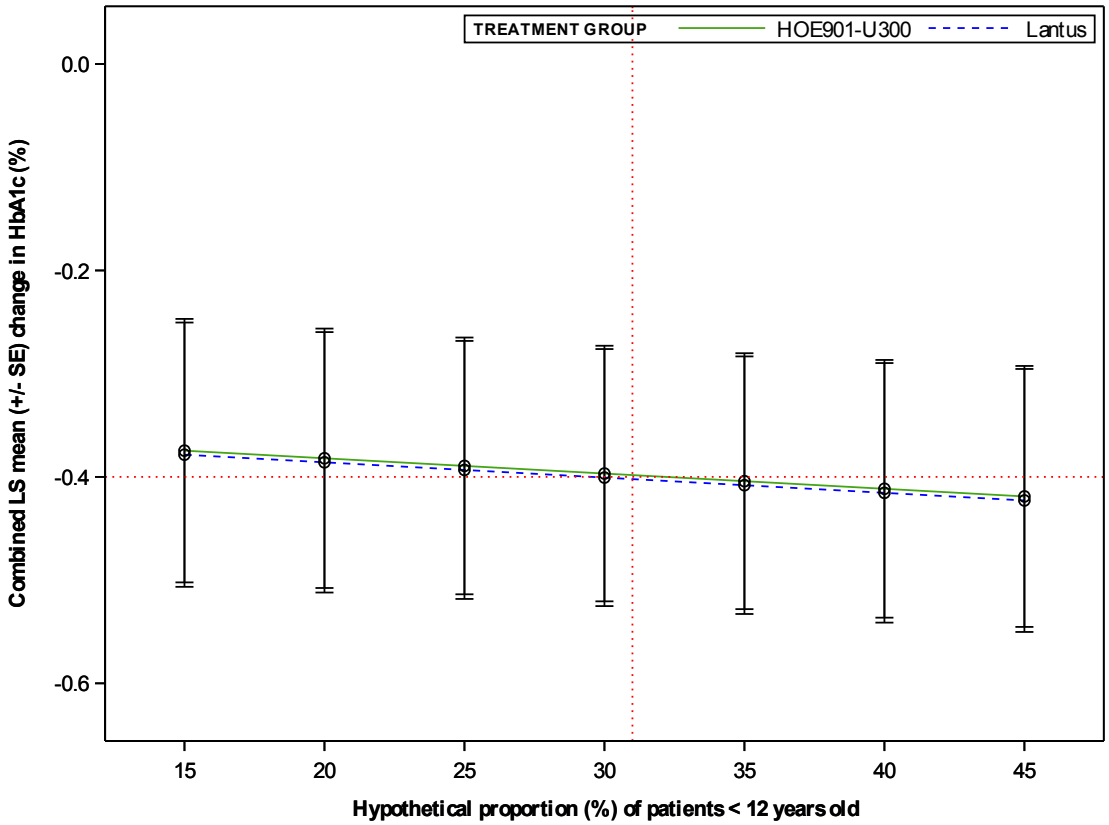
1- modifying the distribution of the randomization stratum of age (from 15% to 45% of patients <12 years old) has a limited impact on the estimated mean change in HbA1c from baseline to Week 26 for both treatment groups (HOE901-U300: combined LS mean HbA1c change varies from -0.375% to -0.419%; Lantus: combined LS mean HbA1c change from -0.379% to -0.423).

2- the mean decrease of HbA1c is, as expected, linked to the value of baseline HbA1c for both treatment groups: the smaller the baseline HbA1c value, the smaller the change from baseline will be. Indeed, for hypothetical mean HbA1c values varying from 7.8% to 9.2%, combined LS mean HbA1c change varies from -0.186% to -0.544% for the HOE901-U300 group, and from -0.190% to -0.548% for the Lantus group).

Conclusion:

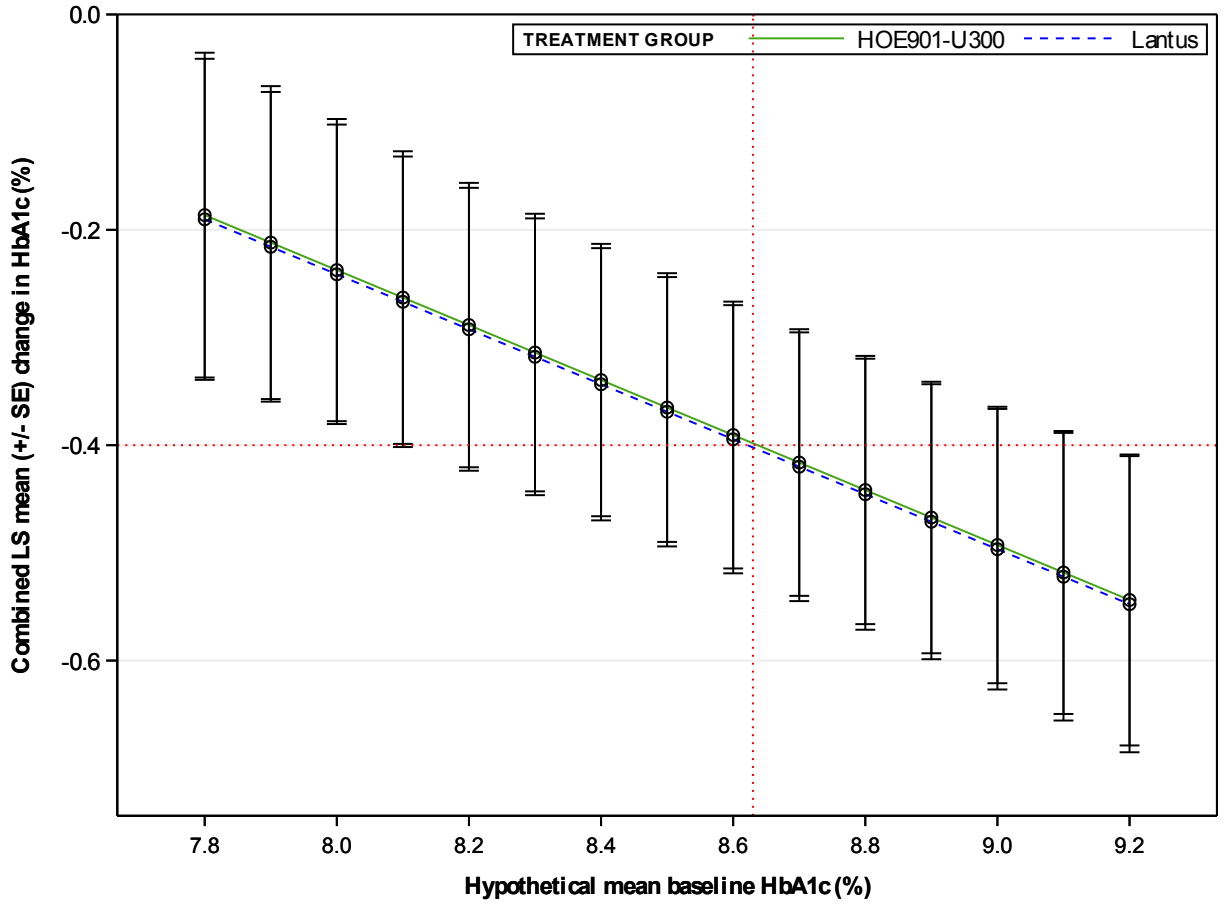
The population assessed in study EFC13957 is sufficiently representative of the future target population in Europe. Additional analyses provided in the documentation shows that the distribution of the age strata does not impact the estimated HbA1c change from baseline for both treatment groups, and that the smaller the baseline HbA1c value, the smaller the change from baseline will be. Of note, whatever the distribution of the age stratum and the mean value of the baseline HbA1c considered in the statistical model, the difference between treatment groups remains exactly the same (LS mean difference of HOE901-U300 versus Lantus: 0.004% [95%CI: -0.172 to 0.179], Table) and do not impact the overall conclusion of the primary analysis.

Figure 2 - Combined LS means (+/- SE) change in HbA1c from baseline to Week 26 by treatment group based on the observed baseline mean HbA1c in the overall ITT population and by varying the hypothetical proportions of patients <12 years old in the target population



Note: Combined LS mean change in HbA1c from baseline to Week 26 for each treatment group obtained from multiple imputation analysis followed by ANCOVA, and calculated using adequate contrasts at Week 26, based on the observed baseline mean HbA1c in the ITT population (i.e. 8.63%) and the hypothetical repartition of patients in the randomization stratum of age (<12 years; ≥12 years)

Figure 3 - Combined LS means (+/- SE) change in HbA1c from baseline to Week 26 by treatment group based on the observed proportions of age strata in the overall ITT population and by varying the hypothetical value of baseline mean HbA1c in the target population



Note: Combined LS mean change in HbA1c from baseline to Week 26 for each treatment group obtained from multiple imputation analysis followed by ANCOVA, and calculated using adequate contrasts at Week 26, based on the observed proportions of patients in the randomization stratum of age in the ITT population (<12 years: 30.9%; ≥12 years: 69.1%) and the hypothetical baseline mean HbA1c

The protocol ensured at least 30% of participants below 12 years and in a sensitivity analysis illustrated that the influence of age distribution on overall study results was minimal.

The HbA1c values in this study are similar to the distribution found in several European registries, and although decrease of HbA1c was dependent on the baseline value this did not differ between treatment arms.

The HbA1c and age distribution correspond to that of the intended treatment population.

Numbers analysed

Outcomes and estimation

Primary efficacy endpoint: HbA1c

As of the data cut-off date, the main 6-months comparative efficacy and safety treatment period of the study has been completed. The 6-months comparative safety extension period was performed.

The efficacy analysis was performed on the ITT population and included 463 patients (233 in Toujeo and 230 in Lantus).

The study met its primary objective as non-inferiority of Toujeo relative to Lantus was demonstrated for HbA1c change from baseline to Week 26. The least squares (LS) mean difference in HbA1c for Toujeo versus Lantus was 0.004% (95% CI [(-0.172 to 0.179]) with the upper bound of the 95% CI lower than the predefined non-inferiority margin of 0.3% (

Table 13).

Statistical superiority of Toujeo over Lantus was not demonstrated (p-value=0.965).

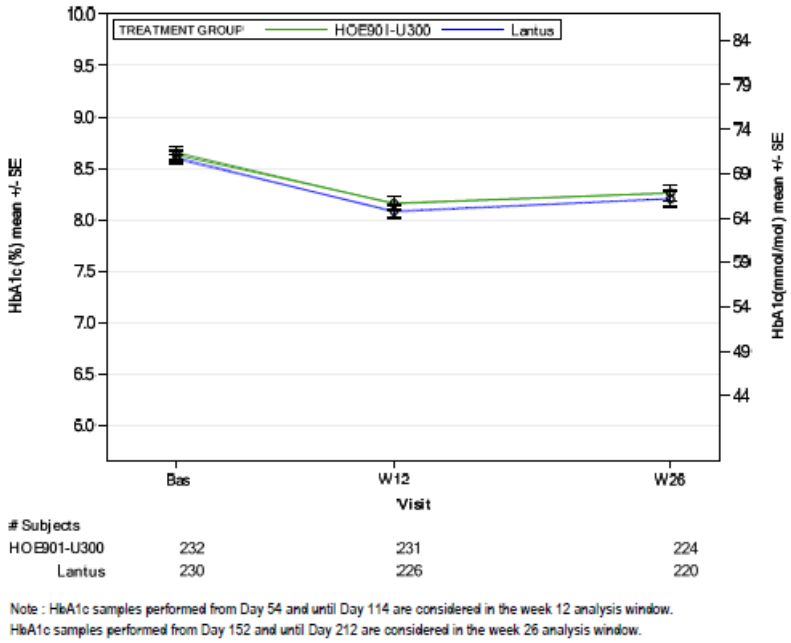
Table 13 - Summary of mean change in HbA1c (%) from baseline to Week 26 endpoint using multiple imputation analysis followed by ANCOVA (ITT estimand) - ITT population

Hba1c (%)	**Toujeo (N=233)**	**Lantus (N=230)**
Baseline		
Number	232	230
Mean (SD)	8.65 (0.88)	8.61 (0.87)
Median	8.55	8.50
Min ; Max	7.0 ; 13.1	6.9 ; 11.3
Change from baseline to Week 26[a]		
Combined LS Mean (SE)	-0.399 (0.063)	-0.402 (0.064)
95% CI	(-0.522 to -0.275)	(-0.527 to -0.278)
Combined LS Mean difference (SE) vs. Lantus	0.004 (0.090)	
95% CI	(-0.172 to 0.179)	
P-value[b]	0.965	

a HbA1c samples performed from Day 152 and until Day 212 are considered in the week 26 analysis window.
b P-value displayed only for the superiority test
Note: Multiple imputation method (1000 imputations) is used to address missing values in the ITT population
Combined estimate for least-square (LS) means and standard errors (SE) are obtained by combining LS means and SE from analysis of covariance (ANCOVA) of the different imputed data sets, using Rubin's formulae
The ANCOVA models include the fixed categorical effect of treatment group, the randomization stratum of age group at screening visit (<12 years and ≥12 years), as well as the continuous fixed covariates of the baseline HbA1c value

In both treatment groups, the mean reduction in HbA1c was gradual during the initial 12 weeks of the treatment period corresponding to the dose titration period, and sustained thereafter (Figure 4).

Figure 4 Mean change (±SE) in HbA1c by visit during the main 6-months randomized period - ITT population



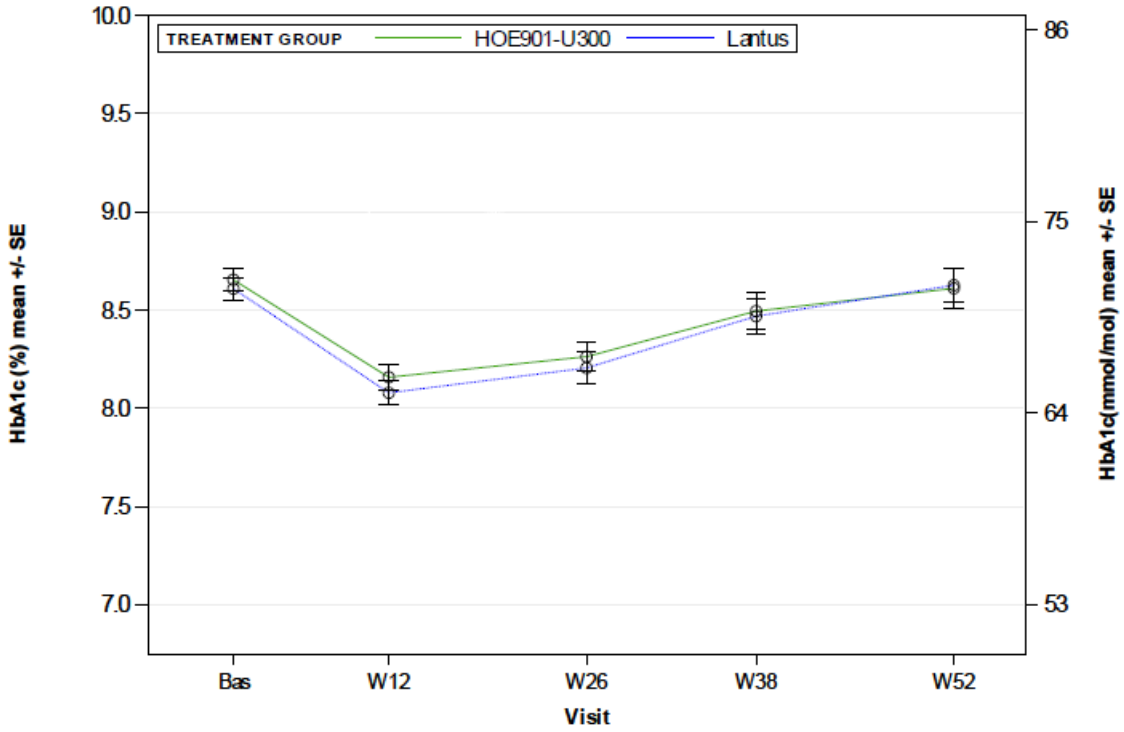
HOE901-U300= Toujeo

Afterwards, in Week 12 to Week 26, there was a slight increase, although mean HbA1c levels were still lower than baseline after 26 weeks, for all patients. Also, the mean HbA1c levels overtime followed a similar trend in both treatment groups. Further, this course of the HbA1c curve in time is known for most trials in diabetic patients.

The primary efficacy variables HbA1c and FPG were measured during the 6-months safety extension as well: HbA1c at Week 38 and at Week 52 and FPG at Week 52. Efficacy data for the 12-months randomized period are presented through descriptive statistics, for the ITT population.

The mean (+/- SE) in HbA1c by visit during the 12-months randomized period is presented in the following figure:

Figure 5 Mean (±SE) in HbA1c by visit during the 12-months randomized period - ITT population



# Subjects					
HOE901-U300	232	231	224	220	220
Lantus	230	226	220	218	215

Note : HbA1c samples performed from Day 54 and until Day 114 are considered in the week 12 analysis window.
HbA1c samples performed from Day 152 and until Day 212 are considered in the week 26 analysis window.
HbA1c samples performed from Day 236 and until Day 296 are considered in the week 38 analysis window.
HbA1c samples performed from Day 334 and until Day 394 are considered in the week 52 analysis window.

It can be concluded that the effect of Toujeo on change in HbA1c during 12-months of treatment was comparable to Lantus in children and adolescents (aged 6–17 years) with T1DM.

Secondary efficacy endpoints

- **Change in fasting plasma glucose (FPG)**

The baseline mean FPG values were similar across the treatment groups (Toujeo: 11.25 mmol/L [202.70 mg/dL]; Lantus: 11.35 mmol/L [204.51 mg/dL]). The LS mean reduction from baseline to Week 26 was similar for both treatment groups (Toujeo: 0.56 mmol/L [10.15 mg/dL]; Lantus: 0.55 mmol/L [9.89 mg/dL]) (Table 14).

Table 8 - Mean change in FPG (mmol/L) from baseline to Week 26 endpoint using multiple imputation analysis followed by ANCOVA (ITT estimand) - ITT population

FPG (mmol/L)	Toujeo (N=233)	Lantus (N=230)
Baseline		
Number	216	215
Mean (SD)	11.25 (5.01)	11.35 (5.07)
Median	11.13	11.17
Min ; Max	0.1 ; 23.6	1.5 ; 25.3
Change from baseline to Week 26[a]		
Combined LS Mean (SE)	-0.563 (0.372)	-0.549 (0.372)
95% CI	(-1.292 to 0.166)	(-1.278 to 0.180)
Combined LS Mean difference (SE) vs. Lantus	-0.014 (0.518)	
95% CI	(-1.030 to 1.002)	

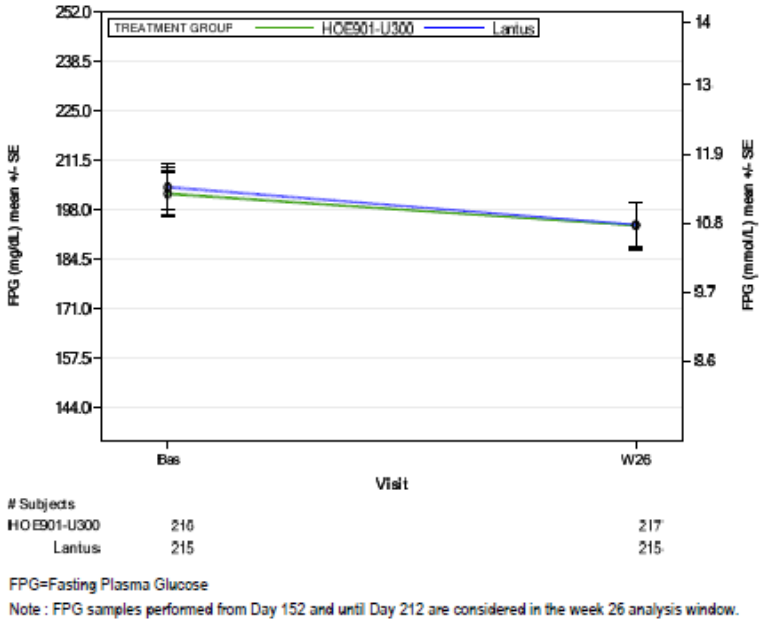
Note: Multiple imputation method (1000 imputations) is used to address missing values in the ITT population.

Combined estimate for least-square (LS) means and standard errors (SE) are obtained by combining LS means and SE from analysis of covariance (ANCOVA) of the different imputed data sets, using Rubin's formulae.

The ANCOVA models include the fixed categorical effect of treatment group, the randomization stratum of age group at screening visit (<12 years and ≥12 years), the randomization strata of screening HbA1c (<8.5, ≥8.5%) as well as the continuous fixed covariates of the baseline FPG value.

Figure 6 - Mean change (±SE) in FPG by visit during the main 6-months randomized period - ITT population

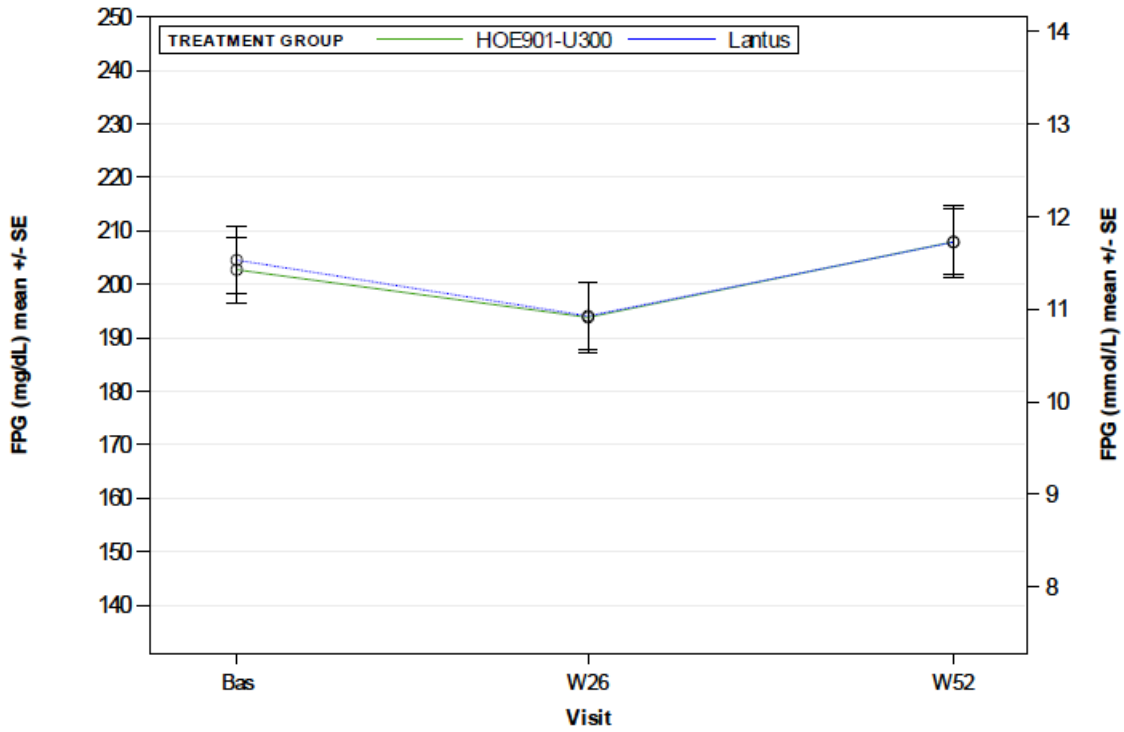
The reduction in mean FPG over time was similar in both treatment groups (Figure 6).



HOE901-U300= Toujeo

The mean (+/- SE) in FPG by visit during the 12-months randomized period is presented in the following figure:

Figure 7 - Mean (±SE) in FPG by visit during the 12-months randomized period - ITT population



FPG=Fasting Plasma Glucose

Note : FPG samples performed from Day 152 and until Day 212 are considered in the week 26 analysis window.

FPG samples performed from Day 334 and until Day 394 are considered in the week 52 analysis window.

The change in FPG over time from baseline to Week 52 was small and similar in both treatment groups. No relevant difference between treatment groups was observed for change from baseline to Week 52 in FPG.

- **Responder analysis: HbA1c target of <7.5% at Week 26 and no event of severe and/or documented hypoglycaemia (SMPG ≤54 mg/dL [3.0 mmol/L]) during last 3 months of the main 6-months randomized period**

The percentage of all patients who reached the pre-specified target *HbA1c of <7.5% at Week 26 and those without an event of severe and/or documented hypoglycaemia (SMPG ≤54 mg/dL [3.0 mmol/L]) during last 3 months of the main 6-months randomized period* was similar in the two treatment groups (Table 15).

Table 9 - Number (%) of patients with HbA1c <7.5% at Week 26 and no severe and/or confirmed documented hypoglycaemia (SMPG <54 mg/dL [3.0 mmol/L]) during the last 3 months of the main 6-months randomized period - ITT population

	Toujeo	Lantus
	(N=233)	(N=230)
Missing HbA1c	9 (3.86)	10 (4.35)
HbA1c responders (HbA1c <7.5%) at Week 26		
N (%)	61 (26.18)	54 (23.48)
RR (95% CI) vs. Lantus[a]	1.11 (0.814 to 1.505)	
HbA1c responders (HbA1c <7.5% at Week 26 without severe and/or documented (SMPG <54 mg/dL) symptomatic hypoglycaemia		
n (%)	10 (4.29)	11 (4.78)
RR (95% CI) vs. Lantus[a]	0.90 (0.401 to 2.026)	

RR=relative risk; a: Based on RR stratified by randomization strata of screening HbA1c (<8.5; ≥8.5%), randomization strata of age at screening (<12 years, ≥12 years), using a CMH methodology.

Note: Patients without any available HbA1c assessment at week 26 and/or with a premature study discontinuation during the main 6-months randomized period are considered as a failure (non-responders) in the analyses.

If any table cell frequency in a stratum is zero, continuity correction is applied.

- **Responder analysis: Fasting plasma glucose (FPG) target FPG (≤130 mg/dL [7.2 mmol/L]) at Week 26 and those without any episode of severe and/or documented hypoglycaemia (SMPG ≤54 mg/dL [3.0 mmol/L]) during the last 3 months of the main 6-months randomized period**

The percentage of patients who reached the pre-specified target FPG (≤130 mg/dL [7.2 mmol/L]) at Week 26 and those without any episode of severe and/or documented hypoglycaemia (SMPG ≤54 mg/dL [3.0 mmol/L]) during the last 3 months of the main 6-months randomized period was similar in the two treatment groups (Table 13).

Table 10 - Number (%) of patients with FPG ≤130 mg/dL and with FPG ≤130 mg/dL at Week 26 without severe and/or documented (SMPG <54 mg/dL) hypoglycaemia - ITT population

	Toujeo (N=233)	Lantus (N=230)
Missing FPG	16 (6.87)	15 (6.52)
FPG responders (FPG ≤130 mg/dL [7.2 mmol/L]) at Week 26		
N (%)	64 (27.47)	61 (26.52)
RR (95% CI) vs. Lantus[a]	1.03 (0.766 to 1.398)	
FPG responders (FPG ≤130 mg/dL [7.2 mmol/L] at Week 26 without severe and/or documented (SMPG <54 mg/dL) symptomatic hypoglycaemia		
N (%)	22 (9.44)	17 (7.39)
RR (95% CI) vs. Lantus[a]	1.27 (0.702 to 2.308)	

FPG=Fasting Plasma Glucose, RR=relative risk; a: Based on RR stratified by randomization strata of screening HbA1c (<8.5; ≥8.5%), randomization strata of age at screening (<12 years, ≥12 years), using a CMH methodology.

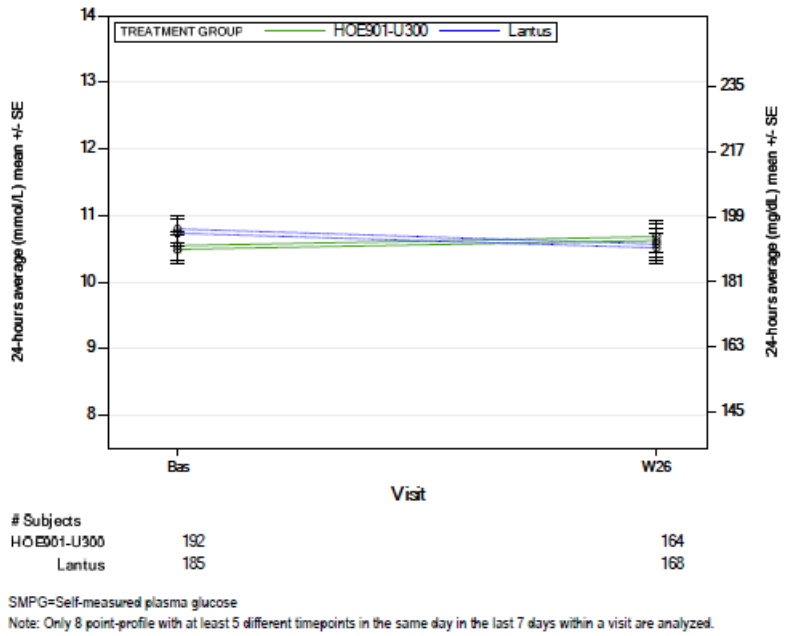
Note: Patients without any available FPG assessment at week 26 and/or with a premature study discontinuation during the main 6-months randomized period are considered as a failure (non-responders) in the analyses.

If any table cell frequency in a stratum is zero, continuity correction is applied.

- **Average plasma glucose (8-point SMPG profiles)**

Based on 8-point SMPG profiles, the mean plasma glucose values at baseline were similar in both treatment groups (Toujeo: 189.48 mg/dL [10.52 mmol/L]; Lantus: 194.47 mg/dL [10.79 mmol/L]). The average 24-hour plasma glucose remained stable at Week 26 in both treatment groups (Toujeo: 193.96 mg/dL [10.77 mmol/L]; Lantus: 187.85 mg/dL [10.43 mmol/L]). The reduction in average plasma glucose from baseline to Week 26 based on 8-point SMPG profiles was similar across the treatment groups (Toujeo: 4.48 mg/dL [0.25 mmol/L]; Lantus: -6.62 mg/dL [-0.37 mmol/L]) (Figure).

Figure 8 - Mean change (±SE) in 24-hour average plasma glucose based on 8-point SMPG profile by visit during the 26-weeks randomized period - ITT population



HOE901-U300= Toujeo

Exploratory efficacy endpoints

- **Change in variability of 24-hour mean plasma glucose (8-point SMPG profiles)**

During the main 6-months treatment period, the change in variability of 24-hour mean plasma glucose based on 8-point SMPG profiles from baseline to Month 6 was similar in both treatment groups (Toujeo: 1.46%; Lantus: 0.69%).

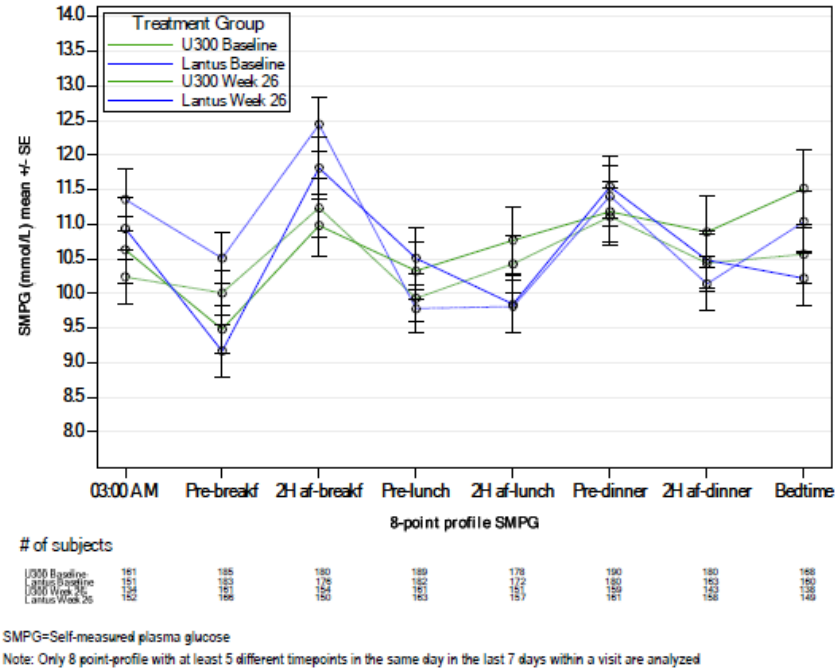
- **Change in 8-point SMPG profiles per time-point**

At baseline and Week 26, the mean 8-point SMPG profiles at each time point, fluctuated throughout the day to a lesser extent in the Toujeo group compared to the Lantus group (Figure 9).

In the Toujeo treatment group, SMPG values across 8-point SMPG profile were comparable between baseline and Week 26. In the Lantus treatment group, SMPG values at baseline were higher than at Week 26 between 3.00 AM and post breakfast and lower than at Week 26 at pre-lunch.

For all other time-points, the SMPG were comparable between baseline and Week 26.

Figure 9 - Mean change (±SE) in plasma glucose based on 8-point profile SMPG profile (mmol/L) per time-point at baseline and at Week 26 - ITT population



SMPG=Self-measured plasma glucose

Note: Only 8 point-profile with at least 5 different timepoints in the same day in the last 7 days within a visit are analyzed

HOE901-U300= Toujeo

- **Average pre-breakfast self-monitored plasma glucose (SMPG)**

The mean reduction in average pre-breakfast SMPG from baseline to Month 6 was slightly greater in the Toujeo group (-23.94 mg/dL [-1.33 mmol/L]) compared to Lantus group (-14.25 mg/dL [-0.79 mmol/L]), with LS mean difference of -4.115 mg/dL (-0.228 mmol/L).

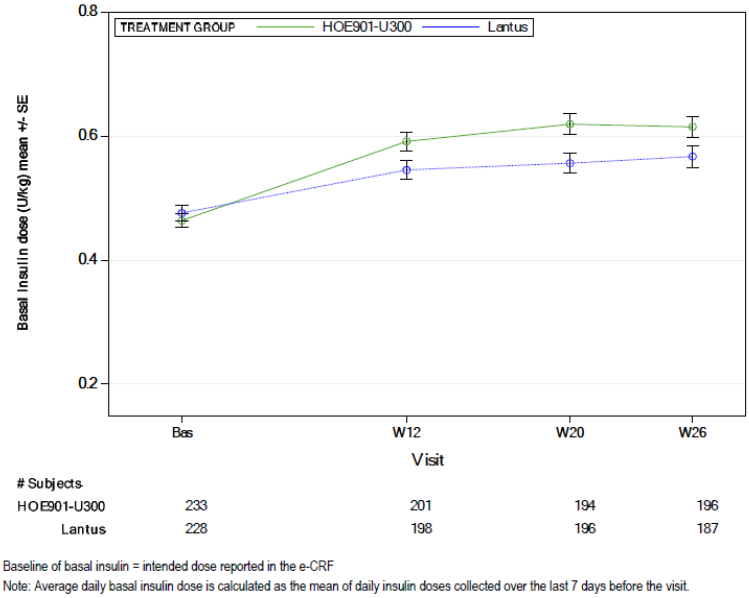
Daily basal insulin dose

In both treatment groups, daily basal insulin dose increased over the course of the trial, with a greater increase in the Toujeo group compared to the Lantus group (HOE901-U300= Toujeo

). The steepest increase in both treatment groups occurred during the first 12 weeks, which corresponded to the main dose titration period of investigational medicinal product (IMP).

The mean daily basal insulin dose at baseline was similar in the 2 treatment groups. The mean percent change (%) in daily basal insulin dose (standard deviation [SD]) from baseline to Week 12 was higher in the Toujeo group (31.73% [30.55]) compared to the Lantus group (15.11% [23.71]). The mean daily basal insulin dose at Week 26 was 8% higher in the HOE901- U300 group (0.615 U/kg) than in the Lantus group (0.567 U/kg) which is consistent with findings in the EDITION program. Similarly, the mean change from baseline to Week 26 was higher in the Toujeo group (0.151 [0.152] U/kg) compared to the Lantus group (0.083 [0.140] U/kg).

Figure 10 Mean (+/- SE) average basal insulin dose (U/kg) by visit during the main 6-months on treatment period – Safety population



HOE901-U300= Toujeo

Consistently with the overall population, the increase in daily basal insulin dosing (U/kg) over time was greater in the Toujeo group than in the Lantus group across all Tanner puberty stages. The difference in dose between Toujeo and Lantus is already known as the formulations are not bioequivalent. However, after 12 weeks, doses remained relatively constant, and no significant changes were seen between the 20 and 26 weeks results.

In both treatment groups, daily mealtime insulin dosing was relatively stable over the course of the trial.

Across all Tanner puberty stages, the daily mealtime insulin dosing was relatively stable over the course of the trial in both treatment groups with a similar trajectory over time to the overall population.

In both treatment groups, total (basal + mealtime) insulin dosing (U/kg) increased during the first 12 weeks of treatment and stabilized thereafter.

Ancillary analyses

Supportive and sensitivity analyses

Efficacy results of the primary endpoint analysis in the post-hoc defined PP population (on-treatment estimand) are consistent with those of the main primary endpoint analysis in the ITT population. The LS mean difference in HbA1c for Toujeo versus Lantus was 0.059% (95%CI: -0.129 to 0.246) during the main 6-months on-treatment period (on-treatment estimand) with the upper bound lower than the predefined non-inferiority margin of 0.3%.

Results from the supportive analysis of the primary efficacy endpoint using all available post-baseline HbA1c data during the main 6-months on-treatment period (on-treatment estimand) indicated consistency with the results of the primary analysis. The LS mean difference in HbA1c for Toujeo versus Lantus was 0.026% (95%CI: -0.155 to 0.207) during the main 6-months on-treatment period (on-treatment estimand) with the upper bound lower than the predefined non-inferiority margin of 0.3%.

Results of the sensitivity tipping point analysis confirmed the robustness of results of the primary efficacy endpoint analysis. Non-inferiority of Toujeo over Lantus was no longer demonstrated only in some extreme scenarios when missing HbA1c change value at Week 26 was highly penalized in the Toujeo group by more than 2.0% (no penalty was applied in the Lantus group).

Results in the per protocol population and in the sensitivity analyses confirmed the results of the primary efficacy analysis.

In addition to the primary analysis, as supportive analysis, the primary endpoint (change in HbA1c from baseline to Week 26) was analyzed by not including all post-baseline data regardless of treatment discontinuation (ITT estimand). Instead, only post-baseline HbA1c values measured under the IMP intake, i.e. during the main 6-months on-treatment period (On-treatment estimand), were included. This supportive analysis was performed in the whole ITT population as for the primary analysis.

A multiple imputation approach followed by an ANCOVA was used to analyze the primary endpoint during the main 6-months on-treatment period. In the main analysis, for patients who discontinued the treatment, imputations were based on post-treatment values that are not used in this on-treatment supportive analysis. For this supportive analysis, the imputation could therefore not be done separately for patients who prematurely discontinued the treatment and for those who completed the main 6-months treatment period as done for the primary analysis. Consequently all missing changes in HbA1c from baseline to week 26 or available changes in HbA1c from baseline to week 26 measured after treatment discontinuation were imputed as follows:

Missing data was imputed 1,000 times using a model estimated from baseline HbA1c and all post-baseline on-treatment HbA1c values observed during the main 6-months period in the whole ITT population. The imputation models (MCMC method to create dataset with a monotone missing pattern, then regression method) included all available on-treatment HbA1c changes from baseline (at week 12 and week 26) to handle missing primary endpoint. Each complete dataset with observed or imputed changes from baseline to week 26 was then analyzed using an ANCOVA model, including the fixed categorical effects of the treatment group, the randomization stratum of age group at screening visit (<12 years and ≥12 years), as well as the continuous fixed covariates of the baseline HbA1c value. The model provided baseline adjusted least squares (LS) means estimates at Week 26 for both treatment groups (using adequate contrasts at Week 26, based on the observed proportions of patients in the randomization age stratum and the observed baseline mean HbA1c in the ITT population), as well as the differences of these estimates with their corresponding SEs and 95% CIs. Finally, combined results from these 1,000 analyses were obtained using Rubin's formula.

Subgroup analyses

For each subgroup, the primary efficacy variable was analyzed using the ITT population.

The treatment effect was consistent across most subgroups as defined by the baseline and demographic characteristics except for "screening HbA1c" subgroups (<8.5 and ≥8.5%); a significant treatment-by-subgroup interaction (p=0.0353) was reported for these two subgroups. The LS mean difference in HbA1c for Toujeo versus Lantus was -0.25% (95% CI [(-0.529 to 0.037]) for patients with a screening HbA1c <8.5% and 0.14% (95% CI [(-0.084 to 0.373]) for patients with a screening HbA1c ≥8.5%.

While the study was not powered to demonstrate non-inferiority in these subgroups, the upper bound of the 95% CI is lower than 0.4% (former non-inferiority limit) and even lower than 0.3% for the subgroup of screening HbA1c <8.5% supporting the conclusion of non-inferiority of Toujeo versus Lantus in all patients, regardless of screening HbA1c level. More precisely, this interaction seems to come from an extreme low value of the LS mean change in HbA1c in the Lantus group of patients with HbA1c <8.5% at screening. Indeed, the LS mean change observed in the subgroup <8.5% are as expected, respectively for each

treatment group, lower than those in the subgroup ≥8.5% with the difference being greater in Lantus group than in Toujeo group.

No significant treatment-by-subgroup interaction was reported for other prespecified subgroups, including by randomization stratum of age, Tanner puberty stage, C-peptide, duration of diabetes, and eGFR categories.

By randomization stratum of age (<12 years versus ≥12 years)

Analysis of primary efficacy endpoint by randomization stratum of age (<12 years versus ≥12 years) showed that the decrease in HbA1c was slightly more pronounced in patients from the younger age group than in older age group, with no difference between treatment arms. For patients <12 years of age, the mean LS reduction (SE) in HbA1c was -0.500 (0.113)% in the Toujeo group and -0.505 (0.114)% in the Lantus group, whereas for patients ≥12 years of age, the mean LS reduction (SE) in HbA1c was -0.353 (0.076)% and -0.356 (0.076)% in the Toujeo and Lantus groups, respectively.

Summary of main study

The following table summarise the efficacy results from the main study 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 33. Summary of Efficacy for trial EFC13957

Title: 6-Months, Multicenter, Randomized, Open-label, 2-Arms, Parallel-group Study Comparing the Efficacy and Safety of a New Formulation of Insulin Glargine and Lantus Injected Once Daily in Children and Adolescents age 6 – 17 years with Type 1 Diabetes Mellitus with a 6-months Safety Extension Period (EDITION JUNIOR 6-months; EFC13957 6-months)			
Study identifier	EFC13957 6-months		
Design	Open-label, 1:1 randomized, active-controlled, 2-arm parallel-group, multicenter international study comparing HOE901-U300 versus Lantus		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		6-months N/A 6-months
Hypothesis	The non-inferiority of Toujeo versus Lantus was considered as demonstrated if this upper bound of the 2-sided 95% confidence interval (CI) for the difference in the mean change in HbA1c between Toujeo and Lantus was <0.3%.		
Treatments groups	Toujeo 300 U/mL solution		Once-daily injection, in combination with a mealtime fast-acting insulin. Dosage titrated to a fasting (preprandial) SMPG target from 90 to 130 mg/dL (5.0 to 7.2 mmol/L), inclusive, while avoiding hypoglycaemia - SC using a Toujeo SoloSTAR pen
	Lantus (insulin glargine 100 U/mL solution)		- Once-daily injection in combination with a mealtime fast-acting insulin. Dosage titrated to a fasting (preprandial) SMPG target from 90 to 130 mg/dL (5.0 to 7.2 mmol/L), inclusive, while avoiding hypoglycaemia - SC using a Lantus SoloSTAR pen
Endpoints and definitions	Primary endpoint	Change in HbA1c (%) from baseline to Month 6/Week 26	To test if upper bound of the 2-sided 95% confidence interval (CI) for the difference in the mean change in HbA1c between Toujeo and Lantus was <0.3%

	Secondary endpoint	HbA1c values of <7.5% at Week 26	Percentage of patients with HbA1c values of <7.5% at Week 26 overall and without any episode of severe and/or documented (SMPG <54 mg/dL; 3.0 mmol/L) hypoglycaemia during the last 3 months of the main 6-months randomized period
	Secondary endpoint	Fasting plasma glucose (mg/dL; mmol/L) at Week 26	Change in fasting plasma glucose (FPG) from baseline to Week 26
	Secondary endpoint	FPG ≤130 mg/dL (7.2 mmol/L) at Week 26	Percentage of patients with FPG ≤130 mg/dL (7.2 mmol/L) at Week 26 overall and without any episode of severe and/or documented (SMPG <54 mg/dL; 3.0 mmol/L) hypoglycaemia during the last 3 months of the main 6-months randomized period
	Secondary endpoint	SMPG (mg/dL; mmol/L) at Week 26	Change in mean plasma glucose based on 8-point SMPG profiles from baseline to Week 26
	Other safety observation	Anti-insulin antibodies in relation to efficacy endpoint (HbA1c) at Week 26	Change in HbA1c from baseline by treatment-emergent AIA and treatment emergent AIA at last on-treatment value
	Secondary exploratory endpoint	Pre-breakfast SMPG (mg/dL; mmol/L) at Week 26	Change in average pre-breakfast SMPG from baseline to Week 26
	Secondary endpoints	All – at 12-months	Evaluated at Week 52 and at intermediary timepoints (Week 12, Week 20, Week 38) when applicable
Database lock	31 May 2018 (6-months)		

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population and time point description	Intent to treat, at Week 26		
Descriptive statistics and estimate variability	Treatment group	Toujeo 300 U/mL	Lantus (insulin glargine 100 U/mL)
	Number of subjects	233	230
	HbA1c % (mean)	8.65	8.61
	SD	0.88	0.87
	HbA1c <7.5% overall and without any episode of severe and/or documented hypoglycaemia (N)	Overall: 61 Without hypoglycaemia: 10	Overall: 54 Without hypoglycaemia: 11
	Percentage %	Overall: 26.18 Without hypoglycaemia: 4.29	Overall: 23.48 Without hypoglycaemia: 4.78
	Fasting plasma glucose mmol/L (mean)	11.25	11.35
	SD	5.01	5.07

	Fasting plasma glucose ≤130 mg/dL (7.2 mmol/L) overall and without any episode of severe and/or documented hypoglycaemia (N)	Overall: 64 Without hypoglycaemia: 22	Overall: 61 Without hypoglycaemia: 17
	Percentage %	Overall: 27.47 Without hypoglycaemia: 9.44	Overall: 26.52 Without hypoglycaemia: 7.39
	SMPG mg/dL (mean)	4.48	-6.62
	SD	70.19	64.48
	HbA1c % with/out TE AIA and TE AIA at last on-treatment value (mean)	With TE AIA: 8.650 With/out: 8.668 With TE AIA at last on-treatment value: 8.711 With/out: 8.658	8.891 8.554 8.893 8.565
	SD	With TE AIA: 0.924 With/out: 0.894 With TE AIA at last on-treatment value: 0.921 With/out: 0.892	1.001 0.813 1.040 0.827
	Pre-breakfast SMPG mg/dL (mean)	-23.94	-14.25
	SD	61.73	62.92
Effect estimate per comparison	Primary endpoint; Change in HbA1c %	Comparison groups	Toujeo vs Lantus
		LS mean difference	0.004
		95% CI	-0.172 to 0.179
		P-value	0.965
	Secondary endpoint; HbA1c <7.5% overall and without any episode of severe and/or documented hypoglycaemia (N)	Comparison groups	Toujeo vs Lantus
		Relative risk	Overall: 1.11 Without hypoglycaemia: 0.90
		95% CI	Overall: 0.814 to 1.505 Without hypoglycaemia: 0.401 to 2.026
	Secondary endpoint; Change in fasting plasma glucose mmol/L	Comparison groups	Toujeo vs Lantus
		LS mean difference	-0.014
		95% CI	-1.030 to 1.002
	Secondary endpoint; Fasting plasma glucose ≤130 mg/dL (7.2 mmol/L) overall and without any episode of severe and/or documented hypoglycaemia (N)	Comparison groups	Toujeo vs Lantus
		Relative risk	1.03
		95% CI	0.766 to 1.398
	Secondary endpoint; SMPG mg/dL	Comparison groups	Toujeo vs Lantus
		LS mean difference	7.292
		95% CI	-5.198 to 19.781
	Other safety observation; HbA1c % with/out TE AIA and TE AIA at last on-treatment value	Comparison groups	Toujeo vs Lantus
		LS mean difference	With TE AIA: -0.014 No TE AIA: 0.042 With TE AIA at last on-treatment value: 0.085 No TE AIA at last on-treatment value: 0.037

		95% CI	With TE AIA: -0.4496 to 0.4213 No TE AIA: -0.1575 to 0.2417 With TE AIA at last on-treatment value: -0.3855 to 0.5555 No TE AIA at last on-treatment value: -0.1599 to 0.2343
	Secondary endpoint; Pre-breakfast SMPG mg/dL	Comparison groups	Toujeo vs Lantus
		LS mean difference	-4.115
		95% CI	-14.634 to 6.404
Note	Efficacy results of the primary endpoint analysis in the post-hoc defined PP population (on-treatment estimand) were analyzed as supportive analysis and are consistent with those of the main primary endpoint analysis in the ITT population.		
Analysis description	**Secondary analysis**		
	Change from baseline in HbA1c (%) week 26; Toujeo vs Lantus 0.059% (95%CI: -0.129 to 0.246)		

2.4.2.2. *T2DM: Extrapolation of adult T2DM and paediatric T1DM data to support use of Toujeo in paediatric patients with T2DM*

Introduction

Study EFC13957 is the only study conducted with Toujeo in paediatric patients with T1DM. In support of treatment of paediatric patients with T2DM, a comparative analysis was performed to evaluate similarities in response to treatment with Toujeo in adult patients with T1DM (Study EFC12456) and T2DM (Studies EFC12347 and EFC11628), to support extrapolation from children and adolescents (aged 6-17 years) with T1DM (study EFC13957) to T2DM populations.

Additionally, as further support of this extrapolation, a comparison of pathophysiology, disease progression, treatment recommendations in adults and paediatric patients has been provided, as well as an overview of external pharmacology and clinical response data for insulin treatment in paediatric T2DM, which is presented below.

Paediatric T2DM pathophysiology

The pathophysiology of paediatric T2DM appears to be similar to that in adults (Table 20). Nearly all youth with T2DM are obese and come from families and populations with a high prevalence and/or high risk of T2DM. Paediatric T2DM occurs most often during the second decade of life often overlapping with the physiologic rise in insulin resistance around puberty with a median age of diagnosis of 13.5 years. Although the incidence of T2DM in children and adolescents has been increasing globally, it is still a relatively low overall number of patients with an estimated prevalence in Europe of approximately 2.5:100000. However, a prevalence of impaired glucose tolerance and T2DM as high as 6.7% was found in a large group of children and adolescents with obesity in Germany

T1DM represents the most common form of diabetes in youth and has unique aspects of management in the paediatric population, such as changes in insulin sensitivity related to growth and sexual maturation, ability to provide self-care and supervision in the child care, adverse effects on cognition of hypoglycaemia and hyperglycaemia as well as effects of diabetic ketoacidosis (DKA).

All types of diabetes result in hyperglycaemia and are diagnosed based on the same plasma glucose or HbA1c criteria. As in adults, T2DM in children and adolescents occurs when endogenous insulin secretion is not sufficient to meet the increased demand caused by insulin resistance, leading to relative insulin deficiency and consequently hyperglycaemia. Similarly to adult T2DM, T2DM in the younger age group is commonly associated with other metabolic abnormalities related to obesity and insulin resistance such as dyslipidemia, hypertension, polycystic ovary syndrome or fatty liver.

Unlike T1DM, there is no identified autoimmune process leading to an absolute insulin deficiency in paediatric T2DM, which rather results from genetic, metabolic and socio-economical causes.

Although insulin resistance occurs in both T2DM and T1DM, it is significantly more severe in paediatric T2DM. Furthermore, it appears that there are differences in insulin sensitivity and β-cell function between T2DM in youth and adults with similar degrees of hyperglycaemia that include greater insulin resistance for any degree of adiposity in paediatric T2DM.

Paediatric T2DM disease progression

Insulin secretion in paediatric T2DM depends on the disease status and can vary from a delayed and exaggerated response to absolutely diminished secretion over time. Studies showed that at the time of diagnosis, insulin secretion is already severely impaired in adolescents with T2DM, and the decline in insulin secretion is more rapid in adolescents compared to adults with T2DM as shown in the TODAY study. Moreover, several large studies indicate that diabetes related comorbidities such as kidney disease, retinopathy, neuropathy and hypertension are prevalent at the time of diagnosis in paediatric T2DM and increase rapidly over time.

Paediatric T2DM disease manifestation and treatment recommendations

Table 20 summarizes the characteristics of T1DM and T2DM in the different populations.

The presentation of paediatric T2DM can vary from asymptomatic hyperglycaemia or glucosuria without ketonuria detected during a medical check-up or mild polyuria/polydipsia up to ketoacidosis or rarely hyperglycaemic hyperosmolar state. Between 5% to 25% of paediatric T2DM patients have ketoacidosis at presentation. Consistent with the similar pathophysiology of T2DM in children and in adults a similar therapeutic approach is recommended, including lifestyle modification to support weight loss (diet and exercise).

The glycaemic goals of initial treatment in paediatric T2DM are similar to those recommended in adults with an HbA1c of less than 7.0% and in some situations <6.5% (19). Long-term glycaemic control is more likely to be achieved if the therapy is intensified to maintain the HbA1c target (treat-to-target). The selection of the initial treatment is determined by the severity of the hyperglycaemia and its symptoms as well as the presence or absence of ketosis/ketoacidosis. Initial pharmacologic treatment in paediatric T2DM should include metformin alone or with insulin; in patients with ketosis/ketonuria/ketoacidosis or HbA1c >8.5% initial insulin treatment is usually required. A once-a-day intermediate or basal insulin is often effective in attaining metabolic control. Because adherence to insulin therapy is a challenge in youth with T2DM, treatment initiation with a single daily dose of a long-acting insulin analogue may be preferred. If the patient is started on metformin monotherapy and fails to reach target HbA1c of <7% or <6.5% within 4 months, addition of basal insulin should be considered. In some cases if life-style changes with or without concomitant metformin treatment are successful and result in reduction of body weight and improvement of glycaemic control, insulin treatment may be discontinued. Conversely, if HbA1c target is not attained on combination metformin and basal insulin, initiation of prandial insulin should be considered to reach glycaemic targets.

Table 11 - Commonly observed characteristics of paediatric T1DM, T2DM and adult T2DM

Clinical characteristic	Pediatric T1DM	Pediatric T2DM	Adult T2DM
Hyperglycemia	Present	Present	Present
Obesity	Not common/depending on the population	Severe	Severe/moderate
Pathophysiology	Autoimmune disorder with an absolute insulin deficiency	Insulin resistance with relative insulin deficiency Metabolic Syndrome	
Gender	Male = female	Female > male	Male > female
Beta cells failure	At diagnosis	Rapid	Slow
Relatives with diabetes	Not common	Very common	Common
Insulin, C-peptide	Very low	High	High
Ketoacidosis	Common	Up to 25%	Uncommon
B-cell autoantibodies	Almost all	Uncommon	Uncommon
Diabetes related complications (cardiovascular, neuropathy, renal disease, eye)	High/moderate risk	High risk	Moderate risk
Impact of physical growth and hormonal changes due to puberty	Present	Present	Absent

Source: Table modified from Reinehr, T 2013; Abbreviations: T1DM: Type 1 diabetes mellitus; T2DM: Type 2 diabetes mellitus.

Overview of external pharmacology and clinical response data of insulin treatment in paediatric T2DM

In order to review the published information on the clinical efficacy of insulin treatment in paediatric T2DM, a literature research was performed in Pubmed (focusing on the search terms 'insulin', 'paediatrics or adolescents or youth' and 'type 2' and the article type 'clinical trial'). The literature research revealed three relevant clinical studies containing information on clinical efficacy of insulin treatment (Table 21).

Table 12 - Overview of external clinical studies performed in paediatric patients with T2DM receiving insulin treatment

Author, year	Population, Age	Treatment	Number of patients	Study period
RISE Consortium, 2018 (21)	T2DM or IGT Age mean (SD): 14.9 (2.0) Age mean (SD): 13.9 (2.1)	Treatment 1: Insulin glargine (3 month) followed by metformin (9 month) Treatment 2: Metformin alone (12 month)	N_{tot}=91 $N_{Treatment\ 1}$=44 $N_{Treatment\ 2}$=47	12 month treatment period
Sellers and Dean, 2004 (22)	T2DM Age mean (SD): 13.3 (1.3)	Premixed 30/70 insulin	N=18	<16 weeks
Wheeler et al., 2018 (23)	T2DM Age 10-14 years: 47.6% Age 15-17 years: 52.4%	Treatment 1: Insulin detemir + metformin Treatment 2: NPH insulin + metformin	N_{tot}=42 $N_{Treatment\ 1}$=20 $N_{Treatment\ 2}$=22	26 weeks

Abbreviations: IGT: Impaired glucose tolerance; SD: Standard deviation; T2DM: Type 2 diabetes mellitus

Study design and clinical efficacy

The U100 formulation of insulin glargine (Lantus) is approved for the treatment of paediatric patients with T2DM and was investigated in this population in a recent clinical trial (Restoring Insulin Secretion (RISE) Paediatric Medication Study). In this study, 91 patients between 10-19 years of age were included, of which 40% were patients with T2DM and 60% patients showed impaired glucose tolerance (IGT). Patients were

either drug-naïve or received metformin treatment prior to the start of the study. Mean HbA1c of the study population at baseline was 5.7%. The focus of this study was to investigate the effect of insulin glargine treatment on β-cell function (two coprimary surrogate endpoints derived from hyperglycaemic clamp studies). The study provided also information about the efficacy of insulin glargine in terms of HbA1c reduction. Although as expected no preservative effect on the β-cell function was observed, HbA1c decreased significantly ($p<0.05$) from baseline after 3 months of treatment with insulin glargine. The decrease in HbA1c from baseline after 3 months of treatment with insulin glargine was approximately 0.1%. Considering the low HbA1c of 5.7% at baseline, the fact that metformin was stopped at baseline, and the short treatment period, this change from baseline is considered to be indicative of the efficacy of insulin glargine in paediatric patients with T2DM.

Two additional studies investigated the clinical efficacy of basal insulin treatment other than insulin glargine in T2DM paediatric populations characterized by higher baseline HbA1c values. Sellers and Dean assessed short-term insulin therapy (<16 weeks) with a pre-mixed 30/70 insulin in 18 adolescents with T2DM, aged 10-18 years. The authors did not describe unambiguously the number of insulin-naïve patients. Acknowledging the high mean HbA1c value of 12.8% at baseline, a marked treatment effect was observed after up to 16 weeks (mean HbA1c value of 7.6% at end of study).

In the recent study by Wheeler et al., efficacy and safety of long-term insulin treatment over 26 weeks was investigated in paediatric patients with T2DM (Table 21). In total, 42 patients, between 10 and 17 years of age were treated with either insulin detemir (Treatment 1) or NPH insulin (Treatment 2). Nine of the 42 patients were insulin naïve. This study showed a decrease in HbA1c from 8.7% and 9.0% at baseline to 8.11% in both groups after 26 weeks of treatment with insulin detemir and NPH insulin, respectively.

Insulin dosing

For initiation of an insulin treatment, identifying a safe starting dose is crucial. In the three studies presented in this section, patients received starting doses that were safe and well tolerated (Table 22).

- In the RISE Paediatric Medication Study, the paediatric patients with IGT received a starting dose of Lantus of 0.25 U/kg. For the paediatric patients with T2DM, the starting dose of Lantus of 0.4 U/kg was twice the proposed starting dose of Toujeo of 0.2 U/kg. After 11-12 weeks of individual titration to the fasting plasma glucose target value, the mean dose of Lantus clearly increased. No patients showed severe hypoglycaemia or acute metabolic decompensation.
- In the clinical study described by Sellers and Dean, paediatric patients received a starting dose of 0.5 U/kg premixed 30/70 insulin split into two doses. Following individual titration, the maximum mean dose of 0.76 U/kg was achieved after 2-3 weeks. No hypoglycaemic events requiring external help occurred in this study.
- In the clinical study described by Wheeler et al, for insulin-naïve patients the same starting dose was administered in both treatment groups (i.e. for insulin detemir and NPH insulin). Patients who were treated with insulin already prior to study start received equivalent units of the respective study insulins. This resulted in mean insulin doses at baseline of 0.342 U/kg and 0.226 U/kg for insulin detemir and NPH insulin, respectively. After 26 weeks of individual titration to the fasting plasma glucose target value, the mean doses of the basal insulins clearly increased to 0.884 U/kg and 0.818 U/kg for insulin detemir and NPH insulin, respectively. During the study, no severe hypoglycaemic events were reported and the rate of symptomatic and confirmed hypoglycaemia was low for both basal insulins.

Table 13- Starting doses, fasting plasma glucose targets and individually titrated doses in the clinical studies conducted in paediatric populations with T2DM

Author, year Insulin	Starting doses for patients [U/kg/day]	Fasting plasma glucose target [mmol/L]	Mean (SD) individually titrated dose [U/kg/day]
RISE Consortium, 2018 (21) **Insulin glargine**	IGT: 0.25 T2DM: 0.4	4.4-5.0	Week 11-12: 0.7 (0.4)
Sellers and Dean, 2004 (22) **Premixed 30/70 insulin**	0.5 administered in two doses	4.0-7.0	Max. mean dose: 0.76 at 2-3 weeks
Wheeler et al., 2018 (23) **Insulin detemir** **NPH insulin**	0.1-0.2 (max. dose of 10 U/day)[a]	4.0-6.0	26 weeks: Insulin detemir: 0.884 NPH insulin: 0.818

a Represents starting dose for insulin-naïve patient; Insulin-experienced patients were switched to equivalent units of the respective study insulins. Abbreviations: IGT: Impaired glucose tolerance; max.: Maximum; SD: Standard deviation; T2DM: Type 2 diabetes mellitus.

Limitations and conclusions

The RISE Paediatric Medication Study provided limited information about the long-term efficacy of insulin glargine treatment in paediatric population with T2DM because Lantus was administered for 3 months. Furthermore, the study population did not exclusively comprise paediatric patients with T2DM but also youth with IGT. Finally, the low mean HbA1c value of 5.7% at baseline precluded a marked treatment response. Despite these limitations, the RISE Paediatric Medication Study indicated the efficacy of insulin glargine in paediatric patients with T2DM.

In the study described by Sellers and Dean, treatment of a low number of paediatric patients with T2DM with a premixed insulin was investigated up to 16 weeks only. The insulin premix consisted of a basal insulin portion and a mealtime insulin portion, which confounds the treatment effect of the basal insulin portion. However, considering the marked observed treatment effect, it is reasonable to assume that the basal insulin portion contributed substantially to the overall efficacy.

In the study described by Wheeler et al., the efficacy of basal insulins other than insulin glargine were investigated in two paediatric populations with T2DM. These paediatric populations comprised insulin-naïve and insulin-experienced patients with T2DM. An analysis of the treatment outcome in these two sub-populations was not performed. Despite this limitation, the analysis of the pooled data from both populations demonstrated the long-term (26 weeks) efficacy of insulin detemir and NPH insulin in the paediatric populations with T2DM.

In summary, three studies were identified that assessed basal insulin treatment in paediatric patients with T2DM. In these studies, efficacy of insulin glargine administered as Lantus as well as of various other basal insulins in paediatric populations with T2DM was observed. Since insulin glargine lowers HbA1c, CHMP agrees that it is reasonable to assume that insulin glargine when administered as Toujeo is also effective in paediatric patients with T2DM. In all three studies, the basal insulins were shown to be safe and well tolerated. The starting doses were markedly lower than the individually up-titrated doses, indicating the safety of the selected starting doses.

Extrapolation of adult T2DM and paediatric T1DM data to support use of Toujeo in paediatric patients with T2DM

Methods

A comprehensive extrapolation was made presenting qualitative and quantitative evidence supporting the extrapolation of the data from adult T2DM patients and paediatric patients with T1DM to children and adolescents aged 6 years and older with T2DM.

Despite the differences in underlying pathophysiology between T1DM (autoimmune β-cell destruction, usually leading to absolute insulin deficiency) and T2DM (insulin resistance and progressive β-cell failure), both result in hyperglycaemia in adults, children, and adolescents.

Response to treatment with Toujeo in both T1DM and T2DM patient populations and across age groups is expected to be similar for the following reasons:

- insulin is generally effective in reducing hyperglycaemia and attaining glycaemic targets in diabetes mellitus,
- Toujeo was shown to be effective in adult T1DM and across adult patients with T2DM using different treatment regimens, and
- insulin is always titrated to achieve individualized glycaemic targets.

To support this hypothesis, the applicant has undertaken a qualitative comparison of the efficacy (and safety) data of Toujeo across different patient populations included in the Toujeo clinical development program:

Table 14 - Overview of studies (or study periods) supporting inclusion of T2DM paediatric patients in the Toujeo labeling and completed by the dossier cut-off date

Study	Population	Treatment groups	Number of randomized patients	Study period included in the analysis
Phase 3 study in paediatric T1DM				
EFC13957	T1DM paediatric patients on basal + mealtime insulin Ages 6-17 years	Toujeo or Lantus	N=463 (233 with Toujeo and 230 with Lantus)	6-months main study period
Phase 3 study in adult T1DM				
EFC12456	T1DM adult patients on basal + Toujeo or mealtime insulin	Toujeo or Lantus	N=549 (274 with Toujeo and 275 with Lantus)	6-months main study period
Phase 3 studies in adult T2DM				
EFC11628	T2DM adult patients on basal +mealtime insulin	Toujeo or Lantus	N=807 (404 with Toujeo and 403 with Lantus)	6-months main study period
EFC12347	Insulin-naïve T2DM adult patients	Toujeo or Lantus	N=878 (439 with Toujeo and 439 with Lantus)	6-months main study period

All three adult studies were similar in design to each other and to study EFC13957 in paediatric patients. They were 6-months, multicentre, randomized, open-label, parallel-group studies comparing the efficacy and safety of Toujeo and Lantus injected once daily.

The efficacy endpoints assessed were HbA1c and FPG. To leverage information on efficacy (and safety) in study patient populations considered as particularly relevant to paediatric patients with T2DM, several subgroups of interest were defined.

1. Paediatric subgroups in study EFC13957 (T1DM):

    - Adolescents 10–18 years of age
    - Adolescents 10–18 years of age with a BMI ≥85th percentile at baseline

2. Adult subgroups from insulin-naïve patients in study EFC12347 (T2DM):

    - Subjects on metformin prior to the study and continued metformin during treatment
    - Subjects with BMI ≥30 kg/m² at baseline
    - Subjects by age categories <50, 50 - 65 and ≥65 years

The above subgroups are considered particularly representative of children and adolescents with T2DM as obesity and concomitant metformin use are common in such patients. In addition, insulin dose data from study EFC12347 in insulin-naïve adult T2DM starting basal insulin in combination with oral anti-diabetic drugs (OAD) can be considered pertinent to support dosing information for adolescent patients with T2DM. The subgroups by age category in study EFC12347 will allow evaluation of insulin dose information and treatment effect across different age groups.

All qualitative and quantitative analyses performed were descriptive and no formal statistical test was performed.

Results

Baseline characteristics

The baseline characteristics of patients included in the four studies were representative for patients with T1DM as well as T2DM. As expected, the mean age and BMI were higher in the T2DM. The demographic and baseline characteristics (other than disease-related) were generally similar across the different subgroups of interest in the paediatric and insulin-naïve adult populations (Table 24).

Table 15 Demographics and patient characteristics at baseline for the Toujeo treatment group - Randomized population (abbreviated)

		T1DM - EFC12456 (in combination with meal time insulin) - adult (N=274)	T2DM - EFC11628 (in combination with meal time insulin)- adult (N=404)	T2DM - EFC12347 (insulin-naïve)- adult (N=435)	T1DM - EFC13957- paediatric (N=233)
Age	[Mean (SD)]	46.4 (13.9)	60.1 (8.5)	58.2 (9.9)	12.9 (2.9)
Gender [n (%)]	Male	149 (54.4%)	217 (53.7%)	253 (57.6)	128 (54.9)
Race [n (%)]	White	232 (84.7%)	371 (91.8%)	347 (79.0)	211 (90.6)
	Black	14 (5.1%)	26 (6.4%)	44 (10.0)	8 (3.4)
	Asian	24 (8.8%)	6 (1.5%)	39 (8.9)	11 (4.7)
Body weight (kg)	[Mean (SD)]	81.9 (20.4)	106.2 (21.5)	95.1 (23.3)	53.5 (18.1)
BMI (kg/m²)	[Mean (SD)]	27.6 (5.5)	36.6 (6.8)	32.8 (6.9)	-
BMI percentile	[Mean (SD)]	-	-	-	67.5 (26.6)

BMI = Body Mass Index

Glycaemic control variables at baseline differed slightly in the four studies, but these differences were consistent with the type of patient population enrolled in each study. Mean HbA1c at baseline was highest in T1DM paediatric patients and in insulin-naïve T2DM adult patients, while mean FPG at baseline was highest in both adult and paediatric T1DM populations (Table 25).

Table 16 Baseline data relative to insulin administration for the Toujeo treatment group - Randomized population (abbreviated)

	T1DM - EFC12456 (in combination with meal time insulin) - adult (N=274)	T2DM - EFC11628 (in combination with meal time insulin)- adult (N=404)	T2DM - EFC12347 (insulin-naïve)- adult (N=435)	T1DM - EFC13957- paediatric (N=233)
Basal insulin daily dose (U) - Mean (SD)	27.52 (18.75)	70.33 (32.28)	18.35 (5.19)	24.67 (11.87)
Basal insulin daily dose (U/kg) - Mean (SD)	0.323 (0.173)	0.674 (0.290)	0.193 (0.027)	0.464 (0.170)
Mealtime insulin daily dose (U) - Mean (SD)	26.43 (20.06)	54.27 (36.15)	-	26.10 (15.09)
Mealtime insulin daily dose (U/kg) - Mean (SD)	0.318 (0.198)	0.512 (0.334)	-	0.489 (0.233)
Total insulin daily dose (U) - Mean (SD)	53.95 (35.34)	125.04 (58.18)	-	50.87 (22.57)
Total insulin daily dose (U/kg) - Mean (SD)	0.645 (0.324)	1.189 (0.529)	-	0.951 (0.305)

For EFC11628, EFC12347 and EFC12456, daily basal insulin dose at baseline is the actual starting IMP dose of basal insulin as reported by the investigator into the e-CRF at the day of the first IMP intake.

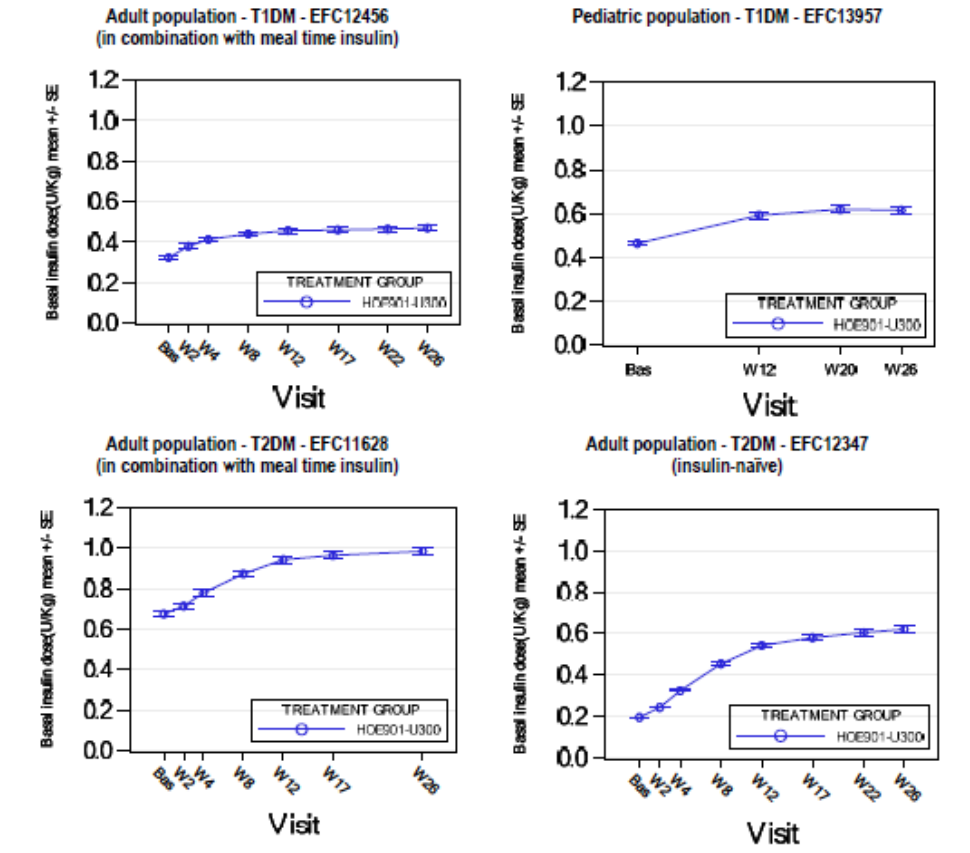
For EFC11628 and EFC12456, daily mealtime insulin dose at baseline is the actual starting daily dose of mealtime reported by the investigator into the e-CRF at the day of the first IMP intake; daily total insulin dose at baseline is the actual starting daily dose of total (basal plus mealtime)

Insulin For EFC13957, daily basal insulin dose at baseline is the intended IMP dose of basal insulin as reported by the investigator into the e-CRF at the day of the first IMP intake; daily mealtime insulin dose at baseline is the median of mealtime insulin daily doses of the 3 first days from the first IMP; daily total insulin dose at baseline is the intended dose of basal insulin plus median of mealtime insulin daily dose

Insulin dosing

In all 4 studies, the mean daily dose of Toujeo increased during the course of the study, and with a similar trajectory over time.

Figure 2 Mean (+/- SE) in average daily basal insulin (U/Kg) dose by visit during the 6-months on-treatment period for Toujeo treatment group - Safety population



BAS = Baseline corresponding to actual starting IMP dose reported in the e-CRF for EFC12456, EFC11628 and EFC12347 and to intended dose reported in the e-CRF for EFC13957

Note: Mean of daily insulin doses collected in the week before each visit.

For all EFC12347 patients rescued during the 6-month period, only the post-baseline insulin measurements before rescue and during the 6-month on-treatment period are presented.

HOE901-U300= Toujeo

In all populations/studies the steepest dose increase occurred during the first 12 weeks, consistent with the main titration period. Mean daily dose levels varied depending on the study, with the highest mean doses overtime observed in advanced T2DM patients treated with basal-bolus regimen (study EFC11628).

The mean change in daily basal insulin dosing (Toujeo) from baseline to Month 6 was higher in T2DM patients than in T1DM patients.

Small increases in **daily mealtime insulin doses** were observed across adult studies (except Study EFC12347 with a basal-OAD regimen). At Month 6, the mean mealtime insulin dose was lowest in adult T1DM patients.

Efficacy

The HbA1c and FPG data across the four studies indicate a similar treatment response to Toujeo in both T1DM and T2DM patients.

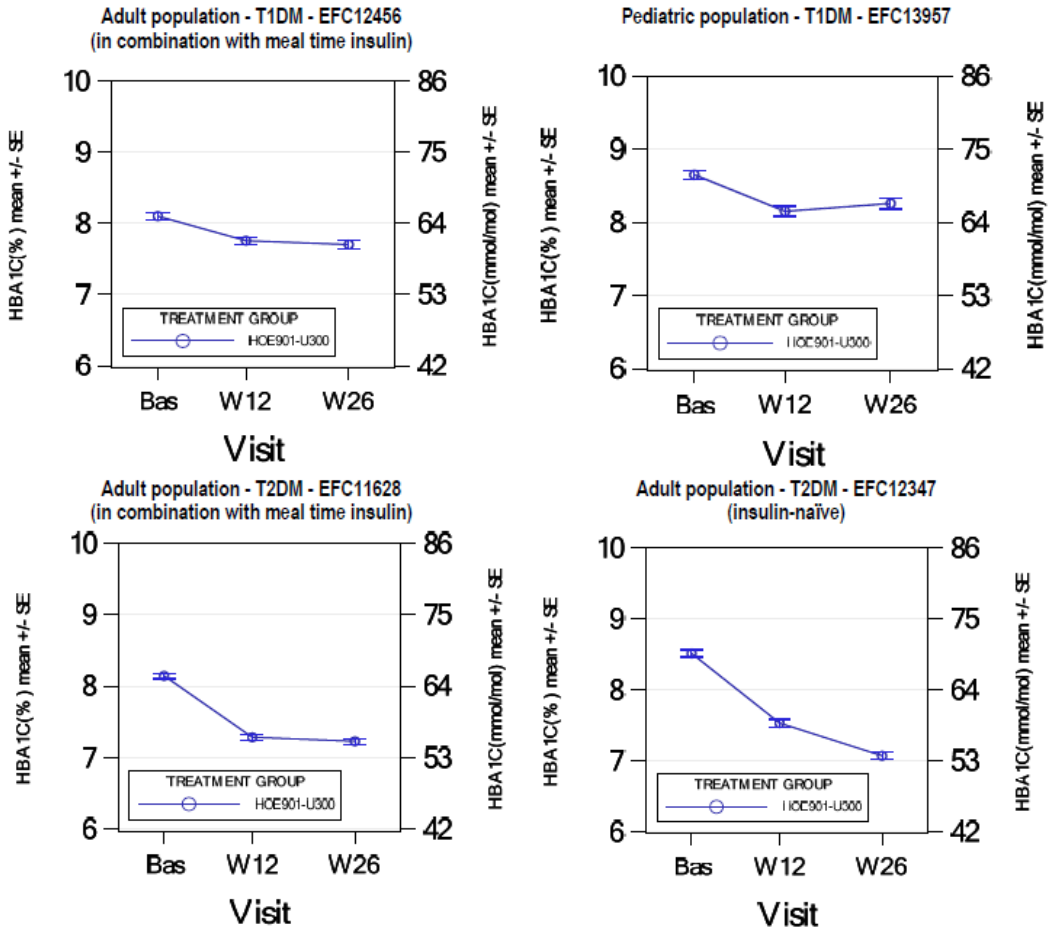
Table 17 HbA1c (%) observed and change from baseline value by visit during the 6-months on-treatment period for the Toujeo treatment group - mITT/ITT population

HbA1c (%)	T1DM - EFC12456 (in combination with meal time insulin) - adult (N=274)	T2DM - EFC11628 (in combination with meal time insulin) - adult (N=404)	T2DM - EFC12347 (insulin-naïve)- adult (N=435)	T1DM - EFC13957- paediatric (N=233)
Baseline				
Number	273	404	432	232
Mean (SD)	8.11 (0.77)	8.15 (0.78)	8.51 (1.05)	8.65 (0.88)
Week 12				
Number	239	382	391	227
Mean (SD)	7.76 (0.84)	7.29 (0.80)	7.53 (1.04)	8.15 (1.05)
Change from baseline to Week 12				
Number	239	382	391	227
Mean (SD)	-0.38 (0.76)	-0.85 (0.74)	-0.97 (1.00)	-0.50 (0.89)
Month 6				
Number	224	362	360	221
Mean (SD)	7.70 (0.99)	7.23 (0.84)	7.07 (0.96)	8.26 (1.12)
Change from baseline to Month 6				
Number	224	362	360	221
Mean (SD)	-0.41 (0.98)	-0.90 (0.82)	-1.41 (1.11)	-0.40 (0.98)

Note: For all EFC12347 patients rescued during the 6-months period, only the post-baseline HbA1c measurements before rescue and during the 6-months on-treatment period are presented.

The trajectories of the reductions in HbA1c and FPG over time were similar in all studies, although greater in T2DM patients than in T1DM patients. HbA1c and FPG levels both decreased primarily during the first 12 weeks of treatment, corresponding to the initial titration period, and thereafter continued to decrease gradually or remained stable (Figure 12 and Figure 13).

Figure 3 - Mean (+/- SE) in HbA1c by visit during the 6-months on-treatment period for Toujeo treatment group - mITT/ITT population



HOE901-U300= Toujeo

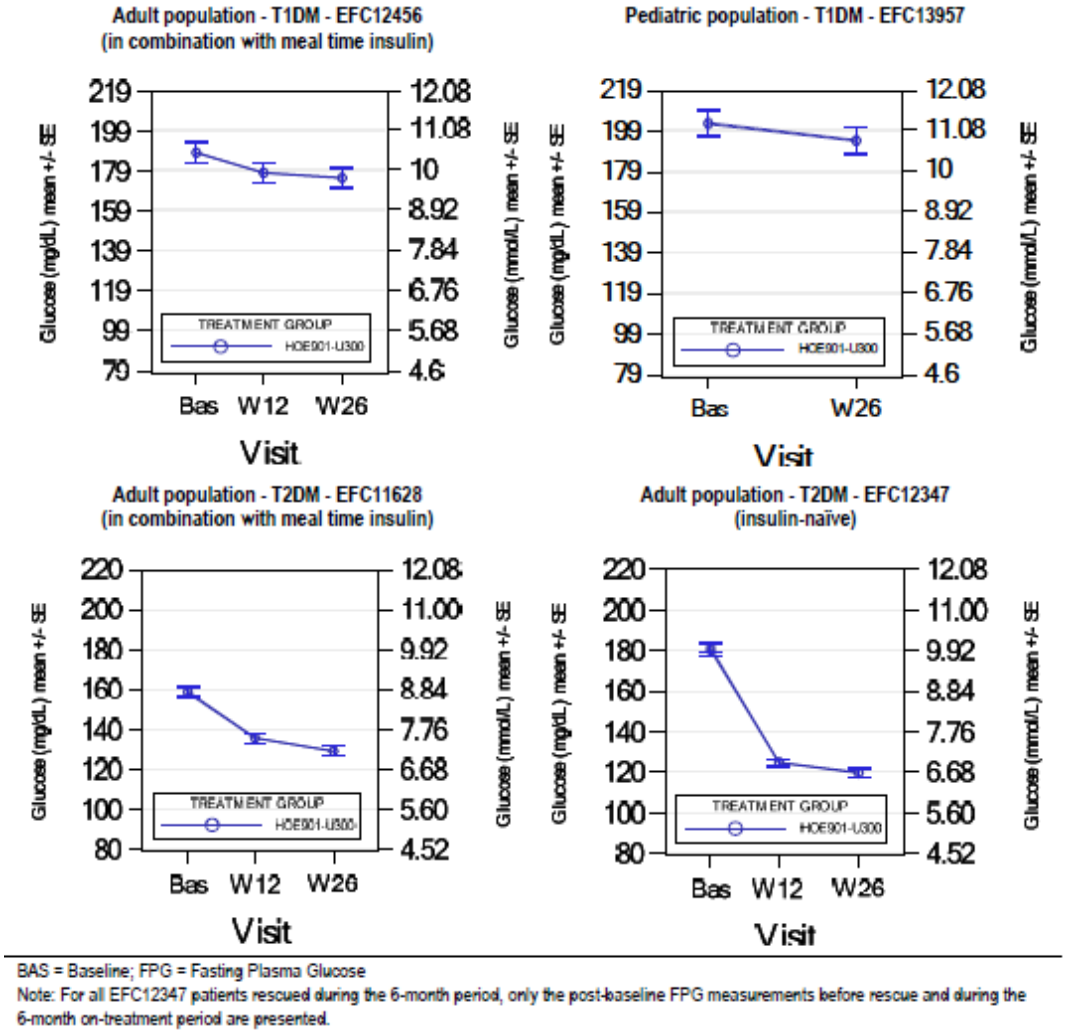
BAS = Baseline

Note: For all EFC12347 patients rescued during the 6-months period, only the post-baseline HbA1c measurements before rescue and during the 6-months on-treatment period are presented.

At Month 6, mean HbA1c levels were higher in T1DM patients, particularly in paediatric patients, than in adult T2DM patients.

Consistent with HbA1c reduction, FPG decreased in all studies, as expected with a greatest reduction observed in T2DM patients, and particularly in insulin-naïve patients (Figure 13).

Figure 4 - Mean (+/- SE) in FPG by visit during the 6-months on-treatment period for Toujeo treatment group - mITT/ITT population



BAS = Baseline; FPG = Fasting Plasma Glucose
Note: For all EFC12347 patients rescued during the 6-month period, only the post-baseline FPG measurements before rescue and during the 6-month on-treatment period are presented.

HOE901-U300= Toujeo

Reductions in HbA1c and FPG across the different subgroups of interest in the paediatric T1DMpatients and insulin-naïve adult populations were similar and consistent with the results observed across the total populations of the four studies.

Efficacy discussion and conclusions

Treatment with Toujeo in individually titrated adult patients with T1DM and T2DM in studies EFC12456, EFC11628 and EFC12347 as well as paediatric T1DM patients was effective in improving glycaemic control as demonstrated by lowering of mean HbA1c and mean FPG from baseline. The reductions in HbA1c and FPG are similar and seem to follow a similar pattern of response in adults and children. These results sufficiently support that Toujeo will also be effective in children with T2DM.

Overall, the evaluated efficacy parameters were consistent across the patient populations and different subgroups with characteristics considered to be particularly relevant for the paediatric T2DM population. The magnitude of treatment response was similar between adult and paediatric T1DM patients, while it was more pronounced in T2DM patients, particularly as expected in insulin initiating T2DM patients. Overall, the available efficacy data with Toujeo is considered to be applicable to the paediatric T2DM population.

Safety T2DM

Incidence of hypoglycaemia

As expected, more patients with T1DM and advanced T2DM patients treated with basal bolus regimen experienced at least one event of any hypoglycaemia during the main 6-months TEAE period compared to insulin-naïve T2DM patients who initiated a basal-supported oral therapy regimen (Table 27). In addition, more patients with T1DM experienced at least one nocturnal hypoglycaemia event (in any category) than T2DM patients (Table 28).

During the first 8 weeks of study treatment, when most of the increase of the basal insulin dose occurred (titration period), the percentage of T1DM patients reporting at least one event of hypoglycaemia of any category was similar to that reported during the maintenance treatment period. More T2DM patients reported at least one event of any hypoglycaemia during the maintenance period compared to the titration period.

Table 18 Number (%) of patients with at least one hypoglycaemia event per type of hypoglycaemia (ADA classification) during the 6-months TEAE period by study period for the Toujeo treatment group - Safety population (abbreviated)

Type of hypoglycaemia, n (%)	T1DM - EFC12456 (in combination with meal time insulin)-adult (N=274)	T2DM - EFC11628 (in combination with meal time insulin)-adult (N=404)	T2DM - EFC12347 (insulin-naïve)-adult (N=435)	T1DM - EFC13957-paediatric (N=233)
Any hypoglycaemia event				
Overall	257 (93.8)	337 (83.4)	217 (49.9)	228 (97.9)
≤8weeks	245 (89.4)	266 (65.8)	118 (27.1)	219 (94.0)
>8weeks to ≤ Month 6	227 (82.8)	306 (75.7)	186 (42.8)	216 (92.7)
Severe hypoglycaemia				
Overall	18 (6.6)	20 (5.0)	4 (0.9)	14 (6.0)
≤8weeks	9 (3.3)	6 (1.5)	1 (0.2)	3 (1.3)
>8weeks to ≤ Month 6	11 (4.0)	18 (4.5)	3 (0.7)	12 (5.2)

Table 19 Number (%) of patients with at least one nocturnal (00:00-05:59) hypoglycaemia event per type of hypoglycaemia (ADA classification) during the 6-months TEAE period by study period for the Toujeo treatment group - Safety population (abbreviated)

Type of nocturnal hypoglycaemia, n (%)	T1DM - EFC12456 (in combination with meal time insulin)-adult (N=274)	T2DM - EFC11628 (in combination with meal time insulin) - adult (N=404)	T2DM - EFC12347 (insulin-naïve)-adult (N=435)	T1DM - EFC13957-paediatric (N=233)
Any hypoglycaemia event				
Overall	191 (69.7)	183 (45.3)	88 (20.2)	170 (73.0)
≤8weeks	130 (47.4)	109 (27.0)	38 (8.7)	112 (48.1)
>8weeks to ≤ Month 6	165 (60.2)	151 (37.4)	74 (17.0)	146 (62.7)
Severe hypoglycaemia				
Overall	6 (2.2)	8 (2.0)	0	7 (3.0)
≤8weeks	4 (1.5)	3 (0.7)	0	3 (1.3)
>8weeks to ≤ Month 6	3 (1.1)	5 (1.2)	0	4 (1.7)

Overview of adverse events

In all studies, the percentages of patients who had at least 1 TEAE were relatively similar for all studies:

Table 20 Treatment emergent adverse events during the main 6-months TEAE period for the Toujeo treatment group - Safety population

n (%)	T1DM - EFC12456	T2DM - EFC11628	T2DM - EFC12347	T1DM - EFC13957-

	(in combination with meal time insulin)- adult (N=274)	(in combination with meal time insulin)-adult (N=404)	(insulin-naïve)-adult (N=435)	paediatric (N=233)
Patients with any TEAE	167 (60.9)	228 (56.4)	247 (56.8)	152 (65.2)
Patients with any treatment emergent SAE	17 (6.2)	26 (6.4)	24 (5.5)	17 (7.3)
Patients with any TEAE leading to death	1 (0.4)	1 (0.2)	1 (0.2)	1 (0.4)
Patients with any TEAE leading to permanent treatment discontinuation	3 (1.1)	6 (1.5)	5 (1.1)	2 (0.9)

Significant adverse events: hypoglycaemia

Serious hypoglycaemia was more frequently reported in T1DM paediatric and adult patients, however, it also occurred in advanced T2DM patients treated with basal bolus regimen:

Table 21 Number (%) of patients experiencing at least one serious hypoglycaemia during the 6-months TEAE period for the Toujeo treatment group - Safety population

Preferred term, n (%)	T1DM - EFC12456 (in combination with meal time insulin) - adult (N=274)	T2DM - EFC11628 (in combination with meal time insulin)-adult (N=404)	T2DM - EFC12347 (insulin-naïve) - adult (N=435)	T1DM - EFC13957- paediatric (N=233)
Any serious hypoglycaemia	10 (3.6)	3 (0.7)	0	6 (2.6)
Hypoglycaemic unconsciousness	1 (0.4)	2 (0.5)	0	5 (2.1)
Hypoglycaemic seizure	1 (0.4)	0	0	3 (1.3)
Hypoglycaemia	9 (3.3)	1 (0.2)	0	0

Based on these observations, it is therefore reasonable to expect that the risk of hypoglycaemia in Toujeo-treated patients would not be increased in children and adolescents with T2DM compared to those with T1DM.

Percentages of adult and paediatric patients with at least one hypoglycaemic event, and for a severe event, were highest for T1DM patients, less frequent for T2DM adults, and still lower for the insulin-naïve T2DM adults. The same pattern was seen for nocturnal hypoglycaemia. The results do not point towards a different risk of hypoglycaemia in the paediatric population with T2DM.

Significant adverse events: hypersensitivity

The proportion of patients with hypersensitivity reactions and injection site reactions was low in the T1DM and T2DM trials. In T1DM paediatric patients, the proportion of patients with either hypersensitivity reactions or injection site reactions was similar across the two subgroups of interest. In insulin-naïve adult patients, the proportion of patients with either hypersensitivity reactions or injection site reactions was similar across the different subgroups of interest (Table 31).

Table 22 Number (%) of patients experiencing at least one TEAE (Hypersensitivity reaction or Injection site reaction)

Preferred term, n (%)	T1DM - EFC12456 (in combination with meal time insulin) - adult (N=274)	T2DM - EFC11628 (in combination with meal time insulin)- adult (N=404)	T2DM - EFC12347 (insulin-naïve)- adult (N=435)	T1DM - EFC13957- paediatric (N=233)
Any hypersensitivity reaction	6 (2.2)	9 (2.2)	17 (3.9)	11 (4.7)
Any injection site reaction	1 (0.4)	2 (0.5)	0	5 (2.1)

During 6 months of treatment, the percentage of Toujeo-treated patients with at least 1 TEAE, including hypersensitivity reactions and injection site reactions, was similar between the T1DM and T2DM studies for the overall populations and across the different subgroups of interest. Anti-insulin antibody response was also similar across the studies.

Anti-insulin antibodies

Anti-insulin antibodies (AIA) results were similar in studies EFC12456, EFC11628 and EFC13957 (all in patients already receiving insulin at baseline). Of the patients with a negative antibody status at baseline, a conversion to positive status occurred at least once during 6-months treatment period with Toujeo in 48.5%, 39.0%, and 36.7% of patients, respectively (Table 32), whereas the reverse conversion from a positive AIA status at baseline to negative status occurred in a smaller number of patients in the 3 trials (3.6%, 9.4%, and 2.8%, respectively).

Table 23 Summary of Anti-insulin antibody response assessed throughout the main 6-months TEAE period according to the baseline AIA status for the Toujeo treatment group - Safety population (abbreviated)

	T1DM - EFC12456 (in combination with meal time insulin) - adult (N=274)	T2DM - EFC11628 (in combination with meal time insulin)- adult (N=404)	T2DM - EFC12347 (insulin-naïve)- adult (N=435)	T1DM - EFC13957- paediatric (N=233)
Baseline AIA status positive				
AIA status: [n(%)][a]				
Number	165	233	23	179
Negative	6 (3.6)	22 (9.4)	5 (21.7)	5 (2.8)
Positive	159 (96.4)	211 (90.6)	18 (78.3)	174 (97.2)
Cross reactivity: [n(%)][b, c]				
Number	159	211	18	164
Yes	145 (91.2)	177 (83.9)	17 (94.4)	163 (99.4)
Baseline AIA status negative				
AIA status: [n(%)][a]				
Number	97	164	391	30
Negative	50 (51.5)	100 (61.0)	315 (80.6)	19 (63.3)
Positive	47 (48.5)	64 (39.0)	76 (19.4)	11 (36.7)
Cross reactivity: [n(%)][b, c]				
Number	47	64	76	10
Yes	35 (74.5)	51 (79.7)	71 (93.4)	9 (90.0)

AIA: anti-insulin antibody; NA = Not available

a A patient is defined as AIA positive if the patient is positive at any time during the 6-months TEAE period

b The denominator is the number of patients with an AIA status assessed post baseline in the considered baseline AIA status category

c Cross reactivity is assessed in case of positive AIA status, the denominator is the number of patients with a positive post baseline AIA status and a cross reactivity assessed post baseline in the considered baseline AIA status category

d Titer refers to maximal titer during the main 6-months TEAE period among titers assessed by visit in case of positive AIA status

Results were slightly different in insulin-naïve T2DM patients (Study EFC12347), as conversion from negative status at baseline to positive status occurred in 76/391 patients (19.4%) during 6-months treatment period with Toujeo, while reversion from positive status at baseline to negative status occurred in 5/23 of patients (21.7%).

In T1DM paediatric patients, similar AIA results were observed across the two subgroups of interest. In insulin-naïve adult patients, similar AIA results were observed across the different subgroups of interest.

Safety discussion T2DM

Comparison of hypoglycaemia event data across the four studies used in this extrapolation showed that the paediatric and adult patients with T1DM or advanced T2DM treated with basal-bolus regimen experienced, in general, more (severe) hypoglycaemia/(severe) nocturnal hypoglycaemia during the main 6-months TEAE period compared to adult insulin-naïve T2DM patients. This is expected based on their disease background. However, in the paediatric study, the incidence of hypoglycaemia was similar in the Toujeo and the Lantus group. The incidence of hypoglycaemia per type of hypoglycaemia did not show unexpected numbers or trends.

Percentages of adult and paediatric patients with any (serious) treatment emergent adverse event were similar.

Percentages of adult and paediatric patients with at least one hypersensitivity reaction or injection site reaction, were in the similar range.

Anti-insulin antibody response was similar across patients in the four studies. Conclusions on the evidence supporting use of Toujeo in paediatric T2DM

Safety parameters were in the same range for adults and children with T1DM. The results do not point towards a different risk for children or adolescents with T2DM, compared to adults with T2DM.

2.4.3. Discussion on clinical efficacy in paediatric patients with T1DM

Design and conduct of clinical studies

To support the efficacy (and safety) of Toujeo in paediatric patients with T1DM, the applicant performed 1 phase 3b study in which Toujeo was compared with Lantus (Study EFC13957). In general, the design and statistical analysis are overall considered acceptable.

In the study, a total of 616 patients were screened in 105 study centres across 24 countries worldwide. Of these, 463 patients were randomized 1:1; 233 patients to Toujeo and 230 patients to Lantus. During the 6-months on-treatment period, the percentage of patients who discontinued treatment was 3.4% in the Toujeo group compared with 5.2% in the Lantus group. A similar percentage of patients discontinued due to TEAEs (Toujeo: 1 patients [0.4%] and Lantus: 1 patients [0.4%]). There were no relevant differences between groups in percentage of patients for each reason of treatment discontinuation. There was 1 death during the study, which concerned a patient in the Toujeo overall group (0.4%).

Baseline characteristics and demographics were similar between treatment groups. The mean age of patients was 12.9 years with 30.9% patients aged <12 years and 69.1% patients aged ≥12 years. Overall, 51.2% of patients were male, 30.2% of patients were Hispanic or Latino, and 92.1% were White. By Tanner stages, the majority of patients were adolescents (48.6%) while 26.5% were pre-pubertal and 24.9% were

adults. At baseline, 62.4% of patients were within a healthy body mass index (BMI) range (5th-<85th percentile) while 17.1% of patients were obese (BMI ≥95th percentile).

At baseline, a total of 461 patients (Toujeo: 233; Lantus: 228) were exposed to study treatment and were included in the safety population for analysis of exposure.

Assessment of paediatric data on clinical efficacy

Primary efficacy endpoint

The LS mean difference in HbA1c between baseline and week 26 for Toujeo versus Lantus was 0.004% (95% CI [(-0.172 to 0.179]) with the upper bound of the 95% CI lower than the predefined non-inferiority margin of 0.3%. Non-inferiority of Toujeo relative to Lantus was demonstrated for HbA1c change from baseline to Week 26. Therefore, the primary objective of the study was met. These results are confirmed also by an analysis on the PP population.

For both groups, there was a decrease in the primary endpoint mean-HbA1c-change during the first 12 weeks of the study. Afterwards, in Week 12 to Week 26, values stabilized although there was a slight increase. However HbA1c levels were still lower than baseline after 26 weeks, for all patients. Also, the mean HbA1c levels overtime followed a similar trend in both treatment groups. Further, this course of the HbA1c curve in time is known for most trials in diabetic patients.

Secondary efficacy endpoints

The secondary efficacy endpoints between Week 26 and baseline are in support of the reduction in HbA1c, with similar values and trends. The reduction in mean FPG over time was similar in both treatment groups. Responder rates for the pre-specified target HbA1c of <7.5% at Week 26 and for the pre-specified target FPG (≤130 mg/dL [7.2 mmol/L]) during the last 3 months of the main 6-months randomized period was similar in the two treatment groups. The reduction in average plasma glucose from baseline to Week 26 based on 8-point SMPG profiles was similar across the treatment groups at Week 26. With regard to the change in 8-point SMPG profiles per time-point, at baseline and Week 26, the mean 8-point SMPG profiles at each time point, fluctuated throughout the day to a lesser extent in the Toujeo group compared to the Lantus group.

Mean daily insulin dose increased in all treatment groups during the first weeks, but the increase was larger with Toujeo as compared to Lantus. The difference in dose between Toujeo and Lantus is already known: both formulations are not bioequivalent. However, after 12 weeks, doses remained relatively constant, and no significant changes were seen between 6 months and 12 months results.

2.4.4. Conclusions on the clinical efficacy

The scope of this application is to extend the indication for use in children from 6 years and above.

To support the efficacy and safety of Toujeo in paediatric patients with T1DM, the applicant performed 1 phase 3b study in which Toujeo was compared with Lantus (Study EFC13957) in children and adolescents with T1DM, of which the first 26 weeks were submitted to support efficacy. At baseline, a total of 461 patients (Toujeo: 233; Lantus: 228) were exposed to study treatment. Baseline characteristics and demographics were similar between treatment groups. Non-inferiority of Toujeo relative to Lantus was demonstrated for HbA1c change from baseline to Week 26.

The LS mean difference in HbA1c between baseline and week 26 for Toujeo versus Lantus was 0.004% (95% CI [(-0.172 to 0.179]). Non-inferiority of Toujeo relative to Lantus was demonstrated for HbA1c change from baseline to Week 26. Therefore, the primary objective of the study was met.

The secondary efficacy endpoints between Week 26 and baseline are in support of the HbA1c results, with

similar values and trends. The baseline mean FPG values were similar across the treatment groups (Toujeo: 11.25 mmol/L [202.70 mg/dL]; Lantus: 11.35 mmol/L [204.51 mg/dL]). The LS mean reduction from baseline to Week 26 was similar for both treatment groups (Toujeo: 0.56 mmol/L [10.15 mg/dL]; Lantus: 0.55 mmol/L [9.89 mg/dL]).

In support of treatment of paediatric patients with T2DM, a comparative analysis was performed to evaluate similarities in response to treatment with Toujeo in adult patients with T1DM (Study EFC12456) and T2DM (Studies EFC12347 and EFC11628), to support extrapolation from children and adolescents (aged 6-17 years) with T1DM (study EFC13957) to T2DM populations. Additionally, as further support of this extrapolation, a comparison of pathophysiology, disease progression, treatment recommendations in adults and paediatric patients has been provided, as well as an overview of external pharmacology and clinical response data for insulin treatment in paediatric T2DM.

Treatment with Toujeo in individually titrated adult patients with T1DM and T2DM in studies EFC12456, EFC11628 and EFC12347 as well as paediatric T1DM patients was effective in improving glycaemic control as demonstrated by lowering of mean HbA1c and mean FPG from baseline. Overall, the evaluated efficacy parameters were consistent across the patient populations and different subgroups with characteristics considered to be particularly relevant for the paediatric T2DM population. The magnitude of treatment response was similar between adult and paediatric T1DM patients, while it was more pronounced in T2DM patients, particularly as expected in insulin initiating T2DM patients. Overall, the available efficacy data with Toujeo is considered to be applicable to the paediatric T2DM population.

2.5. Clinical safety

Introduction

In Study EFC13957, the safety endpoints included:

- Hypoglycaemia
- Hyperglycaemia with ketosis
- Treatment-emergent AEs (TEAEs) (including injection site reactions and hypersensitivity reactions), AEs leading to death, adverse events leading to permanent discontinuation of study drug, serious AEs (SAE) and adverse events of special interest (AESIs) defined for the study as symptomatic overdose with IMP/non-investigational medicinal product (NIMP), increased alanine aminotransferase (ALT) levels (≥3 x upper limit of normal), and pregnancy
- Anti-insulin antibody (AIA) in relation to hypoglycaemia and TEAEs including injection site and hypersensitivity reactions
- Other safety variables: chemistry and hematology laboratory parameters, physical examinations, vital signs, BMI percentiles, and Tanner puberty stage (pre-pubertal, adolescent, adult).

All safety analyses were performed using the safety population, defined as the randomized population who received at least 1 dose of IMP, and was analyzed according to treatment received rather than according to the randomization group. No statistical testing was performed on safety parameters for between-group differences.

Beside Study EFC13957, there are no other clinical studies in the paediatric population; therefore, no pooling of studies was performed for integrated safety analysis.

Patient exposure

The study treatment exposure during the main 6-months on-treatment period was considered to be adequate and appropriate to make valid safety conclusions. Mean exposure was similar in both treatment groups, 180 days (26 weeks) for Toujeo and 179 days (26 weeks) for Lantus. Most patients were treated for more than 25 weeks, 92.7% for Toujeo and 93.4% for Lantus.

Adverse events

During the main 6-months TEAE period, the percentage of patients with TEAEs, serious TEAEs, or TEAEs leading to death or permanent treatment discontinuation was similar in the Toujeo and Lantus groups (Table 34).

Table 24 Summary of treatment-emergent adverse events in the main 6-months TEAE in study EFC13957: safety population

	Toujeo (N=233)		Lantus (N=228)	
	n (%)	E(R)	n (%)	E(R)
Total patient years		114.57		111.95
Patients with any TEAE	152 (65.2)	437(3.81)	150 (65.8)	422(3.77)
Patients with any treatment emergent SAE	17 (7.3)	23(0.20)	21 (9.2)	27(0.24)
Patients with any TEAE leading to death	1 (0.4)	2(0.02)	0	0
Patients with any TEAE leading to permanent treatment discontinuation	2 (0.9)	3(0.03)	2 (0.9)	2(0.02)

TEAE: Treatment emergent adverse event, SAE: Serious adverse event; n(%) = number and percentage of patients with at least one TEAE; E(R) = number of events and event rate per patient-years; Note: Total patient years correspond to the cumulative patient years exposure to the main 6-months TEAE period

The most commonly reported TEAEs (i.e., ≥10% of patients in either group) at the primary SOC level with a similar percentage of patients in the Toujeo and Lantus groups, respectively were infections and infestations (41.6% and 46.1%), Gastrointestinal Disorders (14.6% and 9.6%), Nervous system Disorders (12.4% and 9.2%), Respiratory, Thoracic and Mediastinal Disorders (12.0% and 5.3%) Metabolism and Nutrition disorders (11.2% and 16.7%) and General disorders and administration site conditions (10.3% and 9.6%).

The most frequently reported TEAEs by PT in the Toujeo and Lantus groups, respectively were nasopharyngitis (12.9% and 13.6%), headache (7.3% and 5.7%), upper respiratory tract infection (6.9% and 5.7%), and ketosis (6.4% and 10.1%).

Serious adverse event/deaths/other significant events

Severity

Treatment-emergent AEs were predominantly of mild to moderate intensity. In both treatment groups, the most frequently reported severe TEAEs by PT were hypoglycaemic unconsciousness (Toujeo: 2.1%; Lantus: 3.1%) and hypoglycaemic seizure (Toujeo: 1.3%; Lantus: 3.1%).

Causality

The proportions of patients with at least one TEAE considered related to IMP were low and comparable between the two treatment groups, 6.0% for Toujeo and 8.3% for Lantus.

Table 25 TEAE(s) considered related to treatment by the investigator, by PT during the main 6-months TEAE period - Safety population

	Toujeo (N=233)		Lantus (N=228)	
Preferred term (PT)	n (%)	E(R)	n (%)	E(R)
Total patient years		114.57		111.95
Any class	**14 (6.0)**	**18(0.16)**	**19 (8.3)**	**29(0.26)**
Ketosis	1 (0.4)	1(0.01)	3 (1.3)	6(0.05)
Obesity	0	0	1 (0.4)	1(0.01)
Overweight	2 (0.9)	2(0.02)	1 (0.4)	1(0.01)
Hyperglycaemia	0	0	2 (0.9)	2(0.02)
Hypoglycaemic unconsciousness	2 (0.9)	2(0.02)	3 (1.3)	3(0.03)
Somnolence	1 (0.4)	1(0.01)	0	0
Hypoglycaemic seizure	1 (0.4)	1(0.01)	2 (0.9)	2(0.02)
Injection site atrophy	1 (0.4)	1(0.01)	2 (0.9)	2(0.02)
Injection site hypertrophy	1 (0.4)	1(0.01)	2 (0.9)	3(0.03)
Injection site pain	5 (2.1)	6(0.05)	3 (1.3)	3(0.03)
Injection site reaction	0	0	1 (0.4)	1(0.01)
Malaise	1 (0.4)	1(0.01)	0	0
Drug ineffective	0	0	1 (0.4)	1(0.01)
Weight increased	0	0	1 (0.4)	1(0.01)
Accidental overdose	2 (0.9)	2(0.02)	3 (1.3)	3(0.03)

TEAE: Treatment emergent adverse event, SAE: Serious adverse event

n(%) = number and percentage of patients with at least one TEAE

E(R) = number of events and event rate per patient-years; total patient years correspond to the cumulative patient years exposure to the main 6-months TEAE period

Note: Table sorted by SOC and HLGT, HLT, PT by alphabetic order (only PT given)

No unexpected safety issues have occurred. In general, the spectrum of related adverse advents for this 6 months of treatment was comparable between the Toujeo and the Lantus group and in line with section 4.8 of the SmPC for Toujeo for adults.

Deaths

During the main 6-months TEAE period, 1 patient from the Toujeo group reported 2 treatment-emergent SAEs (PTs: Fall and Completed suicide) leading to death on Day 147 of the study. This fatal event was considered not related to the IMP.

Serious adverse events

The percentage of patients who experienced SAEs was similar in both treatment groups: 7.3% and 9.2% for Toujeo and Lantus, respectively.

The SOC with the highest proportion of SAEs in the Toujeo group was Nervous System Disorders (3.0% versus 4.4% in the Lantus group). Most of these events were hypoglycaemia-related. The number of patients with at least one serious TEAE of hypoglycaemia was numerically lower in the Toujeo group (2.6%) versus Lantus group (4.4%). In each treatment group, 1.3% of patients reported serious TEAEs of hypoglycaemia related to IMP. No serious hypoglycaemic event led to permanent treatment discontinuation.

Hypersensitivity reactions

In the paediatric study, the incidence of hypersensitivity reactions reported was also slightly higher for Toujeo: 7.3% for Toujeo and 4.8% for Lantus after 6 months. The effect of the higher concentration of the injected fluid for Toujeo, or the age of children may make them more susceptible.

The applicant was requested to provide an overview of incidence of hypersensitivity reactions.

From the non-clinical toxicology evaluation, no specific effect of the higher concentration of the injected fluid for Toujeo was to be expected. From the available data on background occurrence of hypersensitivity reactions in children with T1DM compared to children from the general population, no suggestion of a difference was observed.

In the paediatric study there was a slight imbalance in medical history, with 9 of 17 (52.9%) patients with hypersensitivity reaction on Toujeo having a confounding factor for hypersensitivity compared to 4 of 11 (36.4%) patients on Lantus. In those cases the hypersensitivity reaction was not suggestive of a causal association with Toujeo or Lantus.

In the 6-months safety extension period, the number of cases was balanced, as 4 patients in each treatment group experienced hypersensitivity reactions. After the complete 12-months study period, the incidence of hypersensitivity reactions was 9.0% for Toujeo and 6.6% for Lantus.

Further, it may be possible that the higher reporting rates of hypersensitivity during the main 6-months part of the study were related by the the open-label design, leading to more reported events in the Toujeo group, being the investigational medicine.

From the data presented by the applicant it can be concluded that there is no suggestion that Toujeo, due to the higher concentration of the injected fluid than the control, may cause more hypersensitivity reactions.

Laboratory findings

Overall, the percentages of patients with a potentially clinically significant abnormality (PCSA) in clinical laboratory variables were similar between the Toujeo and Lantus treatment groups. No hematologic or biochemical safety signals were detected in either treatment group. No relevant mean changes from baseline to Week 26 were reported for any of the renal or hepatic function parameters in either treatment group. Across the subgroup of age (<12 and ≥12 years), the results were consistent with that of the overall population.

No PCSA in hematologic or clinical chemistry parameters was reported as a serious TEAE or TEAE leading to permanent treatment discontinuation during the main 6-months TEAE period.

No patient in either treatment group had hepatic enzyme elevations that met the clinical criteria for Hy's law, and no drug-induced liver toxicity was reported during the main 6-months TEAE period.

CHMP concluded that no unexpected safety issues have occurred within the routine laboratory parameters, nor were any relevant changes from baseline reported in both treatment groups.

Safety in special populations

Hypoglycaemia

Hypoglycaemia events were not considered as AEs except for events resulting in seizure, unconsciousness, or coma and for any other hypoglycaemia event fulfilling the criteria of an SAE.

Incidence of hypoglycaemia

During the main 6-months TEAE period, almost all patients had at least one event of 'any' hypoglycaemia at any time of the day (Toujeo: 97.9%; Lantus: 98.2%) (Table 36). The percentage of patients with at least one nocturnal hypoglycaemia event (in any category) was also similar in both treatment groups (Toujeo: 73.0%; Lantus: 71.9%).

Severe hypoglycaemia at any time of the day was reported by 14 patients (6.0%) in the Toujeo group and 20 patients (8.8%) in the Lantus group. Severe hypoglycaemia during the nocturnal period (00:00-05:59) was reported by 7 patients in each treatment group. For the composite categories of severe and/or documented hypoglycaemia (SMPG ≤70 mg/dL [3.9 mmol/L] and <3.0 mmol/L [54 mg/dL]), the incidence at any time of day and during the nocturnal period was similar between treatment groups. None of the patients permanently discontinued treatment due to the severe hypoglycaemia event.

Table 26 Number (%) of patients with at least one hypoglycaemia event (per ADA classification) during the main 6-months TEAE period - Safety population

	All hypoglycaemia		Nocturnal hypoglycaemia (00:00-05:59)	
Type of hypoglycaemia n(%)	**Toujeo (N=233)**	**Lantus (N=228)**	**Toujeo (N=233)**	**Lantus (N=228)**
Any hypoglycaemia	228 (97.9)	224 (98.2)	170 (73.0)	164 (71.9)
Severe Hypoglycaemia	14 (6.0)	20 (8.8)	7 (3.0)	7 (3.1)
Documented Symptomatic Hypoglycaemia				
≤ 3.9 mmol/L (70 mg/dL)	216 (92.7)	211 (92.5)	138 (59.2)	137 (60.1)
< 3.0 mmol/L (54 mg/dL)	166 (71.2)	164 (71.9)	48 (20.6)	40 (17.5)
Probable Symptomatic Hypoglycaemia	20 (8.6)	27 (11.8)	8 (3.4)	12 (5.3)
Asymptomatic Hypoglycaemia				
≤ 3.9 mmol/L (70 mg/dL)	197 (84.5)	192 (84.2)	84 (36.1)	73 (32.0)
< 3.0 mmol/L (54 mg/dL)	104 (44.6)	117 (51.3)	19 (8.2)	17 (7.5)
Pseudo-hypoglycaemia				
> 3.9 mmol/L (70 mg/dL)	30 (12.9)	30 (13.2)	14 (6.0)	13 (5.7)
Severe and/or documented hypoglycaemia[a]				
≤ 3.9 mmol/L (70 mg/dL)	226 (97.0)	223 (97.8)	163 (70.0)	160 (70.2)
< 3.0 mmol/L (54 mg/dL)	187 (80.3)	191 (83.8)	63 (27.0)	57 (25.0)
Hypoglycaemia not classified -non-severe[b]	3 (1.3)	7 (3.1)	1 (0.4)	3 (1.3)
Hypoglycaemia not classified – severity unknown[c]	28 (12.0)	30 (13.2)	7 (3.0)	8 (3.5)

TEAE = Treatment emergent adverse event.

n (%) = number and percentage of patients with at least one hypoglycaemia event

a Severe and/or documented hypoglycaemia= severe and/or documented by plasma glucose ≤ 3.9 mmol/L (70 mg/dL) (resp. <3.0 mmol/L (54mg/dL)).

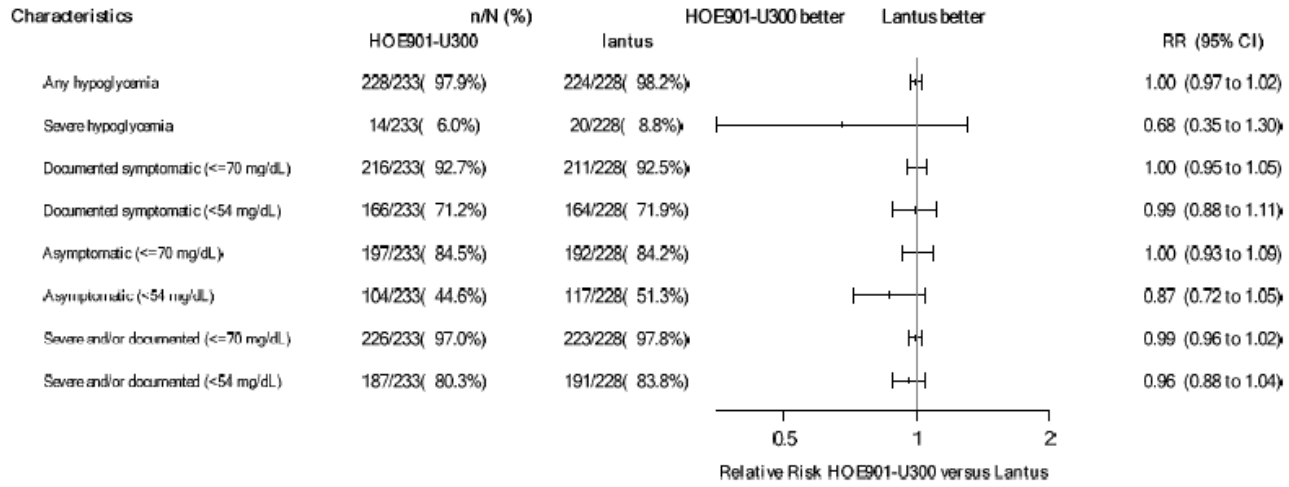
b Event not assigned to any of the pre-specified ADA categories due to missing and/or conflicting data but determined not to have met the criteria of severe hypoglycaemia

c Event not assigned to any of the pre-specified ADA categories due to missing and/or conflicting data, where the category of severe hypoglycaemia cannot be excluded

Any hypoglycaemia (at any time of day)

Across most of the ADA and ISPAD-defined categories, at any time of the day, a similar percentage of patients in the Toujeo and Lantus groups reported at least one event of hypoglycaemia. The percentage of patients with at least one event of severe hypoglycaemia was numerically lower in the Toujeo group:

Figure 5 Number (%) of patients with at least one hypoglycaemia event per type of hypoglycaemia (ADA and ISPAD classification) during the main 6-months TEAE period - Safety population



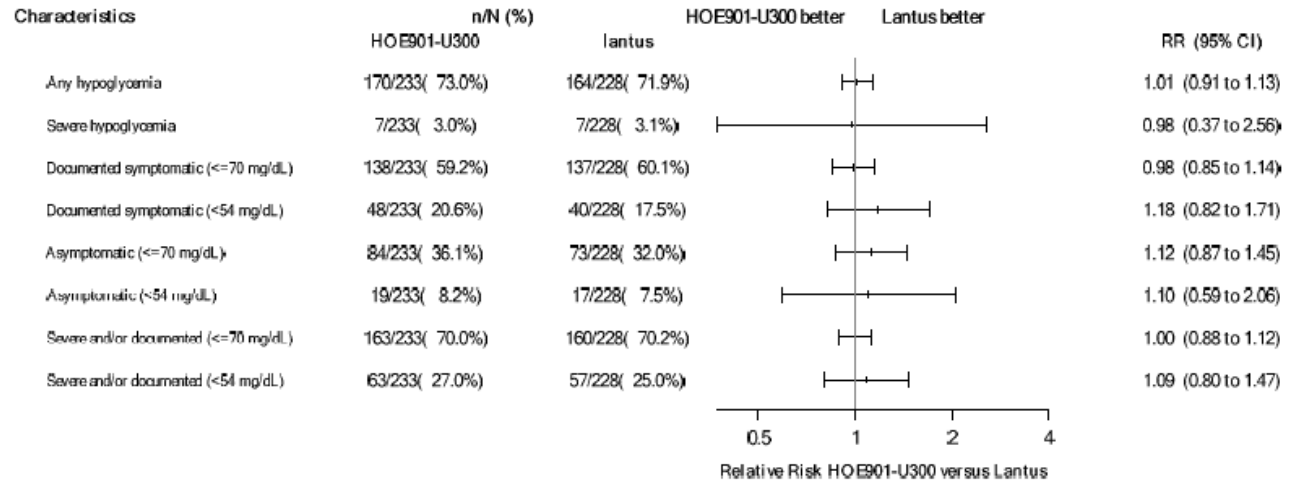
TEAE = Treatment emergent adverse event, RR=Relative risk, CMH: Cochran-Mantel-Haenszel
Note: Based on RR stratified by randomization strata of screening HbA1c (<8.5 or ≥8.5 %) and age group at screening visit (<12 years and ≥12 years), using a CMH methodology.
Severe and/or documented hypoglycemia= severe and/or documented by plasma glucose ≤ 3.9 mmol/L (70 mg/dL) (resp. <3.0 mmol/L (54 mg/dL)).

From first injection of IMP to end of Week 8 covering the time of the insulin change-over and initial titration of IMP, the percentage of patients with at least one event of 'any' hypoglycaemia was similar in the Toujeo group (94.0%) and the Lantus group (96.1%). Similar results were observed from the start of Week 9 to Month 6 (Toujeo: 92.7%; Lantus: 93.9%).

Nocturnal hypoglycaemia (00:00 – 05:59)

Across ADA and ISPAD-defined categories, a similar percentage of patients in the Toujeo and Lantus groups reported at least one event of nocturnal hypoglycaemia (00:00 - 05:59) (Toujeo: 73.0%; and Lantus: 71.9%) including 'severe' nocturnal hypoglycaemia (Toujeo: 3.0%; and Lantus: 3.1%) (Figure 8). This finding was corroborated by the analysis of nocturnal hypoglycaemia events defined by sleep status, where the incidence was also comparable between treatment groups.

Figure 6 Number (%) of patients with at least one nocturnal hypoglycaemia event (00:00-5:59), by ADA and ISPAD classification, during the main 6-months TEAE period - Safety population



TEAE = Treatment emergent adverse event, RR=Relative risk, CMH: Cochran-Mantel-Haenszel
Note: Based on RR stratified by randomization strata of screening HbA1c (<8.5 or ≥8.5 %)and age group at screening visit (<12 years and ≥12 years), using a CMH methodology.
Severe and/or documented nocturnal hypoglycemia= severe and/or documented nocturnal by plasma glucose ≤ 3.9 mmol/L (70 mg/dL) (resp. <3.0 mmol/L (54 mg/dL)).

The percentage of patients with at least one event of 'any' nocturnal hypoglycaemia from 00:00 - 05:59 from first injection of IMP to end of Week 8 and from the start of Week 9 to Month 6 was similar in both treatment groups.

Hypoglycaemia events per patient-year of exposure

For most ADA and ISPAD-defined categories of hypoglycaemia, the number of 'any' hypoglycaemia events per patient-year of exposure was similar in both treatment groups (at any time of day: Toujeo: 91.80 and Lantus: 92.66; nocturnal: Toujeo: 8.56 and Lantus: 8.22) with the exception of severe hypoglycaemia**.**

Table 27 Number of hypoglycaemia events per patient-year of exposure per type of hypoglycaemia (ADA and ISPAD classification) during the main 6-months TEAE period - Safety population

	All hypoglycaemia		**Nocturnal hypoglycaemia (00:00-05:59)**	
Type of hypoglycaemia event Number of events (rate per patient-years)	**Toujeo (N=233)**	**Lantus (N=228)**	**Toujeo (N=233)**	**Lantus (N=228)**
Total patient years	114.57	111.95	114.57	111.95
Any hypoglycaemia	10518(91.80)	10373(92.66)	981(8.56)	920(8.22)
Severe Hypoglycaemia	21(0.18)	30(0.27)	7(0.06)	9(0.08)
Documented Symptomatic Hypoglycaemia				
≤ 3.9 mmol/L (70 mg/dL)	6658(58.11)	6404(57.21)	636(5.55)	567(5.06)
< 3.0 mmol/L (54 mg/dL)	983(8.58)	970(8.66)	85(0.74)	80(0.71)
Probable Symptomatic Hypoglycaemia	51(0.45)	95(0.85)	12(0.10)	23(0.21)
Asymptomatic Hypoglycaemia				
≤ 3.9 mmol/L (70 mg/dL)	3335(29.11)	3282(29.32)	277(2.42)	283(2.53)
< 3.0 mmol/L (54 mg/dL)	426(3.72)	472(4.22)	32(0.28)	26(0.23)
Pseudo-hypoglycaemia				
> 3.9 mmol/L (70 mg/dL)	126(1.10)	197(1.76)	36(0.31)	21(0.19)
Severe and/or documented hypoglycaemia[a]				
≤ 3.9 mmol/L (70 mg/dL)	10341(90.26)	10077(90.02)	933(8.14)	875(7.82)
< 3.0 mmol/L (54 mg/dL)	1481(12.93)	1565(13.98)	124(1.08)	119(1.06)
Hypoglycaemia not classified - non-severe[b]	9(0.08)	118(1.05)	2(0.02)	4(0.04)
Hypoglycaemia not classified – severity unknown[c]	318(2.78)	247(2.21)	11(0.10)	13(0.12)

TEAE = Treatment emergent adverse event. Total patient years correspond to the cumulative patient years exposure to the main 6-months TEAE period

a Severe and/or documented hypoglycaemia= severe and/or documented by plasma glucose ≤ 3.9 mmol/L (70 mg/dL) (resp. <3.0 mmol/L (54 mg/dL)).

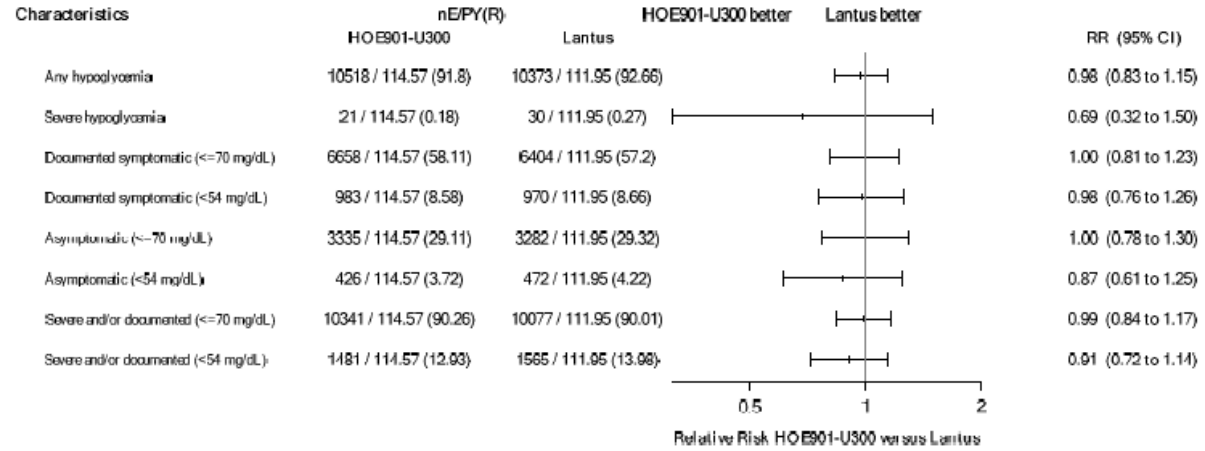
b Event not assigned to any of the pre-specified ADA categories due to missing and/or conflicting data but determined not to have met the criteria of severe hypoglycaemia

c Event not assigned to any of the pre-specified ADA categories due to missing and/or conflicting data, where the category of severe hypoglycaemia cannot be excluded

For most ADA and ISPAD-defined categories of hypoglycaemia, the number of 'any' hypoglycaemia events per patient-year of exposure was similar in both treatment groups (at any time of day: Toujeo: 91.80 and Lantus: 92.66; nocturnal: Toujeo: 8.56 and Lantus: 8.22) with the exception of severe hypoglycaemia. This was mainly due to a difference in day time hypoglycaemia but was also seen, to a lesser extent, in the nocturnal hypoglycaemia. In the initial application, it was shown that mealtime insulin in combination with basal insulin contributes to the increase in the number of daytime hypoglycaemia events.

The event rate per patient-year of exposure for severe hypoglycaemia at any time of day was numerically lower in the Toujeo group (0.18) versus the Lantus group (0.27), with a relative risk of 0.69 (95% CI: 0.32 to 1.50) (Figure 9).

Figure 7 Number of hypoglycaemia events per patient-year of exposure per type of hypoglycaemia (ADA and ISPAD classification) and relative risk during the main 6-months TEAE period - Safety population



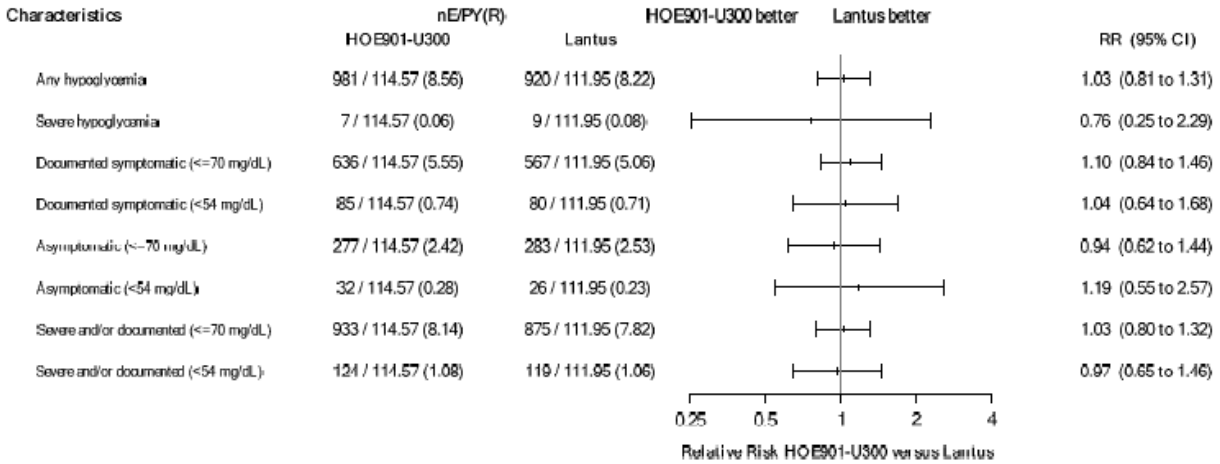
TEAE = Treatment emergent adverse event. RR = relative risk. nE = Number of events. PY = Total patient-years. R = Rate per patient-year

Note: RR based on negative binomial model with actual treatment groups (HOE901-U300 , Lantus), randomization strata of screening HbA1c (<8.5 or ≥8.5 %), randomization strata of age group at screening visit (<12 years and ≥12 years) as fixed effects, and logarithm of the treatment-emergent period as offset.

Severe and/or documented hypoglycemia= severe and/or documented by plasma glucose ≤ 3.9 mmol/L (70 mg/dL) (resp. <3.0 mmol/L (54 mg/dL)).

For the composite category of nocturnal severe and/or documented hypoglycaemia (SMPG ≤70 mg/dL [3.9 mmol/L]), event rate per patient-year of exposure was 8.14 for Toujeo group and 7.82 for Lantus (Figure 10).

Figure 8 Number of nocturnal hypoglycaemia event (00:00-5:59) per patient-year of exposure per type of hypoglycaemia (ADA and ISPAD classification) and relative risk during the main 6-months TEAE period - Safety population



TEAE = Treatment emergent adverse event. RR = relative risk. nE = Number of events. PY = Total patient-years. R = Rate per patient-year

Note: RR based on negative binomial model with actual treatment groups (HOE901-U300 , Lantus), randomization strata of screening HbA1c (<8.5 or ≥8.5 %), randomization strata of age group at screening visit (<12 years and ≥12 years) as fixed effects, and logarithm of the treatment-emergent period as offset.

Severe and/or documented nocturnal hypoglycemia= severe and/or documented nocturnal by plasma glucose ≤ 3.9 mmol/L (70 mg/dL) (resp. <3.0 mmol/L (54 mg/dL)).

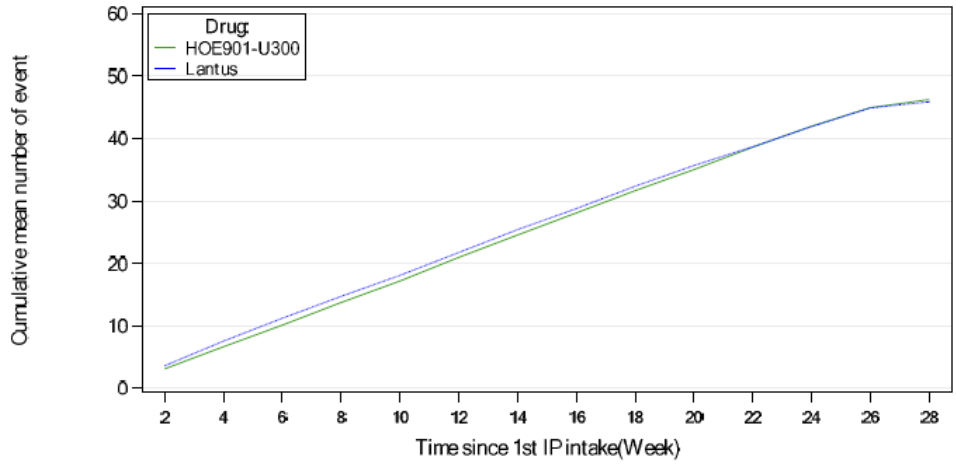
HOE901-U300= Toujeo

During the first 8 weeks of treatment, corresponding to the period just after the insulin changeover and covering the initial titration of Toujeo and Lantus, the 'any' hypoglycaemia event rate per patient-year of exposure was numerically lower in the Toujeo group (92.06) versus the Lantus group (100.03), with a relative risk of 0.90 (95% CI: 0.76 to 1.07).

Distribution of severe and/or documented hypoglycaemia

Over the 24-hour day, the percentage of patients with severe and/or documented hypoglycaemia events (SMPG ≤70 mg/dL [3.9 mmol/L]) was similar between treatment groups. The cumulative mean number of severe and/or documented hypoglycaemia events (SMPG ≤70 mg/dl [3.9 mmol/L]) per patient increased with a very similar pace over time in both treatment groups (Figure 11).

Figure 9 Cumulative mean number of severe and/or documented (≤3.9 mmol/L [70 mg/dL]) hypoglycaemia event per patient during the main 6-months TEAE period - Safety population



HOE901-U300= Toujeo

Likewise, the cumulative mean number of severe and/or documented (≤3.9 mmol/L (70 mg/dL) nocturnal (00:00 - 5:59) hypoglycaemia event per patient increased with a very similar pace over time in both treatment groups.

Blinded external endpoint assessment committee review of severe hypoglycaemia

The independent blinded committee reviewed all severe or possibly severe hypoglycaemia events reported during the main 6-months treatment period, representing a total of 52 events in 34 patients. All but one of these events were classified by the Committee as severe hypoglycaemia. For the event not confirmed to be severe hypoglycaemia, the patient was considered as capable of treating themselves but received assistance.

Subgroup analyses of hypoglycaemia

Across the prespecified subgroups, the treatment effect was consistent with the results for the overall study population at any time of the day. During the nocturnal period (00:00-5:59) the treatment effect was consistent with the results for the overall study population, with the exception of the gender subgroup which showed a significant treatment-by-subgroup interaction (p-value 0.0254). The percentage of patients with at least one severe and/or documented nocturnal hypoglycaemia event (SMPG ≤70 mg/dL [3.9 mmol/L]) in the Toujeo group was lower than the Lantus group in male patients (64.8% vs. 74.3%), and higher than the Lantus group in female patients (76.2% vs. 66.4).

Subgroups of patients <12 and ≥12 years of age

In both treatment groups, the percentage of patients <12 years of age with at least one severe and/or documented (SMPG ≤70 mg/dL [3.9 mmol/L]) hypoglycaemia event was comparable at any time of the day (Toujeo: 97.3%; Lantus group: 97.1%) and during the nocturnal period (Toujeo: 69.9%; Lantus group: 60.9%). Similarly, the percentage of patients ≥12 years of age with at least one severe and/or documented (SMPG ≤70 mg/dL [3.9 mmol/L]) hypoglycaemia event was similar in both treatment groups at any time of the day (Toujeo: 96.9%; Lantus group: 98.1%) and during the nocturnal period (Toujeo: 70.0%; Lantus group: 74.2%).

Tanner puberty stage

In both treatment groups, the percentage of adolescent patients with at least one severe and/or documented (SMPG ≤70 mg/dL [3.9 mmol/L]) hypoglycaemia event was comparable at any time of the day (Toujeo: 97.5%; Lantus group: 99.0%) and during the nocturnal period (Toujeo: 71.1%; Lantus group: 72.8%). Similar results were reported for the other Tanner puberty stages (i.e., pre-pubertal and adult).

Supportive analysis based on all low SMPG

A sensitivity analysis based on all SMPG values measured by the study glucometers was performed and revealed no differences between treatment groups with respect to the percentage of patients with SMPG values ≤3.9 mmol/L (70 mg/dL) (Toujeo: 97.9%; Lantus: 96.9%).

Hypoglycaemia conclusions

During the main 6-months TEAE period, the majority of patients had at least one event of 'any' hypoglycaemia, 97.9% for Toujeo and 98.2% for Lantus.

Across the ADA and ISPAD-defined categories of hypoglycaemia, at any time of the day and during the nocturnal period, the percentages of patients and event rates per patient-year of exposure were similar in both treatment groups, except for severe hypoglycaemia, where the incidence (and event rates) at any time of the day was numerically lower in the Toujeo group (6.0% [0.18]) compared to the Lantus group (8.8% [0.27]), with a relative risk of 0.68 (95% CI: 0.35 to 1.30).

No patients permanently discontinued treatment due to a hypoglycaemia event.

Analyses of the incidence of severe and/or documented hypoglycaemia (SMPG ≤70 mg/dL [3.9 mmol/L]) by subgroups (randomization stratum of age group [<12 and ≥12 years], randomization stratum of screening HbA1c [<8.5%, ≥8.5 %], baseline BMI percentile, baseline Tanner puberty stage and baseline prebreakfast SMPG) showed consistent results with the overall population at any time of the day and during the nocturnal period. For the subgroup of gender, the percentage of patients with at least one severe and/or documented nocturnal hypoglycaemia event (SMPG ≤70 mg/dL [3.9 mmol/L]) was respectively 64.8% in the Toujeo group versus 74.3% in the Lantus group in the males patients and 76.2% in the Toujeo group versus 66.4% in the Lantus group among the female patients (Section 11.2.6).

From first injection of IMP to end of Week 8, covering the time of the insulin change-over and initial titration of Toujeo and Lantus, the incidence of at least one event of "any" hypoglycaemia was similar in the Toujeo group (94.0%) and the Lantus group (96.1%).

For event rates per patient-year of exposure, the values were numerically lower for "any" hypoglycaemia in the Toujeo group (92.06) compared to the Lantus group (100.03), with a relative risk of 0.90 (95% CI: 0.76 to 1.07).

In summary, over 26-weeks of treatment in paediatric patients with T1DM, Toujeo had a similar hypoglycaemia incidence and event-rate compared to Lantus across all categories but severe hypoglycaemia. For severe hypoglycaemia, a numerically lower incidence and event-rate was observed among Toujeo-treated patients. Change-over from pre-study Lantus basal insulin formulation to Toujeo and up-titration of the Toujeo dose over the initial 8-weeks treatment period was accompanied with a numerically lower event rate for "any" hypoglycaemia in the Toujeo group compared to the Lantus group.

Other significant adverse events

Hyperglycaemia with ketosis and diabetic ketoacidosis

The proportion of patients with at least one TEAE of hyperglycaemia and ketosis was numerically lower in the Toujeo group (6.4% [15 patients]) compared to the Lantus group (11.8% [27 patients]) (Table 38).

One patient (0.4%) in the Toujeo group and 4 patients (1.8%) in the Lantus group reported TEAE of DKA. The number DKA events and event rate per patient-years was 1 [0.01] in the Toujeo group compared to 5 [0.04] the Lantus group. Diabetic ketoacidosis was reported as a serious TEAE in 1 patient (0.4%) in the Toujeo group and 2 patients (0.9%) in the Lantus group. None of these TEAEs were considered related to IMP.

Table 28 Number (%) of patients with at least one TEAE of hyperglycaemia with ketosis by PT during the main 6-months TEAE period - Safety population

	Toujeo (N=233)		Lantus (N=228)	
Preferred Term	**n (%)**	**E(R)**	**n (%)**	**E(R)**
Total patient years		114.57		111.95
Any hyperglycaemia with ketosis	15 (6.4)	34 (0.30)	27 (11.8)	46 (0.41)
Ketosis	15 (6.4)	33 (0.29)	23 (10.1)	41 (0.37)
Diabetic ketoacidosis	1 (0.4)	1 (0.01)	4 (1.8)	5 (0.04)

TEAE: Treatment emergent adverse event, PT: Preferred term
MedDRA 21.0
n (%) = number and percentage of patients with at least one TEAE linked to hyperglycaemia with ketosis
E(R) = number of events and event rate per patient-years, linked to hyperglycaemia with ketosis
Note: Table sorted by decreasing frequency of PT based on incidence in the Toujeo treatment group
Hyperglycaemia with ketosis adverse events are identified using Company MedDRA Queries CMQ00027
Total patient years correspond to the cumulative patient years exposure to the main 6-months TEAE period

Hypersensitivity reactions and injection site reactions

Treatment-emergent injection site reactions were reported by low and comparable percentages of patients in both treatment groups, 4.7% for Toujeo and 5.7% for Lantus. The most commonly reported PTs were injection site pain (2.1% for Toujeo and 1.3% for Lantus) and injection site atrophy (1.7% for Toujeo and 2.6% for Lantus). None of the events was severe in intensity and the events were considered related to the IMP in 2.6% of patients in the Toujeo group and 3.1% of patients in the Lantus group. Treatment-emergent hypersensitivity reactions were reported by low percentages of patients in each treatment group, 7.3% for Toujeo and 4.8% for Lantus. Treatment-emergent hypersensitivity reactions by individual PT were reported in <2% of patients in either treatment group. None of the events was severe in intensity or serious in nature. None of the events were considered related to the IMP.

Table 29 Injection site and Hypersensitivity reactions by PT during the main 6-months TEAE period - Safety population

	Toujeo (N=233)		Lantus (N=228)	
Preferred Term	**n (%)**	**E(R)**	**n (%)**	**E(R)**
Total patient years		114.57		111.95

Any injection site reactions	11 (4.7)	16 (0.14)	13 (5.7)	20 (0.18)
Any hypersensitivity reactions	17 (7.3)	18 (0.16)	11 (4.8)	12 (0.11)

TEAE: Treatment emergent adverse event, PT: Preferred term
n (%) = number and percentage of patients with at least one TEAE linked to local tolerability at injection site
E(R) = number of events and event rate per patient-years, linked to local tolerability at injection site
Note: Table sorted by decreasing frequency of PT based on incidence in the Toujeo treatment group
Injection site reactions are identified using Company MedDRA Queries CMQ00011
Total patient years correspond to the cumulative patient years exposure to the main 6-months TEAE period

Immunogenicity assessments (insulin antibodies)

At baseline, a similar percentage of patients in both treatment groups were positive for anti-insulin antibody (AIA) (Toujeo: 77.7% and Lantus: 79.8%). During the main 6-months TEAE period, the percentage of patients with a treatment-emergent AIA response (ie, treatment-boosted or treatment-induced AIAs) was similar in both treatment groups with a median peak titer of 4.0.

The percentages of patients positive for AIA slightly increased during the main 6-months on-treatment period and were similar in both the treatment groups. As expected, the percentages of patients with antibodies cross-reacting with human insulin were similar in both treatment groups and ranged between 76.2% and 84.1% during the study.

Treatment-emergent AIAs had no impact on the insulin dose requirements or safety parameters (including hypoglycaemia, hypersensitivity and injection site reactions, TEAEs, and SAEs) in either treatment group.

In addition, there was no relationship between the maximal AIA titers and insulin doses or safety parameters, regardless of treatment-emergent AIA status. Based on the independent blinded external endpoint assessment committee's review of hypersensitivity events in patients with treatment-induced or treatment-boosted AIAs, 3 out of 4 patients with such events (Toujeo: 2 patients-PTs Bronchospasm and Prurigo; Lantus: 1 patient-PT Rash pustular) were classified as AIA-mediated hypersensitivity events.

Safety related to drug-drug interactions and other interactions

2.5.1. Interaction effects

During the 6-months TEAE period, the incidence and pattern of common TEAEs (HLTs with an incidence ≥2%), SAEs, and clinical laboratory abnormalities across the prespecified subgroups of age (<12 and ≥12 years) and gender were consistent with the results for the overall population. The majority of patients (approximately 90%) in each treatment group were White; this precludes any comparison of the incidence of TEAEs across racial subgroups.

Drug-drug interactions were not evaluated in this study (EFC13957) and therefore, no new information is available.

Discontinuation due to adverse events

AEs leading to permanent treatment discontinuation

Two patients (0.9%) in each treatment group reported TEAEs leading to permanent treatment discontinuation (2 patients (0.9%) in each group). Events were somnolence, malaise, and ALT increase in the Toujeo group and injection site pain and ALT increase in the Lantus group.

2.5.2. Discussion on clinical safety

Study EFC13957 is the only clinical study in the paediatric population. Safety endpoints were hyperglycaemia with or without ketosis, adverse events (including injection site reactions and hypersensitivity reactions), antibodies to insulin, routine laboratory, and Tanner puberty stage.

The safety population was 233 children and adolescent patients with T1DM treated with Toujeo and 228 treated with Lantus. Mean exposure was 180 days (26 weeks) for Toujeo and 179 days (26 weeks) for Lantus and most patients were treated for more than 25 weeks, 92.7% for Toujeo and 93.4% for Lantus.

During the 6-months TEAE period, almost all patients had at least one event of 'any' hypoglycaemia at any time of the day (Toujeo: 97.9%; Lantus: 98.2%). The percentage of patients with at least one nocturnal hypoglycaemia event (in any category) was also similar in both treatment groups (Toujeo: 73.0%; Lantus: 71.9%). Severe hypoglycaemia at any time of the day was reported by 14 patients (6.0%) in the Toujeo group and 20 patients (8.8%) in the Lantus group. Severe hypoglycaemia during the nocturnal period (00:00-05:59) was reported by 7 patients in each treatment group. None of the patients permanently discontinued treatment due to the severe hypoglycaemia event.

During the main 6-months treatment period, no new or unexpected safety signals were observed. The overall proportion of subjects with an AE during the study period was similar across the two treatment groups (65.2% for Toujeo and 65.8% for Lantus). The most frequently reported TEAEs by PT in the Toujeo and Lantus groups, respectively were nasopharyngitis (12.9% and 13.6%), headache (7.3% and 5.7%), upper respiratory tract infection (6.9% and 5.7%), and ketosis (6.4% and 10.1%). In both treatment groups, the most frequently reported severe TEAEs by PT were hypoglycaemic unconsciousness (Toujeo: 2.1%; Lantus: 3.1%) and hypoglycaemic seizure (Toujeo: 1.3%; Lantus: 3.1%).

Adverse events considered related were low and comparable between the two treatment groups, 6.0% for Toujeo and 8.3% for Lantus. In general, the spectrum of related adverse advents for this 6 months of treatment was comparable between the Toujeo and the Lantus group and in line with section 4.8 of the SmPC for Toujeo for adults.

No new signal was found with regards to adverse events of interest hypersensitivity reactions and injection site reactions, which were reported by low percentages of patients in each treatment group. Hypersensitivity reactions was reported slightly more for Toujeo: 7.3% (n=17) for Toujeo and 4.8% (n=11) for Lantus. The known related adverse event 'lipohypertrophy' (frequency 'common' in section 4.8 of the SmPC of Toujeo and Lantus) was not reported.

Overall, the AE profile was in accordance with the SmPC for Lantus and Toujeo without any difference of clinical significance between the two treatment groups.

At baseline, a similar percentage of patients in both treatment groups were positive for insulin antibodies (AIA) (Toujeo: 77.7% and Lantus: 79.8%). The percentages of patients positive for AIA slightly increased during the main 6-months on-treatment period and were similar in both treatment groups. The percentages of patients with antibodies cross-reacting with human insulin were similar in both treatment groups and ranged between 76.2% and 84.1% during the study. Assessment of time-dependent changes in HbA1c and AIA development showed no evidence of the development of immunologically-mediated insulin resistance to Toujeo.

The full safety data set including 52 weeks of treatment further support the safety in paediatric T1DM patients.

2.5.3. Conclusions on clinical safety

Toujeo and Lantus both contain insulin glargine but are administered in formulations, that are not bioequivalent. Although Lantus (100 IU) has since long been used in paediatric patients aged from 2 years, Toujeo (300 IU) has only been approved for adults. Within the study period of 26 weeks currently submitted, safety of the two preparations was evaluated and no new or unexpected safety signals were identified in Toujeo-treated patients compared to Lantus-treated patients, with regard to incidence and frequency of hypoglycaemia and other adverse events of special interest. The spectrum of TEAEs was comparable between the Toujeo group and de Lantus group.

No difference in adverse pattern was noted between treatment groups over the first 26 weeks of the paediatric study, and this was supported by the full safety data set including 52 weeks.

2.5.4. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.6. 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 6.1 is acceptable.

The MAH is reminded that, within 30 calendar days of the receipt of the Opinion, an updated version of Annex I of the RMP template, reflecting the final RMP agreed at the time of the Opinion should be submitted to h-eurmp-evinterface@emea.europa.eu.

The CHMP endorsed this advice without changes.

The CHMP endorsed the Risk Management Plan version 6.1 with the following content:

Safety concerns

Summary of the safety concerns	
Important identified risks	Medication error due to mix-up between long-acting (basal) and short-acting (bolus) insulins
Important potential risks	Malignancies Medication errors: • Mix-up between long-acting 100 units/mL and 300 units/mL strength insulin products • Unnecessary dose or unit recalculation • Switching patients between standard 100 units/mL and 300 units/mL strength insulin products without dose adjustment
Missing information	Use in pregnancy (U300 only)

Considering the data in the safety specification, the safety concerns listed above are appropriate.

Pharmacovigilance plan

There are no planned or ongoing additional pharmacovigilance activities.
Routine pharmacovigilance is considered sufficient to identify and characterise the risks of the product.
Specific adverse event follow-up questionnaires are in place to monitor the medication error risks associated with use of insulin glargine.

Risk minimisation measures

Safety concern	Risk minimization measures
Medication error due to mix-up between long-acting (basal) and short-acting (bolus) insulins	**Routine risk minimization measures:** U100 SmPC: Labelled in sections 4.4 and 6.6. PL: Labelled in section 3. IFU: Step 1 U300 SmPC: Labelled in sections 4.4 and 6.6. PL: Labelled in sections 2 and 3. IFU: "Learn to inject" and Step 1-A. To enhance differentiation (not only in countries where U100 vial and syringe are marketed) a different trade name is a way to prevent patient medication error or dispensing errors. The proposed trade name for U300 Insulin glargine is TOUJEO (Toujeo SoloStar for the small size pen, and Toujeo DoubleStar for the large size pen), while LANTUS is used for U100. Medicinal product subject to medical prescription. Packaging (outer carton + label). Each strength and presentation has specific pen design and color, pen label, and outer pack specific color. Those differentiation elements are presented in Module 1.3.2 for Toujeo DoubleStar part of the same submission than this RMP V5.0. **Additional risk minimization measures:** None
Malignancies	**Routine risk minimization measures:** SmPC: None PL: None IFU: None Medicinal product subject to medical prescription. **Additional risk minimization measures:** None
Medication errors Mix-up between long-acting 100 units/mL and 300 units/mL strength insulin products	**Routine risk minimization measures:** U100 SmPC: Labelled in sections 4.4 and 6.6. PL: Labelled in section 3. IFU: Step 1-A Trade names are different. Packaging mentions the strength. Pack, pen and labels have different color and design.

Safety concern	Risk minimization measures
	Medicinal product subject to medical prescription except during switch period, patients should not own products with different concentrations. U300 SmPC: Labelled in sections 4.4 and 6.6. PL: Labelled in sections 2 and 3. IFU: "Learn to inject" and Step 1-A. Trade names are different. Packaging mentions the strength. Pack and pen have different color and design. Medicinal product subject to medical prescription except during switch period, patients should not own products with different concentrations. **Additional risk minimization measures:** None
Unnecessary dose or unit recalculation	**Routine risk minimization measures:** U100 SmPC: None PL: None IFU: None Medicinal product subject to medical prescription. U300 SmPC: Labelled in section 4.2. PL: Labelled in section 3. IFU: Step 4 Medicinal product subject to medical prescription. The dose window of the pen shows the dose in units. **Additional risk minimization measures:** HCP educational material: HCP brochure Patient educational material: Patient brochure to patients treated with TOUJEO DoubleStar.
Switching patients between standard 100 units/mL and 300 units/mL strength insulin products without dose adjustment	**Routine risk minimization measures:** U100 SmPC: Labelled in section 4.2. PL: None IFU: None Medicinal product subject to medical prescription. U300 SmPC: Labelled in sections 4.2 and 4.4. PL: Labelled in sections 2 and 3. IFU: Step 1-A Medicinal product subject to medical prescription. **Additional risk minimization measures:** HCP educational material: HCP brochure Patient educational material: Patient brochure to patients treated with Toujeo DoubleStar
Use in pregnancy (U300 only)	**Routine risk minimization measures:** SmPC: Labelled in section 4.6. PL: Labelled in section 2.

Safety concern	Risk minimization measures
	IFU: None Medicinal product subject to medical prescription. **Additional risk minimization measures:** None

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.8, 5.1, and 5.2 of the SmPC have been updated. The Package Leaflet (PL) is updated accordingly (section 2).

2.7.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable for the following reasons:

No additional user consultation is necessary for Insulin glargine (HOE901) for this variation. Since the indication is extended to paediatric population, the users remain identical and the information to guarantee the safe use of the product also remains identical.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

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

Type 1 diabetes (T1DM) is an autoimmune disease, where the immune system incorrectly targets insulin-producing beta cells in the pancreas until no more insulin is produced. The majority of patients diagnosed are children and adolescents, with peaks in disease presentation at 5 to 9 years of age and around puberty. Globally, the incidence of T1DM continues to rise by 2% to 5% each year. The prevalence of T1DM varies considerably from country to country.

Type 2 diabetes (T2DM) is characterized by the body losing its ability to respond to insulin, i.e. insulin resistance. It is usually diagnosed in people over 30 years old and results from genetic, metabolic and socio-economical causes. Although the incidence of T2DM in the paediatric population is increasing, the absolute number of children and adolescents with T2DM is still relatively low, with an estimated prevalence in Europe of approximately 2.5:100000. However, a prevalence of impaired glucose tolerance and T2DM as high as 6.7% was found in a large group of children and adolescents with obesity in Germany. The pathophysiology of paediatric T2DM appears to be similar to that in adults.

Current treatment options for youth-onset T2DM are limited to two approved drugs: insulin and metformin. Despite hyperinsulinemia and insulin resistance associated with T2DM, supplemental insulin (a larger amount compared to T1DM) is considered generally effective in reducing hyperglycaemia and attaining glycaemic target in paediatric T2DM just as in adult T2DM.

Both T1DM and T2DM are associated with acute and chronic complications.

3.1.2. Available therapies and unmet medical need

Patients with T1DM require insulin replacement therapy, a basal-bolus insulin regimen which is designed to approximate physiologic basal and postprandial insulin release, thereby avoiding hyperglycaemia and hypoglycaemia. Typically a basal insulin analog is given to provide stable blood glucose lowering over the 24-hour day, including during the overnight fast, and a rapid-acting insulin analogue is given with each meal to provide postprandial control.

One of the most frequently used basal insulins is insulin glargine 100 U/mL (a.o. Lantus), a long-acting recombinant analogue of human insulin administered as a single-dose subcutaneous (SC) injection. In the EU, Lantus is indicated for the treatment of diabetes mellitus in adults, adolescents and children aged 2 years and above.

The product under review, insulin glargine 300 U/mL (Toujeo) contains 3-times the amount of insulin and corresponding zinc content. Except for the more concentrated formulation, there is a difference in PK/PD profile between Toujeo and Lantus where Toujeo shows slower and more prolonged absorption resulting in a flatter time-concentration profile compared to Lantus.

Toujeo is currently approved for the treatment of diabetes in adults. With this application, the MAH seeks to extend the indication for Toujeo to include children and adolescents from the age of 6 years.

3.1.3. Main clinical studies

T1DM

As clinical evidence for the efficacy and safety of Toujeo in the treatment of T1DM in the paediatric population, the applicant has submitted the 6-months randomized period of a single phase 3b non-inferiority **Study EFC13957** of in total 52 weeks duration, in which Toujeo was compared to Lantus in children and adolescent patients (aged 6 years to 17 years). Based on dose-response analyses, a need for dose adaptation in the paediatric population was considered not necessary, and the dose regimen for Toujeo recommended for adults was also applied in this paediatric study.

The study included 233 patients to Toujeo and 230 patients to Lantus. Randomization was stratified by age group (6-12 years (143 subjects) and ≥ 12-17 years (320 subjects) and by HbA1c at screening (<8.5% [183 subjects], ≥8.5% [280 subjects]). The demographic and baseline characteristics were balanced between groups. A high proportion of subjects completed the trial (95%).

T2DM

Although the incidence of T2DM in the paediatric population is increasing, the absolute number of children and adolescents with T2DM is still relatively low, making a clinical study not feasible. Therefore, in line with the recommendations of the EMA diabetes guideline (CPMP/EWP/1080/00 Rev. 2), to support the extension of the indication to include children and adolescents with T2DM, a **qualitative comparison** was made of the T1DM paediatric trial discussed above (Study EFC13957) with the efficacy and safety data from three of the four Phase 3 studies in adult patients with T2DM which were included in the initial submission dossier of Toujeo:

- Study EFC12456 included T1DM adult patients on basal + Toujeo or mealtime insulin (N=549 (274 with Toujeo and 275 with Lantus).

- Study EFC11628 included T2DM adult patients on basal +mealtime insulin (N=807 (404 with Toujeo and 403 with Lantus)).
- Study EFC12347 included Insulin-naïve T2DM adult patients (N=878 (439 with Toujeo and 439 with Lantus)).

The efficacy endpoints assessed were HbA1c and FPG. The demographic and baseline characteristics (other than disease-related) were generally similar across the different subgroups of interest in the paediatric and insulin-naïve adult populations.

3.2. Favourable effects

Paediatric patients with T1DM - Study EFC13957

Primary endpoint: The primary efficacy endpoint was HbA1c change from baseline at Week 26. The primary objective was met, as non-inferiority of Toujeo relative to Lantus was demonstrated for HbA1c change from baseline to Week 26 (Toujeo: mean (SD) 8.65% (0.88); Lantus: mean (SD) 8.61% (0.87) . The least squares (LS) mean difference in HbA1c for Toujeo versus Lantus was 0.004% (95% CI [(-0.172 to 0.179]) with the upper bound of the 95% CI lower than the predefined non-inferiority margin of 0.3%.

Mean HbA1c levels over time followed a similar pattern in both treatment groups. The treatment effect was consistent across most of the demographic and other pre-specified subgroups including Tanner puberty stages. In younger children below 12 years, a slightly more pronounced decrease in HbA1c was observed with both Toujeo and Lantus treatments.

Secondary endpoints: At Week 26, a comparable efficacy of Toujeo to Lantus was seen for FPG, for percentage of patients who reached the pre-specified target HbA1c of <7.5% and pre-specified target FPG (≤130 mg/dL [7.2 mmol/L]) overall or without an event of severe and/or documented hypoglycaemia, change in 24-hour mean plasma glucose, and for 8-point SMPG profiles.

Daily insulin dose: Mean daily insulin dose increased in both treatment groups, with the steepest increase between baseline and week 12. Consistent with the overall population, the increase was larger with Toujeo as compared to Lantus and across all Tanner puberty stages. After 12 weeks, doses remained relatively constant, and no significant changes were seen between the 20 and 26 weeks results. At Week 26 the dose was 8% higher in the Toujeo group (0.615 U/kg) than in the Lantus group (0.567 U/kg).

Paediatric patients with T2DM - Extrapolation

Treatment with Toujeo in individually titrated adult patients with T1DM and T2DM in studies EFC12456, EFC11628 and EFC12347 as well as in paediatric T1DM patients was effective in improving glycaemic control as demonstrated by lowering of mean HbA1c and mean FPG from baseline: Toujeo reduced mean change in HbA1c at endpoint (Month 6) compared to baseline in T1DM and T2DM patients (mean HbA1c ranged from 8.11 to 8.65%). The changes in HbA1c from baseline to Month 6 were similar in adult and paediatric T1DM patients, but greater in insulin-naïve T2DM patients. The reduction pattern was similar in all studies: the reduction was greater in insulin-naïve T2DM patients and greatest in the first 12 weeks with a flattening of the curves thereafter. Consistent with HbA1c reduction, FPG decreased in all studies, with a greatest reduction observed in T2DM patients, and particularly in insulin-naïve patients.

3.3. Uncertainties and limitations about favourable effects

There are no uncertainties and limitations about favorable effects within this application.

3.4. Unfavourable effects

Paediatric patients with T1DM - Study EFC13957

Hypoglycaemia: During the 6-months TEAE period, almost all patients had at least one event of 'any' hypoglycaemia at any time of the day (Toujeo: 97.9%; Lantus: 98.2%). The percentage of patients with at least one nocturnal hypoglycaemia event (in any category) was also similar in both treatment groups (Toujeo: 73.0%; Lantus: 71.9%). Severe hypoglycaemia at any time of the day was reported by 14 patients (6.0%) in the Toujeo group and 20 patients (8.8%) in the Lantus group. Severe hypoglycaemia during the nocturnal period (00:00-05:59) was reported by 7 patients in each treatment group. None of the patients permanently discontinued treatment due to the severe hypoglycaemia event.

Adverse events pattern: During the main 6-months treatment period, no new or unexpected safety signals were observed. The overall proportion of subjects with an AE during the study period was similar across the two treatment groups (65.2% for Toujeo and 65.8% for Lantus). The most frequently reported TEAEs by PT in the Toujeo and Lantus groups, respectively were nasopharyngitis (12.9% and 13.6%), headache (7.3% and 5.7%), upper respiratory tract infection (6.9% and 5.7%), and ketosis (6.4% and 10.1%). In both treatment groups, the most frequently reported severe TEAEs by PT were hypoglycaemic unconsciousness (Toujeo: 2.1%; Lantus: 3.1%) and hypoglycaemic seizure (Toujeo: 1.3%; Lantus: 3.1%). Adverse events considered related were comparable between the two treatment groups, 6.0% for Toujeo and 8.3% for Lantus.

No new signal was found with regards to specific adverse events of interest like hypersensitivity reactions, and injection site reactions, which were found in the same range in each treatment group. Hypersensitivity reactions was reported slightly more for Toujeo: 7.3% (n=17) for Toujeo and 4.8% (n=11) for Lantus. The known related adverse event 'lipohypertrophy' (frequency 'common' in section 4.8 of the SmPC of Toujeo and Lantus) was not reported.

Overall the AE profile was in accordance with the SmPC for Lantus and Toujeo without any difference of clinical significance between the two treatment groups.

Immunogenicity assessments (insulin antibodies): At baseline, a similar percentage of patients in both treatment groups were positive for AIA (Toujeo: 77.7% and Lantus: 79.8%). The percentages of patients positive for AIA increased during the main 6-months treatment in both treatment groups. The percentages of patients with antibodies cross-reacting with human insulin were remained similar in both treatment groups and ranged between 76.2% and 84.1% during the study.

The main 6-months treatment period was followed by the 6-months safety extension period of the Phase 3b clinical study EFC13957 (EDITION JUNIOR).

No new safety data or trends have become available from the 6-months safety extension period. It can be concluded that the safety profile of Toujeo was similar to that of Lantus in children and adolescents aged 6 - 17 years with T1DM. The overall incidence of TEAEs during the entire 12-months period was similar between the treatment groups.

The 12-months safety part has been included in the safety part of the Effects **Table 40** as a comparison:

Unfavourable Effects

			6-months		12-months			
Effect	Short description	Unit	Toujeo	Lantus	Toujeo	Lantus	Uncertainties / Strength of evidence	References
Any hypoglycaemia; severe	Patients with at least one hypoglycaemia event; Severe	% (n)	97.9 (228) 6.0 (14)	98.2 (224) 8.8 (20)	99.1 (231) 8.6 (20)	98.7 (225) 11.0 (25)	Event rate per patient-year of exposure for severe hypoglycaemia at any time of day was numerically lower for Toujeo (0.18) versus Lantus (0.27), RR 0.69 (95% CI: 0.32 to 1.50) [6 months]; at 12 months this was 0.16 for Toujeo and 0.18 for Lantus, RR 0.93 (95% CI: 0.47 to 1.87).	Study EFC13957 12 month (EDITION JUNIOR 12 month)
Nocturnal hypoglycaemia; severe	Patients with at least one nocturnal hypoglycaemia event; Severe	% (n)	73.0 (170) 3.0 (7)	71.9 (164) 3.1 (7)	83.7 (195) 4.3 (10)	78.5 (179) 3.1 (7)	This is a subset of 'Any hypoglycaemia' above.	Study EFC13957 12 month (EDITION JUNIOR 12 month)
Hyperglycaemia with ketosis	Patients with hyperglycaemia with ketosis	% (n)	6.4 (15)	11.8 (27)	9.4 (22)	15.8 (36)	Event rate per patient-year of exposure were 220 events (1.92) on Toujeo and 159 events (1.42) on Lantus [6 months] and after 12 months 381 events (1.70) on Toujeo and 202 events (0.93) on Lantus.	Study EFC13957 12 month (EDITION JUNIOR 12 month)
Hypersensitivity	Patients with hypersensitivity reactions	% (n)	7.3 (17)	4.8 (11)	9.0 (21)	6.6 (15)	All were of mild or moderate intensity, none were SAEs.	Study EFC13957 12 month (EDITION JUNIOR 12 month)
Inject site reactions	Patients with injection site reactions	% (n)	4.7 (11)	5.7 (13)	8.2 (19)	7.5 (17)	1 patient on Lantus discontinued due to an injection site reaction	Study EFC13957 12 month (EDITION JUNIOR 12 month)
Hypoglycaemic unconsciousness	Patients with hypoglycaemic unconsciousness	% (n)	2.1 (5)	3.1 (7)	2.6 (6)	4.4 (10)	All events were SAEs and labelled severe, except 2 events on Lantus that was labelled moderate.	Study EFC13957 12 month (EDITION JUNIOR 12 month)
Hypoglycaemic seizure	Patients with hypoglycaemic seizures	% (n)	1.3 (3)	3.1 (7)	3.4 (8)	4.4 (10)	All events were SAEs and labelled severe, except 1 event on Lantus that was labelled moderate.	Study EFC13957 12 month (EDITION JUNIOR 12 month)

Abbreviations: FPG: Fasting plasma glucose; HbA1c: glycated haemoglobin A1c; SD: standard deviation; TEAEs: treatment-emergent adverse events; RR: relative risk; CI: confidence interval; SAE: serious adverse event; TEAE: treatment-emergent adverse event; (n): number

Paediatric patients with T2DM - Extrapolation

Results of safety parameters presented in the extrapolation analysis were in the same range for adults and children with T1DM. The results presented do not point towards a different risk for children with T2DM.

3.5. Uncertainties and limitations about unfavourable effects

Safety results presented do not point towards a different risk for children.

3.6. Effects Table

Table 30 Effects Table for Toujeo, in the treatment of diabetes mellitus in adults, adolescents and children from the age of 6 years, by basal-bolus regimen.

Effect	Short description	Unit	Toujeo	Lantus	Uncertainties / Strength of evidence	References
Favourable Effects						
HbA1c	HbA1c change (SD) from baseline to Week 26	%	8.65 (0.88)	8.61 (0.87)	SoE |: Treatment difference at Week 26: 0.004% (0.090) 95%CI [(-0.172 to 0.179]; p = 0.965 Non-inferiority was demonstrated, as the upper bound of the 95% CI was lower than the predefined non-inferiority margin of 0.3%. These results were obtained in T1DM and may be extrapolated to T2DM (see text).	Study EFC13957 (EDITION JUNIOR)
FPG	FPG change (SD) from baseline to Week 26	Mean mmol/L	11.25 (5.01)	11.35 (5.07)	SoE Treatment difference at Week 26: -0.014 (0.518) 95%CI (-1.030 to 1.002)	Study EFC13957 (EDITION JUNIOR)
Unfavourable Effects						
Any hypoglycaemia; severe	Percentage (n) of patients with at least one hypoglycaemia event during the main 6-months TEAE period; severe	%	97.9 (228) 6.0 (14)	98.2 (224) 8.8 (20)	SoE Event rate per patient-year of exposure for severe hypoglycaemia at any time of day was numerically lower for Toujeo (0.18) versus Lantus (0.27), RR 0.69 (95% CI: 0.32 to 1.50)	Study EFC13957 (EDITION JUNIOR)
Nocturnal hypoglycaemia; severe	Percentage (n) of patients with at least one nocturnal hypoglycaemia event during the main 6-months TEAE period; severe	%	73.0 (170) 3.0 (7)	71.9 (164) 3.1 (7)	This is a subset of 'Any hypoglycaemia' above.	Study EFC13957 (EDITION JUNIOR)
Hyperglycaemia with ketosis	Incidence (n) of patients with hyperglycaemia with ketosis	%	6.4 (15)	11.8 (27)	Event rate per patient-year of exposure were 220 events (1.92) on Toujeo and 159 events (1.42) on Lantus	Study EFC13957 (EDITION JUNIOR)
Hypersensitivity	Incidence (n) of patients with hypersensitivity reactions	%	7.3 (17)	4.8 (11)	All were of mild or moderate intensity, none were SAEs.	Study EFC13957 (EDITION JUNIOR)
Inject site reactions	Incidence (n) of patients with injection site reactions	%	4.7 (11)	5.7 (13)	1 patient on Lantus discontinued due to an injection site reaction	Study EFC13957 (EDITION JUNIOR)
Hypoglycaemic unconsciousness	Incidence (n) of patients with hypoglycaemic unconsciousness	n (%)	2.1 (5)	3.1 (7)	All events were SAEs and labelled severe, except 1 event on Lantus that was labelled moderate.	Study EFC13957 (EDITION JUNIOR)
Hypoglycaemic seizure	Incidence (n) of patients with hypoglycaemic seizures	n (%)	1.3 (3)	3.1 (7)	All events were SAEs and labelled severe.	Study EFC13957 (EDITION JUNIOR)

Abbreviations: FPG: Fasting plasma glucose; HbA1c: glycated haemoglobin A1c; SD: standard deviation; TEAEs: treatment-emergent adverse events; RR: relative risk; CI: confidence interval; SAE: serious adverse event; TEAE: treatment-emergent adverse event; (n): number

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Subjects with T1DM and T2DM require life-long insulin treatment. In order to allow individualized treatment, with the aim of achieving good metabolic control, insulins with different PD profiles are needed. T1DM and especially T2DM are rare in children but insulin treatment is mandatory to prevent death, irrespective of age. With the current submission, data to support the use of Toujeo in children and adolescents aged 6 year and above have been submitted. No adapted device is available to apply Toujeo 300 units/ml in children younger than 6 years.

Importance of favourable effects

In the comparative study in paediatric patients with T1DM, non-inferiority of Toujeo relative to Lantus was demonstrated for HbA1c change from baseline to Week 26. The secondary efficacy endpoints such as FPG between baseline and Week 26 are in support of the HbA1c results, with similar values and trends.

The quantitative analysis (extrapolation) submitted in support of efficacy in paediatric patients with T2DM, shows that Toujeo was effective in adult T1DM, adult T2DM and children with T1DM. The reductions in HbA1c in T2DM are similar and follow a similar pattern of response.

Importance of unfavourable effects

Hypoglycaemia is a common safety concern in patients with T1DM and T2DM on intensive insulin therapy and is therefore important to consider when evaluating the safety profile Toujeo.

In the 26 weeks treatment period of the paediatric T1DM study, the overall risk of hypoglycaemia and the risk of nocturnal hypoglycaemia were similar in both treatment groups. The occurrence of severe hypoglycaemia and SAEs of hypoglycaemia were comparable (and even slightly lower) between Toujeo and Lantus.

No relevant differences were found in other safety parameters between Toujeo and Lantus, such as hyperglycaemia with ketosis, hypersensitivity, and injection site reactions.

In the extrapolation data, safety results collected form adult patients with T1DM, insulin-naïve T2DM, advanced T2DM and paediatric patients with T1DM were compared. The results of this analysis do not point towards a different risk for children with T2DM compared to T1DM.

Since insulin glargine 100 units/ml and Toujeo 300 units/ml are not bioequivalent and are not interchangeable, switching may result in the need for a change in dose and should only be done under strict medical supervision. The educational materials (see key aspects in Annex II) agreed at time of the adult indication are also applicable for children.

3.7.2. Balance of benefits and risks

T1DM:

Non-inferiority of Toujeo relative to Lantus was robustly demonstrated for the efficacy endpoint HbA1c change from baseline to Week 26. The secondary endpoint findings were in line with the primary endpoint finding. Comparable safety of Toujeo versus Lantus was demonstrated..

T2DM:

The presented extrapolation of results in adult patients with T2DM treated with Toujeo to support use in paediatric patients with T2DM is considered adequate and in line with the recommendations of such

approach described in the EMA guideline on clinical investigation in the treatment or prevention of diabetes. The reductions in HbA1c are similar in adult T1DM, T2DM and children with T1DM (26 weeks of study EFC13957) and appear to follow a similar pattern of response. Safety data do not point towards a different risk for children with T2DM. Therefore, these extrapolation data sufficiently support that Toujeo will also be effective and safe in children with T2DM.

3.8. Conclusions

The overall benefit/risk balance of Toujeo is positive in treatment of diabetes mellitus in adolescents and children from the age of 6 years.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of indication to include new population for Toujeo (adolescents and children from the age of 6 years). As a consequence, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance.

The variation leads to amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

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.

In addition, 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.

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 consist of:

- Guide for healthcare professionals
- Patient/carer guide (patient brochure)

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

- Details on how to minimize the safety concern addressed by the additional risk minimization measures through appropriate monitoring and management:
  - That insulin glargine 100 units/ml and insulin glargine 300 units/ml (Toujeo SoloStar and Toujeo DoubleStar) 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 (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, 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.
- Key messages to convey in patients counselling:
  - Patients need to be instructed that insulin glargine 100 units/ml products and Toujeo 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.
- Instructions on how to report medication errors or adverse events: Details for national reporting added at country level.
- Other: The Guide for healthcare professionals is also highlighting the distinction between the different Toujeo presentations:
  - That insulin glargine 300 units/ml is available in two different presentations: Toujeo SoloStar (1.5 mL prefilled pen/450 units) and Toujeo DoubleStar (3 mL prefilled pen/900 units);
  - The dose increment in Toujeo SoloStar is one unit and the dose increment in Toujeo DoubleStar is 2 units;
  - The dose delivered is the one shown in the dose window.

The educational material for patient/carer guide (patient brochure) shall contain the following key elements:

- Detailed description of the modalities used for the self-administration of insulin glargine:

- That insulin glargine 100 units/ml and insulin glargine 300 units/ml (Toujeo SoloStar and Toujeo DoubleStar) 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;
- That they should report medication errors or any side effects. Details for national reporting added at country level;
- That insulin glargine 300 units/ml is available in two different presentations: Toujeo SoloStar (1.5 mL prefilled pen/450 units) and Toujeo DoubleStar (3 mL prefilled pen/900 units). The dose increment in Toujeo SoloStar is one unit and the dose increment in Toujeo DoubleStar is 2 units. The dose delivered is the one shown in the dose window.

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.

Similarity with authorised orphan medicinal products

The CHMP, by consensus, is of the opinion that Toujeo is not similar to Amglidia within the meaning of Article 3 of Commission Regulation (EC) No. 847/200. See Appendix 1.

4.1. Conclusions

The overall benefit/risk balance of Toujeo is positive in treatment of diabetes mellitus in adolescents and children from the age of 6 years.