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Committee for Medicinal Products for Human Use (CHMP)

Assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

Lantus

International non-proprietary name: insulin glargine

Procedure No. EMEA/H/C/000284/P46 052.1

Note

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

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1. Updated Recommendation

Based on the review of the data on safety and efficacy, the Rapporteur considers that the submitted documentation for Lantus (insulin glargine), in the treatment of diabetes mellitus in adults, adolescents and children aged 2 years and above, did not reveal any new or unexpected issues.

No amendments to SmPC, labelling and/or Package Leaflet of Lantus are warranted based on the review of the data on PD, PK and safety of Study EFC11681. There are no outstanding issues.

2. Scientific discussion

2.1. Introduction

Lantus (insulin glargine 100 U/mL injection) had been approved for the treatment of adults, adolescents, and children of 6 years and above with diabetes mellitus, where treatment with insulin is required since 2000 in United States (US) and 2003 in European Union (EU). In 2012, EU expanded the indication to type 1 diabetes mellitus (T1DM) children aged 2 to 5 years old.

In 2010, the MAH issued a clinical trial waiver application to China Food and Drug Administration (CFDA) for label update to be consistent with EU label. CFDA asked Sanofi to conduct a trial in paediatric patients. A Phase 3 clinical study, EFC11681, was thus conducted in Chinese children with T1DM aged at least 6 to less than 18 years to support the indication proposed in China.

In accordance with article 46 of Regulation (EC) No 1901/2006, Sanofi is hereby submitting the final Clinical Study Report (CSR) for Study EFC11681: A 24-week, randomized, open-label, parallel group, multicentre comparison of Lantus® (insulin glargine) given once daily versus Neutral Protamine Hagedorn (NPH) insulin in children with type 1 diabetes mellitus aged at least 6 years to less than 18 years.

The MAH considers that in the context of this submission, no amendments to SmPC, labelling and/or Package Leaflet of Lantus are warranted based on the review of the data on PD, PK and safety of EFC11681 Study.

The study used as a basis for clinical data presented in this dossier was conducted in compliance with Good Clinical Practice (GCP), as required by the ICH E6 Guideline for Good Clinical Practice. The study also meet with the requirements of the Declaration of Helsinki, standard operating procedures for clinical investigations and documentation of the Sponsor, applicable national laws and regulations and the ethical principles of the Directive 2001/20/EC.

2.2. Clinical pharmacology aspects

The company conducted a clinical study (EFC11681) to assess the clinical efficacy Lantus® (insulin glargine) in Chinese children with type 1 diabetes mellitus aged at least 6 years to less than 18 years (see **2.3. Clinical efficacy aspects**). In this study the pharmacokinetics of Lantus® (insulin glargine) was evaluated in a subpopulation, to rule out accumulation tendency of insulin glargine after repeated dosing.

2.2.1. Methods – analysis of data submitted

2.2.1.1 Study population

The plasma concentrations of insulin glargine, M1 and M2 were determined in a subset of 40 patients (PK population) of 107 patients randomized to the Lantus treatment group (40/107, 37%). The company provided a description of the demographics of the whole study population (see **2.3.2.1.)** however no detailed information was provided on the demographics of the PK subpopulation.

2.2.1.2 Pharmacokinetic sampling

The PK samples were obtained following once daily repeated subcutaneous Lantus (insulin glargine) dosing to children with T1DM, aged of at least 6 years to less than 18 years.

The PK samples were collected within a time interval of 9.5 to 16.5 hours following the previous evening injection of Lantus at Week 1, Week 2 or Week 4. Timing of meal time (bolus) insulin was not taken into consideration, because the bioanalytical assay for insulin glargine parent compound and its metabolites M1 and M2 is specific with no interference by other insulin analogues.

2.2.1.3 Analyical methods

Insulin glargine (parent compound) and insulin glargine metabolites M1 and M2 in plasma were determined using immunoaffinity extraction followed by liquid chromatography-tandem mass spectrometry with a lower limit of quantification (LLOQ) of 0.2 ng/mL for all 3 analytes. The bioanalytical report for the determination of insulin glargine parent compound and its metabolites M1 and M2 in plasma was provided. PK samples were collected between 13 febr 2012 and 27 jan 2014 stored at -80°C, shipped and analysed between 24 april 2012 and 20 may 2014 at Sanofi-Aventis Deutschland GmbH,R&D - SCP Disposition, Safety & Animal Research Operational Center Frankfurt, Germany.

2.2.1.4. Statistical methods

Descriptive statistics on plasma concentration data for insulin glargine parent compound and its metabolites M1 and M2 were provided. The statistical analysis included the calculation of the arithmetic means, ranges, evaluation of the interquartile ranges Q1 : Q3 and variation.

2.2.2. Results

Following once daily repeated subcutaneous Lantus (insulin glargine) dosing in a subset of 40 patients, insulin glargine metabolite M1 was the principal circulating compound in plasma. Within a time interval of 9.5 to 16.5 hours following the previous evening injection mean plasma metabolite M1 concentrations were 0.855 ng/mL at Week 1, 0.760 ng/mL at Week 2, and 0.672 ng/mL at Week 4 (see **table PK1**). This indicates that no accumulation of M1 occurred after repeated dosing. Mean plasma concentrations of insulin glargine (parent compound) and insulin glargine metabolite M2 were below LLOQ.

Table PK1 - Summary of plasma concentrations of insulin glargine by visit - PK population

Visit	Plasma concentration [ng/mL] Insulin glargine	M1	M2	Dose [U/kg]
Week 1				
Number	36	36	36	36
Mean (SEM)	<LLOQ	0.855 (0.4169)	<LLOQ	0.314 (0.0158)
SD	NC	2.502	NC	0.095
Median	<LLOQ	0.415	<LLOQ	0.310
Q1 : Q3	<LLOQ: <LLOQ	0.318 : 0.525	<LLOQ : <LLOQ	0.260 : 0.359
Min : Max	<LLOQ : 0.97	<LLOQ : 15.40	<LLOQ : 0.58	0.12 : 0.52
Geometric mean	NC	NC	NC	0.298
Coefficient of variation	247.2812	292.4510	600.0000	30.3322
Week 2				
Number	40	40	40	40
Mean (SEM)	<LLOQ	0.760 (0.2403)	<LLOQ 0.308	(0.0143)
SD	NC	1.520	0.219	0.091
Median	<LLOQ	0.452	<LLOQ	0.306
Q1 : Q3	<LLOQ : 0.210	0.373 : 0.635	<LLOQ : <LLOQ	0.249 : 0.354
Min : Max	<LLOQ : 0.86	0.22 : 9.97	<LLOQ : 1.34	0.14 : 0.52
Geometric mean	NC	0.508	NC	0.294
Coefficient of variation	201.4467	199.9798	425.0889	29.4291
Week 4				
Number	36	36	36	36
Mean (SEM)	<LLOQ	0.672 (0.1657)	<LLOQ	0.328 (0.0150)
SD	NC	0.994	0.202	0.090
Median	<LLOQ	0.456	<LLOQ	0.323
Q1 : Q3	<LLOQ : 0.227	0.377 : 0.580	<LLOQ : <LLOQ	0.272 : 0.373
Min : Max	<LLOQ : 0.95	<LLOQ : 6.14	<LLOQ : 1.21	0.14 : 0.55
Geometric mean	NC	NC	NC	0.316
Coefficient of variation	176.9502	147.9344	600.0000	27.4016

Note: PK concentrations below LLOQ were set as 0 in calculation.
Values < LLOQ (0.200 ng/mL) were displayed as <LLOQ.

The PK sample was not included in PK analysis if PK sample was not collected within predefined time interval of 9.5-16.5 hours post administration or if patient was in NPH insulin arm. The number (percentage) of samples with plasma concentrations above LLOQ are summarized by analyte and Week (visit) as in **Table PK2**

Table PK2 - Number (Percentage) of samples above LLOQ by Analyte by Week - PK population Lantus(N=40)

		Plasma concentration [ng/mL]		
	Number	Insulin glargine	M1	M2
Week 1	36	8 (22.2%)	35 (97.2%)	1 (2.8%)
Week 2	40	11 (27.5%)	40 (100.0%)	4 (10.0%)
Week 4	36	12 12 (33.3%)	33 (91.7%)	1 (2.8%)

2.2.3. Discussion

To rule out accumulation tendency of insulin glargine after repeated dosing, the insulin glargine pharmacokinetic (PK) was evaluated in a subset of 40 children included in clinical study EFC11681. The company should provide detailed information on the demographics of the PK subpopulation to show that a representative subpopulation was selected.

Based on the presented data can be concluded that no accumulation of insulin glargine or its metabolites M1 or M2 occurred after repeated dosing in the selected subpopulation. These findings are in line with previously reported results of other studies in the paediatric population.

2.3. Clinical efficacy aspects

Study EFC11681 was a 24-week, randomised, open-label, parallel group, multicentre comparison of Lantus® (insulin glargine) given once daily versus NPH insulin in Chinese children with type 1 diabetes mellitus aged at least 6 years to less than 18 years.

2.3.1. Methods – analysis of data submitted

2.3.1.1. Objectives

The primary objective of Study EFC11681 was to assess the efficacy of insulin glargine given once daily (QD, pm dosing) on glycated haemoglobin A1c (HbA1c) levels over a period of 24 weeks in children with T1DM aged at least 6 years to less than 18 years.

The secondary objectives were to assess the effects of insulin glargine compared to NPH insulin over 24 weeks on: 1) Percentage of patients reaching International Society of Paediatric and Adolescent Diabetes (ISPAD) recommended target of HbA1c <7.5%, 2) Fasting blood glucose (FBG), 3) Nocturnal blood glucose (BG), 4) 24-hour blood glucose profile based on 8-point self-monitoring of blood glucose (SMBG) values, 5) Daily total insulin dose and basal insulin dose, 6) Rates of all hypoglycaemia (including both asymptomatic and symptomatic hypoglycaemia), symptomatic, asymptomatic, severe symptomatic, nocturnal, and nocturnal symptomatic hypoglycaemia.
In addition, the safety and tolerability of insulin glargine versus NPH insulin based on the occurrence of treatment-emergent adverse events (TEAEs), and anti-insulin and anti-glargine antibody development were assessed.

To rule out accumulation tendency of insulin glargine after repeated dosing, the insulin glargine pharmacokinetic (PK) for all patients treated with insulin glargine in selected sites with approximately 45% of insulin glargine population (see 2.2. Clinical pharmacology aspects).

2.3.1.2. Study population

The population to be studied comprised paediatric patients with T1DM, with an age ranging from 6 years to less than 18 years. The patients had a diagnosis of T1DM for at least 1 year and an HbA1c at screening of <12% and ≥ 7%.

2.3.1.3. Study design

Patients were randomised in a 2:1 manner to receive Lantus as basal insulin given at bedtime (20:00 to 22:00) QD, or NPH insulin dosed once daily at bedtime (20:00 to 22:00) or twice daily in the morning (before breakfast) and at bedtime (20:00 to 22:00), both given as basal plus bolus insulin regimen for 24 weeks. The study was conducted only in China.
Randomization was stratified both by baseline age (<12 years, ≥12 years) and by screening HbA1c (<9%, ≥9%).
Both Lantus and NPH insulin were individually titrated to achieve predefined glycaemic targets.

2.3.1.4. Endpoints

Primary endpoint was the absolute change in HbA1c from baseline to week 24.

Secondary endpoints were percentage of patients reaching ISPAD recommended target of HbA1c <7.5% at Week 24, FBG change from baseline to Week 24, Nocturnal BG change from baseline to

Week 24, change in 24-hour blood glucose profile based on 8-point SMBG values from baseline to Week 24, change in daily total insulin dose and basal insulin dose from baseline to Week 24.

Post hoc analyses were performed for change in daily bolus insulin dose from baseline to Week 24, change in daily insulin (including daily total insulin, daily basal insulin, and daily bolus insulin) dose by body weight, percentage of patients with 7.5%≤HbA1c≤9% and HbA1c >9% at Week 24 (according to the categorization of glycaemic control in Chinese Diabetes Society's Guideline for the diagnosis and treatment of T1DM in China).

The *safety and tolerability* of Lantus versus NPH insulin were assessed based on: rates of all hypoglycaemia (including both asymptomatic and symptomatic hypoglycaemia), symptomatic, asymptomatic, severe symptomatic, nocturnal and nocturnal symptomatic hypoglycaemia during 24-week treatment period, the occurrence of TEAEs, other safety assessments, including laboratories, vital signs, height and weight, and physical examination findings.
Anti-insulin glargine antibody (AGA) and anti-insulin antibody (AIA) status and titre were assessed at screening, Week 4, and Week 24.

2.3.1.5. Statistical methods

The study was aimed to document the efficacy and safety for the use of Lantus (insulin glargine) or NPH but not to test a specific hypothesis.

2.3.1.5.1. Analysis Population

The primary efficacy population was modified Intention To Treat (mITT) population, which included all randomized patients who receive at least one injection of the investigational medicinal product IMP () and have both baseline and at least one post-baseline value of any endpoint, irrespective of compliance with the study protocol and procedures.

2.3.1.5.2. Primary Analysis

As a continuous efficacy parameter, the primary endpoint, absolute change of HbA1c from baseline to Week 24, was analysed using descriptive statistics (number, mean, standard deviation [SD], median, minimum and maximum). For efficacy analysis, the baseline was defined as the last available value prior to the first dose injection of open-label IMP (Lantus or NPH insulin). In case of discontinuation of study drug before Week 24, HbA1c was to be assessed at the time of discontinuation. The Last Observation Carried Forward (LOCF) procedure was to be used by taking this last available post-baseline on-treatment HbA1c measurement as the HbA1c value at Week 24.

2.3.1.5.3. Analysis of secondary endpoints

Missing efficacy endpoint values for all the efficacy variables were imputed from the last available on-treatment value using the LOCF method.

Descriptive statistics (number, mean, SD, median, minimum, and maximum) was provided by treatment for all continuous secondary endpoints using the mITT population.

Categorical secondary endpoints (eg, percentage of patients reaching ISPAD-recommended goals of HbA1c <7.5% at the end-of-treatment visit and the incidence rate of hypoglycaemia) were demonstrated by treatment.

Similarly, for the post hoc analyses, change in daily bolus insulin dose and change in daily insulin dose by body weight were analysed using the descriptive statistics (number, mean, SD, median,

minimum, and maximum), and percentages of patients with 7.5%≤HbA1c≤9% and HbA1c >9% at Week 24 were demonstrated by treatment.

2.3.1.5.4. Analyses of safety data

The safety analysis was conducted on the safety population, defined as all randomized patients who did actually receive at least one dose or partial of a dose of study drug analysed according to the treatment actually received.

The event rate of hypoglycaemia was defined as the total number of episodes divided by the total duration from the first dose of IMP up to 24 hours after the last dose of IMP.

The incidence rate of hypoglycaemia was defined as the total number of patients with at least one episode from the first dose of IMP up to 24 hours after the last dose of IMP divided by the total number of patients in the safety population.

The on-treatment period for other safety variables was defined as the time from the first dose of IMP up to 7 days after the last dose of IMP administration. The TEAEs were defined as adverse events that developed or worsened (according to the investigator's opinion) or became serious during the on-treatment period.

2.3.1.5.5. Analysis of antibody variables

The analyses of antibody data were performed based on the antibody population, defined as all randomized patients who contributed at least one valid blood sample at screening, or Week 4, or Week 24 (the end of treatment) for AGA and AIA assessment.

Percentage of patients with AGA and AIA positive and negative status was summarized by visit for each treatment group. The percent conversions from negative to positive and positive to negative of AGA and AIA status from screening to 4 weeks and from screening to 24 weeks were summarized by treatment group.

AGA and AIA titers, as well as respective percent changes from baseline, each at nominal sampling times were listed and summarized by visit and treatment using descriptive statistics by N, mean, SD, geometric mean, coefficient of variation, standard error mean (SEM), median, minimum, and maximum.

2.3.2. Results

2.3.2.1. Disposition of subjects, demographic data and baseline characteristics

A total of 196 patients were screened, and 162 patients were randomized to insulin glargine treatment group (Lantus) or NPH insulin treatment group (NPH) in a 2:1 ratio from IVRS database. Out of 196 patients, 31 (15.8%) were screen failures and 3 (1.5%) patients were run-in failures. The main reason for screen failures was the exclusion criterion E02 (HbA1c at screening <7% or >12%), which was accountable for 27 patients.
Amongst the 162 randomized patients, 107 patients were randomized to Lantus group and 55 patients to NPH group. One patient [BER1] in the NPH group withdrew consent before receiving any study medication. Thus, 107 patients were treated with Lantus and 54 with NPH insulin.
A total of 156 patients, 106 in the Lantus group and 50 in the NPH group, completed the 24-week treatment. During the treatment period, 1 patient (0.9%) in the Lantus group prematurely discontinued the study treatment and 4 (7.3%) in the NPH group. The patient in the Lantus group withdrew because of poor compliance to protocol. In the NPH group three patients (5.5%) also

withdrew because of poor compliance, while one subject (1.8%) discontinued because of “adverse event”. Table 1 summarizes the patient disposition of all randomized patients.

Table 1: Patient disposition – randomised population

	Lantus (N=107)	NPH (N=55)
Randomized and not treated	0	1 (1.8%)
Subject's request for not treated	0	1 (1.8%)
Poor compliance to protocol	0	1 (1.8%)
Randomized and treated	107 (100%)	54 (98.2%)
Did not complete the study treatment period	1 (0.9%)	4 (7.3%)
Reason for study treatment discontinuation		
Adverse event	0	1 (1.8%)
Lack of efficacy	0	0
Poor compliance to protocol	1 (0.9%)	3 (5.5%)
Other reasons	0	0

Note: Percentages are calculated using the number of randomized patients as denominator.

All patients in the study were Chinese. The demographic and baseline disease characteristics of randomized population were presented in Table 2. Randomization was stratified by age and baseline HbA1c level. The mean age of the study population was 12.3 years and 39.8% of the patients were <12 years. At baseline, 44.1% patients had HbA1c values <9% and 55.9% patients had HbA1c values ≥9%. There were more female patients (60.9%) than male (39.1%); however, the gender distribution was similar between the 2 groups. Baseline body weight and height were balanced between groups. The mean baseline body weight was 42.3 kg (42.8 and 41.3 kg in the Lantus and NPH groups, respectively). Tanner puberty stage distribution was similar between the 2 groups. Overall, 42 (26.1%) patients were preadolescents (Tanner Stage 1) and the others (119 patients, 73.9%) were adolescents (Tanner Stage 2 to 5).
The mean duration of diabetes was 3.83 years in the Lantus group and 3.55 years in the NPH group (Table 8). Only one (1.9%) patient in the NPH group reported any diabetic complication (microalbuminuria).

The mean HbA1c was 8.87% in the Lantus group and 9.12% in NPH. Other baseline efficacy variables were similar between the two treatment groups (Table 3).

Table 2: Demographics and patient characteristics at baseline – safety population

	Lantus (N=107)	NPH (N=54)	All (N=161)
Age (years)			
Number	107	54	161
Mean (SD)	12.3 (3.2)	12.2 (3.5)	12.3 (3.3)
Median (Min:Max)	13.0 (6:17)	13.0 (6:17)	13.0 (6:17)
Age Group (years) [n (%)]			
Number	107	54	161
<12	42 (39.3%)	22 (40.7%)	64 (39.8%)
≥12	65 (60.7%)	32 (59.3%)	97 (60.2%)
Gender [n (%)]			
Number	107	54	161
Male	44 (41.1%)	19 (35.2%)	63 (39.1%)
Female	63 (58.9%)	35 (64.8%)	98 (60.9%)
Baseline Height (cm)			
Number	107	54	161
Mean (SD)	149.2 (16.4)	148.5 (15.8)	149.0 (16.2)
Median (Min:Max)	152.0 (114:186)	151.4 (112:181	152.0 (112:186)
Baseline weight (kg)			
Number	107	54	161
Mean (SD)	42.8 (13.7)	41.3 (12.3)	42.3 (13.2)
Median (Min:Max)	42.7 (21:78)	42.1 (19:76)	42.2 (19:78)
Baseline BMI (kg/m2)			
Number	107	54	161
Mean (SD)	18.7 (2.9)	18.2 (2.6)	18.5 (2.8)
Median (Min:Max)	18.1 (14:27)	17.8 (14:26)	18.1 (14:27)
Randomisation strata of screening HbA1c (%) [n (%)]			
Number	107	54	161
<9%	48 (44.9%)	23 (42.6%)	71 (44.1%)
≥9%	59 (55.1%)	31 (57.4%)	90 (55.9%)
Duration of diabetes (years)			
Number	107	54	161
Mean (SD)	3.83 (2.93)	3.55 (2.25)	3.74 (2.71)
Median (Min:Max)	2.53 (1.0:12.4)	2.93 (1.0:9.6)	2.65 (1.0:12.4)
Tanner puberty stage [n (%)]			
Number	107	54	161
Stage 1	30 (28.0%)	12 (22.2%)	42 (26.1%)
Stage 2	14 (13.1%)	10 (18.5%)	24 (14.9%)
Stage 3	16 (15.0%)	12 (22.2%)	28 (17.4%)
Stage 4	33 (30.8%)	16 (29.6%)	49 (30.4%)
Stage 5	14 (13.1%)	4 (7.4%)	18 (11.2%)

Table 3: Baseline efficacy variables - mITT population

	Lantus (N=107)	NPH (N=54)	All (N=161)
HbA1c (%)			
Number	107	54	161
Mean (SD)	8.87 (1.21)	9.12 (1.29)	8.96 (1.24)
Median (Min:Max)	8.90 (6.6:12.3)	8.90 (7.1:11.8)	8.90 (6.6:12.3)
FBG			
Number	105	52	157
Mean (SD)	10.38 (3.38)	10.20 (2.75)	10.32 (3.18)
Median (Min:Max)	10.08 (3.4:20.4)	10.59 (4.2:17.8)	10.13 (3.4:20.4)
Daily total insulin dose			
Number	107	54	161
Mean (SD)	35.47 (14.86)	35.81 (15.22)	35.58 (14.93)
Median (Min:Max)	32.71 (9.3:76.5)	36.36 (7.9:78.0)	33.57 (7.9:78.0)
Daily basal insulin dose			
Number	107	54	161
Mean (SD)	12.35 (5.79)	12.89 (6.13)	12.53 (5.89)
Median (Min:Max)	11.43 (4.0:30.0)	11.77 (1.9:30.6)	11.71 (1.9:30.6)
Daily total insulin dose by weight			
Number	107	54	161
Mean (SD)	0.84 (0.23)	0.87 (0.29)	0.85 (0.25)
Median (Min:Max)	0.82 (0.3:1.4)	0.82 (0.3:1.6)	0.82 (0.3:1.6)
Daily basal insulin dose by weight			
Number	107	54	161
Mean (SD)	0.29 (0.09)	0.31 (0.12)	0.30 (0.10)
Median (Min:Max)	0.28 (0.1:0.5)	0.32 (0.1:0.6)	0.29 (0.1:0.6)
Daily bolus insulin dose (U)			
Number	107	53	160
Mean (SD)	23.29 (10.28)	23.61 (11.21)	23.40 (10.56
Median (Min:Max)	20.71 (5.3:52.9)	21.29 (6.0:58.0)	20.93 (5.3:58.0)
Daily bolus insulin dose by weight			
Number	107	53	160
Mean (SD)	0.55 (0.18)	0.57 (0.23)	0.56 (0.20)
Median (Min:Max)	0.53 (0.1:1.1)	0.53 (0.2:1.2)	0.53 (0.1:1.2)

2.3.2.2. Efficacy results

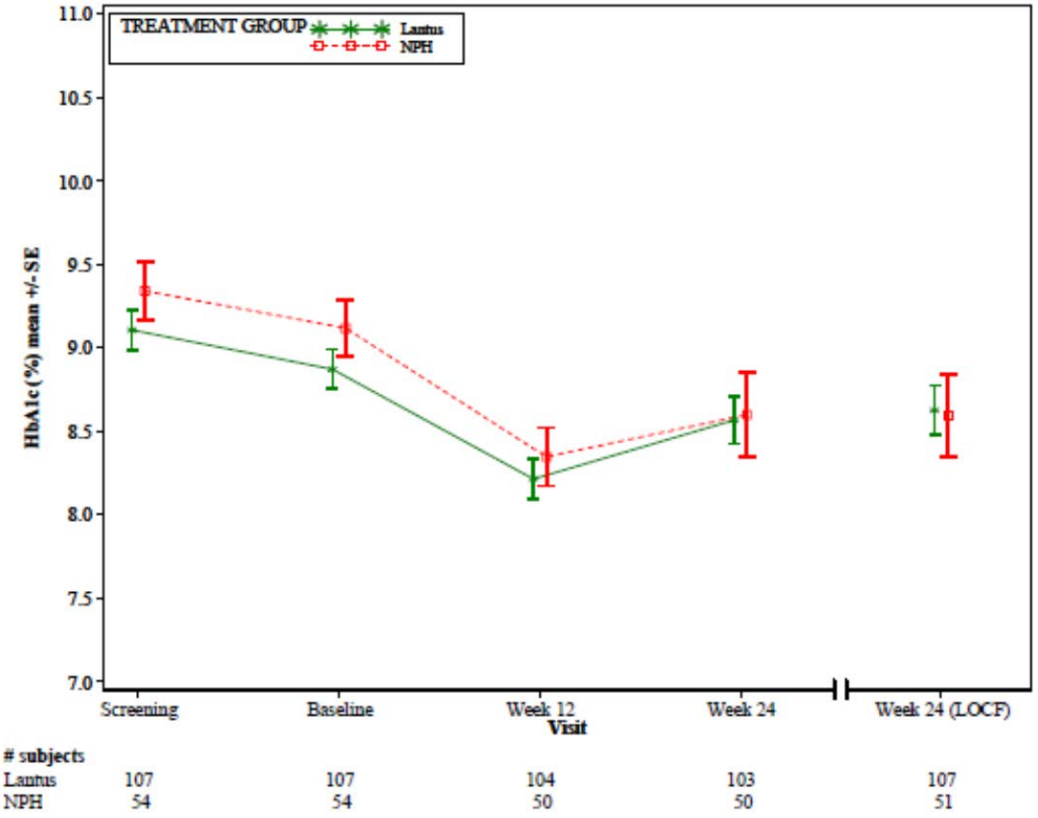
2.3.2.2.1. Primary endpoint

Results for HbA1c are shown in Table 4 and Figure 1.
From baseline to the end of study (Week 24 [LOCF]), mean and median changes in HbA1c were -0.25% and -0.50%, respectively, in the Lantus group, and -0.54% and -0.40%, respectively, in the NPH group.
After 24 weeks Lantus and NPH groups reached similar level of glycaemic control (Lantus: 8.63%; NPH: 8.59%). Of note, Lantus group presented with a low baseline HbA1c in comparison to NPH group.

Table 4: Change in HbA1c (%) from baseline - mITT population

	Lantus (N=107)	NPH (N=54)
Baseline HbA1c (%)		
Number	107	54
Mean (SD)	8.87 (1.21)	9.12 (1.29)
Median (Min:Max)	8.90 (6.6:12.3)	8.90 (7.1:11.8)
Week 24 HbA1c (%)		
Number	107	51
Mean (SD)	8.63 (1.54)	8.59 (1.79)
Median (Min:Max)	8.4 (5.8:13.5)	8.3 (4.5:14.7)
Change from baseline		
Number	107	51
Mean (SD)	-0.25 (1.68)	-0.54 (1.67)
Median (Min:Max)	-0.50 (-4.7:+6.6)	-0.40 (-5.0:+3.6)

Figure 1: Plot of mean HbA1c (%) by visit - mITT population



LOCF = Last observation carried forward.
Note: The analysis excluded measurements obtained after the treatment cessation plus 14 days.
For Week 24 (LOCF), the analysis included measurements obtained up to 14 days after the last dose of the IMP injection.

2.3.2.2.2. Secondary efficacy endpoints

The percentage of patients reaching ISPAD target of HbA1c <7.5% at Week 24 in the Lantus group was 18.7% (20/107), in the NPH group 21.6% (11/51). Post-hoc analyses revealed that 52.3% (56/107) of the patients in the Lantus group and 51.0% (26/51) of the patients in the NPH group had an HbA1c 7.5%≤HbA1c≤9%, while 29% (31/107) of the patients in the Lantus group and 27.4% (14/51) of the patients in the NPH group had an HbA1c >9%.
At Week 24 (LOCF), mean FBG decreased from baseline (0.76 mmol/L) in the Lantus group while increased (1.07 mmol/L) in the NPH group.
In Lantus group, the nocturnal blood glucose (measured at 3:00 AM of SMBG) had remained stable throughout the study, whereas NPH was noted to be fluctuating.
In Lantus group, the 8-point SMBG appeared less fluctuating throughout the day as compared to NPH group.

From baseline to Week 24 (LOCF), the mean **daily total insulin dose** was increased by 6.22 U to 41.69 U in the Lantus group and by 11.51 U to 47.49 U in the NPH group.
Additional analysis on the changes in daily total insulin dose by weight was done after database lock. From baseline to Week 24 (LOCF), the mean daily total insulin dose by weight was increased by 0.072 U/kg to 0.907 U/kg in the Lantus group and by 0.189 U/kg to 1.064 U/kg in the NPH group.

From baseline to Week 24 (LOCF), the mean **daily basal insulin dose** was increased by 2.03 U to 14.37 U for Lantus and by 6.10 IU to 19.02 IU for NPH. Additional analysis on the changes in daily basal insulin dose by weight showed that the mean daily basal insulin dose was increased by 0.024 U/kg to 0.312 U/kg for Lantus and by 0.112 IU/kg to 0.427 IU/kg for NPH.

Additional analyses on changes in **daily bolus insulin dose** and changes in daily bolus insulin dose by weight were done after database lock. From baseline to Week 24 (LOCF), the mean daily bolus insulin dose was increased by 4.07 U (0.05 U/kg) to 27.37 U (0.60 U/kg) in the Lantus group and by 4.75 U (0.06 U/kg) to 28.47 U (0.64 U/kg) in the NPH group.

Table 5: Mean change (SD) in daily insulin dose from baseline to week 24 – mITT population

Insulin dose	Lantus (N=107)	NPH (N=53)	Lantus (N=107)	NPH (N=53)
	Mean change from baseline (SD)		Mean dose at week 24 (SD)	
Daily **total** insulin dose (U)	6.22 (7.54)	11.51 (12.06)	41.69 (17.43)	47.49 (20.35)
Daily total insulin dose by weight (U/kg)	0.072 (0.160)	0.189 (0.257)	0.907 (0.245)	1.064 (0.319)
Daily **basa**l insulin dose (U)	2.03 (3.36)	6.10 (7.09)	14.37 (6.30)	19.02 (9.76)
Daily basal insulin dose by weight (U/kg)	0.024 (0.066)	0.112 (0.136)	0.312 (0.094)	0.427 (0.164)
Daily **bolus** insulin dose (U)	4.07 (5.52)	4.75 (7.07)	27.37 (12.28)	28.47 (13.11)
Daily bolus insulin dose by weight (U/kg)	0.05 (0.12)	0.06 (0.17)	0.60 (0.19)	0.64 (0.23)

In summary, Lantus was effective as basal insulin in the basal + bolus treatment regimen in Chinese patients with T1DM aged at least 6 years to less than 18 years. Both Lantus and NPH insulin improved the glucose control as measured by HbA1c change from baseline to Week 24 and reached similar HbA1c level. In addition, Lantus also provided satisfactory FBG reduction, and stable nocturnal BG and daily SMBG profiles.

2.3.3. Discussion

On request of the China Food and Drug Administration the MAH conducted a phase 3 clinical study in Chinese children with T1DM aged at least 6 to less than 18 years to support the indication proposed to China. In this study, Lantus once daily was compared to NPH insulin in effect on HbA1c after 24 weeks of treatment. Eligible patients were randomised in a 2:1 manner (Lantus:NPH), and randomisation was stratified both by baseline age (<12 years, ≥12 years) and by screening HbA1c (<9%, ≥9%).
The study was aimed to document the efficacy and safety for the use of Lantus (insulin glargine) or NPH but not to test a specific hypothesis.

A total of 196 patients were screened, and 162 patients were randomised to insulin glargine treatment group (Lantus) or NPH insulin treatment group (NPH) in a 2:1 ratio.
Demographic data and baseline characteristics were fairly similar between treatment groups. Baseline HbA1c was somewhat lower in the Lantus group (8.87 vs 9.12 respectively). After 24 weeks HbA1c was decreased in both treatment groups. Mean decrease was lower in the Lantus group (-0.25 vs -0.54%) while median decrease was comparable (-0.50 v -0.40%). Final HbA1c was similar in both groups (8.63 vs 8.59%).

Mean FBG decreased in the Lantus group (-0.76 mmol/L) while increased (1.07 mmol/L) in the NPH group from baseline to Week 24 (LOCF). The difference could be explained by the peak effect of NPH at around 4 to 6 h after injection, while Lantus offered a more stable level of blood glucose control. Bedtime NPH insulin might not have been able to up titrate enough due to the concern of nocturnal hypoglycaemia events, and insufficient basal insulin supply possibly have led to the increase of FBG in the NPH group. In order to compensate this insufficient basal insulin supply, twice-daily NPH insulin or higher dose of bolus insulin could have been used. This is consistent with the finding that Lantus group had a lower dose increased in their mean daily basal, bolus, and total insulin as compared to NPH group, since the basal insulin dose titration mainly depended on the FBG. Similar results were also observed when the insulin doses were divided by body weight.

From these results it can be concluded that Lantus is effective in this Chinese paediatric population.

2.4. Clinical safety aspects

2.4.1. Methods – analysis of data submitted

The safety and tolerability of Lantus versus NPH insulin were assessed based on: rates of all hypoglycaemia (including both asymptomatic and symptomatic hypoglycaemia), symptomatic, asymptomatic, severe symptomatic, nocturnal and nocturnal symptomatic hypoglycaemia during 24-week treatment period, the occurrence of TEAEs, other safety assessments, including laboratories, vital signs, height and weight, and physical examination findings.

2.4.1.1. Definitions of hypoglycaemia

Hypoglycaemia was classified according to the following definitions:

- Asymptomatic hypoglycaemia: Blood glucose values <70 mg/dL (3.9 mmol/L) without clinical symptoms and/or signs validated by site based on data from patient diaries.

- Symptomatic hypoglycaemia: Any event with clinical symptoms that were considered to result from a hypoglycaemic episode with an accompanying blood glucose <70 mg/dL (3.9 mmol/L) validated by site based on data from patient diaries.

- Severe symptomatic hypoglycaemia: Any event with clinical symptoms considered to result from a hypoglycaemic episode for which the subjects required the assistance of a third party (ie, other than the patient or a parent/usual caregiver, eg, from emergency personnel) because the subjects/parents could not treat the event, with acute neurological impairment directly resulting from the hypoglycaemic event.

- Nocturnal hypoglycaemia: Any asymptomatic and/or symptomatic hypoglycaemic event that occurred between 23:00 to 07:00 hours.

- Nocturnal symptomatic hypoglycaemia: Any symptomatic hypoglycaemic event that occurred between 23:00 to 07:00 hours.

2.4.1.2. Analysis

The safety analysis was conducted on the safety population, defined as all randomized patients who did actually receive at least one dose or partial of a dose of study drug analysed according to the treatment actually received.

The event rate of hypoglycaemia was defined as the total number of episodes divided by the total duration from the first dose of IMP up to 24 hours after the last dose of IMP.

The incidence rate of hypoglycaemia was defined as the total number of patients with at least one episode from the first dose of IMP up to 24 hours after the last dose of IMP divided by the total number of patients in the safety population.

The on-treatment period for other safety variables was defined as the time from the first dose of IMP up to 7 days after the last dose of IMP administration. The TEAEs were defined as adverse events that developed or worsened (according to the investigator's opinion) or became serious during the on-treatment period.

Anti-insulin glargine antibody (AGA) and anti-insulin antibody (AIA) status and titre were assessed at screening, Week 4, and Week 24.

2.4.2. Results

2.4.2.1. Exposure

Amongst the 162 randomized patients, 161 patients (99.4%) were exposed to the study treatment (107 on Lantus and 54 on NPH) and were evaluated for safety.
The cumulative duration of treatment exposure was 49.1 patient years in the Lantus group and 23.3 patient years in the NPH group. The mean duration of study treatment was 167.5 days for Lantus group and 157.6 days for NPH group. The majority of patients (106 [99.1%] patients in the Lantus group and 50 [92.6%] patients) had at least 141 days of treatment exposure.

2.4.2.2. Hypoglycaemia

Hypoglycaemia events were documented on a specific hypoglycaemia event form. They were summarized separately from TEAEs.
Table 6 and Table 7 summarise the percentage of patients with hypoglycaemia (incidence rate) and the event rate of hypoglycaemia.

Over the 24-week on-treatment period, 99 [92.5%] patients in the Lantus group and 51 [94.4%] patients in the NPH group experienced at least one episode of **hypoglycaemia**. The number of all hypoglycaemia events per patient year was 68.63 in the Lantus group and 84.58 in the NPH group.

The number of patients and number of events per patient year for **symptomatic hypoglycaemia** was 74 (69.2%) patients with 24.27 events/PY in the Lantus group, and 41 (75.9%) patients with 32.32 events/PY in the NPH group.

Asymptomatic hypoglycaemia was observed in 93 (86.9%) patients in the Lantus group and 47 (87.0%) patients in the NPH group. The number of asymptomatic hypoglycaemia events per patient year was 44.36 in the Lantus group and 52.27 in the NPH group.

The occurrence of **severe symptomatic hypoglycaemia** was rare in both groups. Over the 24-week on-treatment period, 1 (0.9%) patient in the Lantus group and 1 (1.9%) patient in the NPH group each experienced one episode of severe symptomatic hypoglycaemia.

Nocturnal hypoglycaemia was observed in 83 (77.6%) patients in the Lantus group and 42 (77.8%) patients in the NPH group. The number of symptomatic hypoglycaemia events per patient year was 12.97 in the Lantus group and 14.19 in the NPH group.

Forty (40 [37.4%]) patients in the Lantus group and 25 (46.3%) patients in the NPH group experienced at least one episode of **symptomatic nocturnal hypoglycaemia**. The number of nocturnal symptomatic hypoglycaemia events per patient year was 3.58 in the Lantus group and 4.52 in the NPH group.

Table 6: Overview of patients with hypoglycaemia during the on-treatment period – Safety population

Type	Lantus (N=107)	NPH (N=54)
Patients with any hypoglycaemia	99 (92.5%)	51 (94.4%)
Patients with any symptomatic hypoglycaemia	74 (69.2%)	41 (75.9%)
Patients with any asymptomatic hypoglycaemia	93 (86.9%)	47 (87.0%)
Patients with any severe symptomatic hypoglycaemia	1 (0.9%)	1 (1.9%)
Patients with any nocturnal hypoglycaemia	83 (77.6%)	42 (77.8%)
Patients with any nocturnal symptomatic hypoglycaemia	40 (37.4%)	25 (46.3%)

Symptomatic hypoglycaemia = symptomatic hypoglycaemia as defined per protocol.
On-treatment period = the time from the first dose of study medication up to 1 day after the last dose administration.

Table 7: Summary of hypoglycaemia events during the on-treatment period – Safety population

Type	Lantus (N=107)	NPH (N=54)
All hypoglycaemia		
Number of events	3371	2064
Number of events per patient year (SD)[a]	68.63 (69.40)	84.58 (79.25)
Symptomatic hypoglycaemia		
Number of events	1193	790
Number of events per patient year (SD)[a]	24.27 (45.76)	32.32 (43.23)
Asymptomatic hypoglycaemia		

Number of events	2178	1274
Number of events per patient year (SD)[a]	44.36 (48.66)	52.27 (65.28)
Severe symptomatic hypoglycaemia		
Number of events	1	1
Number of events per patient year (SD)[a]	0.02 (0.20)	0.04 (0.31)
Nocturnal hypoglycaemia		
Number of events	637	349
Number of events per patient year (SD)[a]	12.97 (15.03)	14.19 (16.85)
Nocturnal symptomatic hypoglycaemia		
Number of events	176	108
Number of events per patient year (SD)[a]	3.58 (7.31)	4.52 (7.44)

[a] Calculated as the total number of episodes divided by the total duration from the first dose of IP up to 24 hours after the last dose of IMP in years.
On-treatment period = the time from the first dose of study medication up to 1 day after the last dose administration.

2.4.2.3. Adverse events

Over the 24-week on-treatment period, 88/107 (82.2%) patients in the Lantus group and 46/54 (85.2%) patients in the NPH group reported at least one TEAE (Table 8). The most common TEAE by System Organ Class (SOC) was metabolism and nutrition disorders, as reported by 78 (72.9%) patients in the Lantus group and 41 (75.9%) patients in the NPH group. The secondly most common TEAE by SOC was infections and infestations in both treatment groups, as reported by 47 (43.9%) patients in the Lantus group and 27 (50.0%) patients in the NPH group. Common TEAE by preferred term (PT), as reported by more than 5% of the patients in any treatment group included hypoglycaemia (Lantus: 74 [69.2%] patients versus NPH: 41 [75.9%] patients), nasopharyngitis (Lantus: 28 [26.2%] patients versus NPH: 17 [31.5%] patients), upper respiratory tract infection (Lantus: 18 [16.8%] patients versus NPH: 11 [20.4%] patients), diabetic ketoacidosis (Lantus: 2 [1.9%] patients versus NPH: 4 [7.4%] patients), and oropharyngeal pain (Lantus: 3 [2.8%] patients versus NPH: 3 [5.6%] patients).

Treatment-emergent adverse events related to the IMP were reported in 37 (34.6%) patients in the Lantus group and 24 (44.4%) patients in the NPH group. The most common TEAE related to the IMP by PT was hypoglycaemia, as reported by 36 (33.6%) patients in the Lantus group and 22 (40.7%) patients in the NPH group. Other TEAEs related to the IMP included overweight, which occurred in 1 (0.9%) patient in the Lantus group and 1 (1.9%) patient in the NPH group, and dizziness, hunger, injection site swelling, blood glucose increased, each occurring in 1 (1.9%) patient in the NPH group.

A total of 9 patients reported 10 serious TEAEs, including 4 events in 3 (2.8%) patients in the Lantus group and 6 events in 6 (11.1%) patients in the NPH group. The most common serious TEAE by SOC was metabolism and nutrition disorders, including 5 events of diabetic ketoacidosis (reported by 2 [1.9%] patients in the Lantus group and 3 [5.6%] patients in the NPH group) and 1 event of hypoglycaemia (1 [1.9%] patient in the NPH group). All patients recovered from the serious TEAEs after receiving corrective treatment. One serious TEAE was considered by the Investigators as related to study treatment and led to treatment discontinuation: 1 blood glucose increased in 1 patient on NPH.

No death was observed in both treatment groups during the on-treatment period.

Overall injection site and hypersensitivity reactions during the on-treatment period reported in the Lantus group was 1/107 (0.9%) versus 4/54 (7.4%) in the NPH group.

Table 8: Number (%) of patients with TEAE(s) ≥ 2% in any group, presented by primary SOC – Safety population

	Lantus		NPH	
Primary system organ class	**(N=107)**		**(N=54)**	
Any class	88	82.2%	46	85.2%
Infections and infestations	47	43.9%	27	50.0%
Nasopharyngitis	28	26.2%	17	31.51%
Upper respiratory tract infection	18	16.8%	11	20.4%
Blood and lymphatic system disorders	3	2.8%	1	1.9%
Metabolism and nutrition disorders	78	72.9%	41	75.9%
Hypoglycaemia	74	69.2%	41	75.9%
Diabetic ketoacidosis	2	1.9%	4	7.4%
Psychiatric disorders	1	0.9%	2	3.7%
Nervous system disorders	0		3	5.6%
Respiratory, thoracic and mediastinal disorders	6	5.6%	4	7.4%
Gastrointestinal disorders	10	9.3%	6	11.1%
Skin and subcutaneous tissue disorders	1	0.9%	3	5.6%
General disorders and administration site conditions	5	4.7%	7	13.0%
Investigations	5	4.7%	3	5.6%
Injury, poisoning and procedural complications	4	3.7%	4	7.4%

2.4.2.4. Laboratory values, vital signs

Descriptive statistics were provided for red blood cells and platelets, for white blood cells, for metabolic parameters, for electrolytes, for renal function, and for liver function. There were no relevant changes in mean values over time for any of the parameters in either treatment group. In addition, there were no relevant changes in mean values over time for blood pressure and heart rate in either treatment group.
At Week 24, the mean body weight was 45.62 kg in the Lantus group and 43.58 kg in the NPH group. The weight gain from baseline was 3.05 kg in the Lantus group and 2.82 kg in the NPH group.

2.4.2.5. Anti-insulin glargine and anti-insulin antibodies

At screening, 69.2% (74/107) and 60.7% (65/107) of the patients randomized to Lantus group were AGA and AIA positive, respectively, versus 78.2% (43/55) and 69.1% (38/55) of the patients in the NPH group (Table 9). From screening to Week 24, in the Lantus group the incidence of patients with positive AGA and AIA status decreased, both by 4.1%. In the NPH insulin group the number of AIA positive patients increased by 6.9% while the number of AGA positive patients remained at the screening level. Overall, the incidence of antibody positive patients was lower in the Lantus group compared to the NPH group at Week 24 (end of treatment). During the 24-week on-treatment period only small changes in AGA and AIA titres were observed for both treatment groups.

Table 9: Summary of Anti-insulin glargine antibody (AGA) status and Anti-insulin antibody (AIA) status by visit - Antibody population

Antibody status	Lantus (N=107)	NPH (N=54)
AGA status		
Screening		
Negative	33/107 (30.8%)	12/55 (21.8%)
Positive	74/107 (69.2%)	43/55 (78.2%)
Week 24		
Negative	37/106 (34.9%)	11/50 (22.0%)
Positive	69/106 (65.1%)	39/50 (78.0%)
Shift from Negative at Screening to Positive	7/32 (21.9%)	5/10 (50.0%)
Shift from Positive at Screening to Negative	12/74 (16.2%)	6/40 (15.0%)
AIA status		
Screening		
Negative	42/107 (39.3%)	17/55 (30.9%)
Positive	65/107 (60.7%)	38/55 (69.1%)
Week 24		
Negative	46/106 (43.4%)	11/50 (22.0%)
Positive	60/106 (56.6%)	38/50 (76.0%)
Shift from Negative at Screening to Positive	5/41 (12.2%)	5/14 (35.7%)
Shift from Positive at Screening to Negative	10/65 (15.4%)	2/35 (5.7%)

2.4.3. Discussion

No unexpected safety issues were detected. Both Lantus and NPH insulin were safe and well tolerated during the 24-week on-treatment period. There was a consistent trend of lower event rate in the Lantus group for all categories of hypoglycaemia. There were no relevant differences in TEAEs, laboratory values or vital signs.

2.5. Changes to the product information

The MAH does not propose any changes to the product information.

3. Overall conclusion and impact on the benefit/risk balance

On request of the China Food and Drug Administration the MAH conducted a phase 3 clinical study in Chinese children with T1DM aged at least 6 to less than 18 years to support the indication proposed to China. In this study, Lantus once daily was compared to NPH insulin in effect on HbA1c after 24 weeks of treatment. Eligible patients were randomised in a 2:1 manner (Lantus:NPH), and randomisation was stratified both by baseline age (<12 years, ≥12 years) and by screening HbA1c (<9%, ≥9%).

The study was aimed to document the efficacy and safety for the use of Lantus (insulin glargine) or NPH but not to test a specific hypothesis.

A total of 196 patients were screened, and 162 patients were randomised to insulin glargine treatment group (Lantus) or NPH insulin treatment group (NPH).

Demographic data and baseline characteristics were fairly similar between treatment groups. Baseline HbA1c was somewhat lower in the Lantus group (8.87 vs 9.12 respectively). After 24 weeks HbA1c was decreased in both treatment groups. Mean decrease was lower in the Lantus group (-0.25 vs -0.54%) while median decrease was comparable (-0.50 v -0.40%). Final HbA1c was similar in both groups (8.63 vs 8.59%). No detailed information on the demographics of the PK subpopulation was provided. This information should be submitted to show that a representative subpopulation was selected for the assessment of the pharmacokinetic parameters.

Mean FBG decreased in the Lantus group (-0.76 mmol/L) while increased (1.07 mmol/L) in the NPH group from baseline to Week 24 (LOCF). The difference could be explained by the peak effect of NPH at around 4 to 6 h after injection, while Lantus offered a more stable level of blood glucose control. Bedtime NPH insulin might not have been able to up titrate enough due to the concern of nocturnal hypoglycaemia events, and insufficient basal insulin supply possibly have led to the increase of FBG in the NPH group. In order to compensate this insufficient basal insulin supply, twice-daily NPH insulin or higher dose of bolus insulin could have been used. This is consistent with the finding that Lantus group had a lower dose increased in their mean daily basal, bolus, and total insulin as compared to NPH group, since the basal insulin dose titration mainly depended on the FBG. Similar results were also observed when the insulin doses were divided by body weight.

Safety analysis did not reveal any new or unexpected issue. Both Lantus and NPH insulin were safe and well tolerated during the 24-week on-treatment period. There was a consistent trend of lower event rate in the Lantus group for all categories of hypoglycaemia. There were no relevant differences in TEAEs, laboratory values or vital signs.

No accumulation of insulin glargine (parent compound) or insulin glargine metabolites M1 or M2 was observed after repeated dosing of Lantus® in children.

The MAH considers that in the context of this submission, no amendments to SmPC, labelling and/or Package Leaflet of Lantus are warranted based on the review of the data on PD, PK and safety of EFC11681 Study. This can be endorsed.

4. Request for supplementary information

4.1. Major objection

None.

4.2. Other concerns

1. The company should provide detailed information on the demographics of the PK subpopulation to show that a representative subpopulation was selected.

5. Rapporteur's assessment of MAH responses to RSI

Question

The company should provide detailed information on the demographics of the PK subpopulation to show that a representative subpopulation was selected.

Summary of the Applicant's Response

The PK population was defined as all randomized patients who were treated with Lantus and contributed at least the minimum required volume of plasma at Weeks 1, 2, and 4 and who had no major pharmacokinetic protocol violations. This subpopulation included 40 patients.

The detailed information on the demographics of the PK subpopulation is provided below.

SANOFI considers the PK subpopulation representative of the target pediatric population.

Table 1 - Demographics and patient characteristics at baseline - PK population

	Lantus(N=40)
Age (years)	
Number	40
Mean (SD)	11.1 (3.0)
Median	11.5
Min : Max	6 : 17
Age Group (years) [n(%)]	
Number 40	
<12	20 (50.0%)
.12	20 (50.0%)
Gender [n (%)]	
Number	40
Male	14 (35.0%)
Female	26 (65.0%)
Baseline Height (cm)	
Number	40
Mean (SD)	145.9 (16.4)
Median	146.7
Min : Max	117 : 172
Baseline weight (kg)	
Number	40
Mean (SD)	39.6 (12.8)
Median	40.4
Min : Max	21 : 70
Baseline BMI (kg/m2)	
Number	40
Mean (SD)	18.0 (2.5)
Median	17.9
Min : Max	14 : 24
Randomization strata of screening HbA1c (%) [n (%)]	
Number	40
<9%	18 (45.0%)
.9%	22 (55.0%)
Randomization strata of age [n (%)]	
Number	40
<12	20 (50.0%)
.12	20 (50.0%)
Tanner puberty stage [n (%)]	
Number	40
Stage 1	12 (30.0%)
Stage 2	5 (12.5%)
Stage 3	12 (30.0%)
Stage 4	4 (10.0%)
Stage 5	7 (17.5%)

Assessment of the Applicant's Response

PK subpopulation is considered representative of the target pediatric population (children with type 1 diabetes mellitus aged at least 6 years to less than 18 years).

Conclusion

Issue resolved.

6. Updated overall conclusion and impact on the benefit-risk balance

Based on the review of the data on safety and efficacy, the Rapporteur considers that the submitted documentation for Lantus (insulin glargine), in the treatment of diabetes mellitus in adults, adolescents and children aged 2 years and above, did not reveal any new or unexpected issues.

No amendments to SmPC, labelling and/or Package Leaflet of Lantus are warranted based on the review of the data on PD, PK and safety of Study EFC11681. There are no outstanding issues.