EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Lantus

insulin glargine

Procedure No.: EMEA/H/C/000284/II/0075

Note

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

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LIST OF ABBREVIATIONS

Ab	antibody
AE	adverse event
AIA	anti-insulin antibodies
BG	blood glucose
BID	twice daily
CGM	Continuous Glucose Monitoring
CGMS	Continuous Glucose Monitoring System
CI	confidence interval
EMA	European Medicines Agency
FSBG	fingerstick blood glucose
GCP	Good Clinical Practice
HbA1c	glycated hemoglobin A1c
IP	investigational product
ISPAD	International Society for Pediatric and Adolescent Diabetes
LOQ	limit of quantification
MAH	Marketing Organisation Holder
MDI	multiple daily injection (insulin treatment)
mITT	modified intent-to-treat (population)
NPH	Neutral Protamine Hagedorn (insulin)
PDCO	Paediatric Committee (of the European Medicines Agency)
PD	pharmacodynamic(s)
PIP	Pediatric Investigational Plan
PK	pharmacokinetic(s)
QD	once daily
SC	subcutaneous(ly)
SD	standard deviation
SOC	System Organ Class
SmPC	Summary of Product Characteristics
T1DM	type 1 diabetes mellitus
TEAE	treatment-emergent adverse event
U	unit

1. Scientific discussion

1.1. Introduction

Insulin glargine is 21A-Gly-31B-32B-Di-Arg human insulin, a recombinant (Escherichia coli [E coli]) analog of human insulin. Insulin glargine can be considered a 21A-Gly substituted analog of 31B-32B-Di-Arg human insulin, a final intermediate of the maturation of proinsulin to human insulin.

Insulin glargine is indicated for the treatment of adults, adolescents, and children of 6 years or above with diabetes mellitus, where treatment with insulin is required.

Approval for the marketing of insulin glargine was granted in June 2000 in Europe. Lantus (insulin glargine) is currently registered and marketed in more than 100 countries worldwide.

The MAH is requesting an indication extension for Lantus for paediatric population age 1 to less than 6 years old. In support of this variation the MAH submitted one Clinical Study EFC11202 (PRESCHOOL). The study design of this trial was developed in light of the recommendation of the Paediatric Committee (PDCO), and to expand the indication of insulin glargine into the preschool age range (age 1 to less than 6 years) of patients with type 1 diabetes mellitus (T1DM). Its design was proposed in the modified Pediatric Investigational Plan (PIP).

1.2. Quality aspects

N/A

1.3. Non-clinical aspects

The applicant claims for Environmental risk assessment (ERA) exemption in conformity with the ERA guideline since the marketing authorization request concerns an analogue of a naturally occurring protein. Insulin glargine is significantly metabolized in-vivo and is expected to be readily and rapidly degraded in wastewater treatment systems and in the environment. The peptide's structure and mode of action do not indicate any specific risk to the environment.

As such, no additional special precautionary and safety measures need to be imposed regarding the environmental release from use in patients or from disposal of unused products or waste material derived from the product.

The CHMP is in agreement with this justification.

1.4. Clinical Pharmacology aspects

1.4.1. Methods – analysis of data submitted and results

In the clinical efficacy and safety study in children aged 1 – 6 years EFC11202 the pharmacokinetics were estimated. It was a 24-weeks study, in which insulin glargine was compared to NPH insulin. For a comprehensive description of the study, see section 2.5.1.
Following randomization, trial basal insulin was initiated and up-titrated within the first 12 weeks to reach a stable dose. Single blood samples were drawn on 3 occasions in Weeks 1, 2, and 4, before dosing in the morning. Free insulin glargine (parent compound) and insulin glargine metabolites M1 and M2 in plasma were determined with a lower limit of quantification (LOQ) of 0.2 ng/mL.
Plasma concentrations were classified as Ctrough values if blood samples were taken prior or at time of insulin glargine dosing at Week 1, Week 2 or Week 4 and if the previous insulin glargine dose was administered 24±6 hours prior to PK blood sampling. Timing of meal time (bolus) insulins were not

taken into consideration, because of the specificity of the bioanalytical assay for insulin glargine parent compound and its metabolites M1 and M2 with no cross-reactivity with other insulins.
Descriptive statistics on Ctrough data for insulin glargine parent compound and metabolites M1 and M2 by visit are summarized in the table below.

Summary of plasma concentrations of insulin glargine parent compound, metabolite M1 and metabolite M2 (Ctrough) by visit

	Plasma concentration [ng/mL]			
Visit	Insulin glargine Parent (P)	Metabolite M1	Metabolite M2	Dose [U/kg]
Week 1				
Number	46	46	46	46
Mean (SEM)	<LOQ	0.580 (0.1159)	<LOQ	0.334 (0.0191)
SD	NC	0.786	NC	0.130
Median	<LOQ	0.287	<LOQ	0.339
Min : Max	<LOQ : 0.52	<LOQ : 3.30	<LOQ : <LOQ	0.13 : 0.76
Geometric mean	NC	NC	NC	0.310
Coefficient of variation	304.1415	135.5101	NC	38.8830
Week 2				
Number	42	42	42	42
Mean (SEM)	<LOQ	0.458 (0.1081)	<LOQ	0.344 (0.0228)
SD	NC	0.700	NC	0.148
Median	<LOQ	0.267	<LOQ	0.334
Min : Max	<LOQ : 0.54	<LOQ : 3.25	<LOQ : 0.43	0.11 : 0.80
Geometric mean	NC	NC	NC	0.314
Coefficient of variation	382.6467	153.0550	477.2293	42.9066
Week 4				
Number	40	40	40	40
Mean (SEM)	<LOQ	0.452 (0.0923)	<LOQ	0.379 (0.0312)
SD	NC	0.583	NC	0.197
Median	<LOQ	0.323	<LOQ	0.351
Min : Max	<LOQ : 0.43	<LOQ : 2.83	<LOQ : 0.29	0.13 : 1.19
Geometric mean	NC	NC	NC	0.339
Coefficient of variation	247.1674	128.9883	632.4555	52.1034

Note: the dose was adjusted by patient's body weight. It was calculated using the dose at the day prior to the PK sampling divided by the nearest body weight measurement available.
Values < LOQ (0.2 ng/mL) were displayed as <LOQ
PGM=PRODOPS/HOE901/EFC11202/CSR_01/REPORT/PGM/cdc_pcconc_t.sas OUT=REPORT/OUTPUT/i_cdc_pcconc_t_i.rtf (06SEP2011 - 5:06)

In study TDR11626, 30 adult patients with type 1 diabetes mellitus (divided into two study cohorts) with an age range 24 – 57 years [mean (SD): 43.3 (8.7) years] were investigated using the identical bioanalytical method. In this study 0.4U/kg of insulin glargine (U100) was used in both cohorts. Trough concentrations were determined at day 1 through 8 (and in addition 24hours after dosing at day 8).

Mean M1 Ctrough values in the two cohorts ranged from 0.288 to 0.521 ng/mL, and after one week of treatment at day 8 mean M1 Ctrough was: 0.437 and 0.455 ng/mL, respectively.

As for the children, parent compound and metabolite M2 were below LLOQ except for only a few individual samples in some patients (in 2 patients for parent compound and 1 patient for M2) that were above LLOQ.

This comparison demonstrates that the plasma concentration pattern in the children (1 – 6 years) is qualitatively and quantitatively similar to the adults.

1.4.2. Discussion

The pharmacokinetic information from this study is considered minimal. The uncertainty in the measured Ctrough values is large with coefficients of variation of more than 150% in the values of the main metabolite M1. This high variability may be due to the variability in dose, the number of clinical sites used in this study. The only conclusion that can be drawn from these results is that there is no accumulation of the main metabolite (M1) of insulin glargine after multiple dosing.

The pharmacokinetic information with respect to the measured Ctrough values in adults and children was provided. From this comparison can be concluded that the trough concentrations are comparable between both groups of patients. However this comparison is considered of low value due to the large variability in both groups.

The statement in the section 5.2 of the proposed SmPC "revealing plasma concentration patterns similar to adults" has been supported.

1.5. Clinical Efficacy aspects

1.5.1. Methods – analysis of data submitted

Study EFC11202 was a 24-Week multinational, multicenter, randomised, open-label, 2 parallel arms, Phase 3b study comparing the efficacy and safety of insulin glargine (Lantus) as basal insulin, administered once daily before breakfast, versus Neutral Protamine Hagedorn (NPH) insulin administered 1 or 2 times daily in children with T1DM aged at least 1 year to less than 6 years.

The study consisted of 3 phases (see figure below): a *screening period* of 2 to 4-weeks; a 24-week *treatment period*; and a *posttreatment observation period* of 2 weeks.

At randomisation (Visit 2), the patients were stratified with respect to their baseline HbA1c level (<8.5% or ≥8.5%) and hypoglycaemic event rate (number of hypoglycaemic excursions <0.5 or ≥0.5 events per 24 hours, measured with Continuous glucose monitoring system (CGMS)).

Following randomisation, trial basal insulin was initiated and up-titrated within the first 12 weeks to reach a stable dose. Patients in both groups received multiple daily injection regimens with insulin lispro or regular human insulin before main meals (snacks) and/or at bedtime.

Inclusion criteria: Children diagnosed with T1DM at least 1 year before the study start (in order to eliminate fluctuating insulin requirements due to the initial period of T1DM), aged 1 to less than 6 years, having HbA1c at screening not >12% and not <6%, and not taking antihyperglycaemic medications other than insulin. Children had also to have been taking MDI insulin treatment for T1DM for at least 2 months.
Study medication: Insulin (both glargine and NPH) dose was titrated to achieve the following International Society for Pediatric and Adolescent Diabetes (ISPAD)-recommended glycaemic targets without hypoglycaemia:

- Fasting BG between 90 and 145 mg/dL (5.0 to 8.0 mmol/L), inclusive,
- Bedtime BG between 120 and 180 mg/dL (6.7 to10.0 mmol/L), inclusive,
- Nocturnal BG between 80 and 162 mg/dL (4.4 to 9.0 mmol/L), inclusive; and
- HbA1c <7.5%.

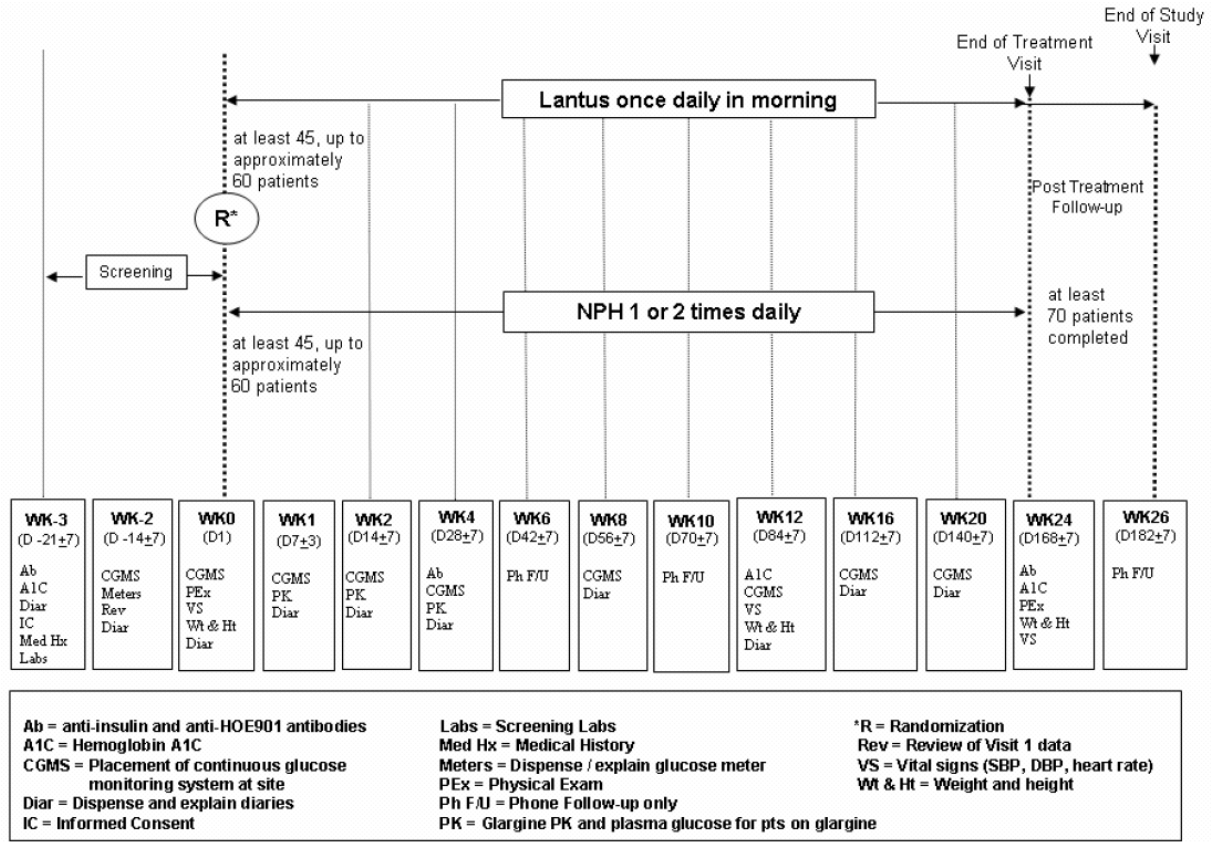
Administration glargine: SC injection once daily (QD) in the morning.

Administration NPH insulin: SC injection QD or twice daily (BID), in the morning and/or at bedtime.

The morning time of injection of insulin glargine was chosen because it has been studied and proven to be just as effective as if given at dinner or bedtime in adults with T1DM (Study HOE901/4007), and because it would permit the in-clinic assessment of insulin glargine PK at "trough" timing relative to the next day's dose (see section III.3.1 Clinical Pharmacology).

For uniformity, lispro insulin was provided as bolus insulin treatment to all patients, although regular human insulin was also allowed as a bolus treatment (though not provided by Sponsor).

Blood glucose registration was performed using a CGMS. A minimum of 6 days of useable glucose values on each of at least 5 occasions during treatment, 2 of which occasions were to occur after Week 14, were to be captured. Furthermore, Fingerstick Blood Glucose (FSBG) values were recorded.



Study design Trial EFC11202

The **primary objective** was to determine the efficacy of insulin glargine dosed in the morning compared to NPH insulin on the rate of "all hypoglycaemia".
Secondary objectives were to assess the effects of insulin glargine versus NPH on HbA1c levels; safety and tolerability; antibodies; and the PK of insulin glargine over the first 4 weeks of treatment.

The **primary variable (endpoint)** was the event rate of "All hypoglycaemia", which consisted of all events occurring in any of the following categories, from the start of treatment with study drug to 24 hours following the last dose of study drug:

- CGMS "low" interstitial glucose excursion (<70 mg/dL (3.9 mmol/L)), confirmed by FSBG measurement within a window from 10 minutes before, to 10 minutes following, the low CGMS excursion (a "low excursion" was a set of any number of consecutive CGM glucose values <70 mg/dL);
- FSBG values <70 mg/dL (3.9 mmol/L); and
- Symptomatic hypoglycaemia episodes

The event rate of "all hypoglycaemia" was defined as the total number of episodes divided by the total duration of the on-treatment period in years (events per patient-year). The on-treatment period for hypoglycaemia was defined as the time from the first dose of investigational product (IP) up to 24 hours after the last dose of IP.
A rule was applied to these events to prevent double-counting, eg, a FSBG value <70 mg/dL that confirmed a low CGM excursion would not count a second time in the primary outcome as a low FSBG value. No primary outcome event could occur within one hour of an earlier primary outcome event.

Secondary efficacy variables included: Rates of symptomatic, severe, nocturnal, nocturnal symptomatic, and severe nocturnal symptomatic hypoglycaemia; HbA1c at 26 weeks; Percentage of patients reaching HbA1c <7.5% at 26 weeks; Average daily BG at 26 weeks, based on CGMS values; Percent of BG within the range of 70 – 180 mg/dL (3.9-10 mmol/L), based on CGMS; Average daily BG, based on CGMS; Blood glucose variability (mean of individual standard deviations [SD] for all CGMS interstitial glucose values); and nocturnal BG variability.
Safety variables Adverse events (primarily, treatment-emergent adverse events [TEAEs]), changes in vital signs and physical examination, and anti-insulin antibodies (AIA) status and titer/binding at screening and Weeks 4 and 24 to assess percent conversion from negative to positive.

Statistical methods: The efficacy analysis population consisted of all randomised patients who received at least one dose of the study medication (modified intent-to-treat population). The primary analysis investigated the event rate of "all hypoglycaemia" during on-treatment period. The ratio of the mean event rates between treatment groups was estimated using the Generalized Linear Model with fixed effect terms for randomisation strata (baseline CGMS number of hypoglycaemic excursions, and baseline HbA1c) and treatment to compare insulin glargine and NPH insulin.
A stepwise closed testing approach was used for the primary analysis to assess non-inferiority and superiority sequentially.
Non-inferiority would be demonstrated if the upper bound of the 95% confidence interval (CI) for the ratio of the rate of all hypoglycaemia in the glargine group to the rate in the NPH group was <1.15. If non-inferiority was demonstrated, superiority would be tested. The tests for the primary endpoint were to be performed one-sided at level $\alpha = 0.025$. The sample size calculation was based on an expected overall rate of "all hypoglycaemia" of 80 events/patient-year of exposure to NPH insulin and 80 events/patient-year of exposure to insulin glargine. Under this assumption, it was expected that a **sample size** of 70 patients total (ie, 35 patients in each treatment group) would provide adequate power to demonstrate that glargine was at least non-inferior to NPH. It was planned to randomise at least 45 and up to approximately 60 patients in each of the 2 treatment groups, so that at least 70 patients would complete the 24 weeks of treatment.

This study was conducted in *61 centers* (*72* were initiated) in 16 countries. In total, 54 patients were enrolled from European countries.

A total of 165 patients were screened and 125 were randomised to treatment with insulin glargine or NPH insulin in a 1:1 ratio. Forty patients (24.2%) failed the screening selection process, mainly due to

noncompliance with the study required CGM performance and other procedures (17.9%). Out of 125 randomised patients, 61 were randomised to insulin glargine and 64 to NPH insulin. One patient randomised to the NPH group received insulin glargine. This patient was analyzed in the randomised treatment group (NPH insulin) for efficacy and in the actually exposed treatment group (insulin glargine) for safety.

Table below summarises the patient disposition for each treatment group. A total of 111 patients completed the 24-week study treatment: 57 (93.4%) patients treated with insulin glargine compared to 54 (84.4%) patients treated with NPH. Among the completers, 99 patients (48 for insulin glargine and 51 for NPH insulin) satisfied the protocol required CGM performance. The mean number of days during treatment that the CGM device was worn in the insulin glargine group was 82.5, versus a mean of 76.2 days in the NPH group.

More patients in the NPH group (10 [15.6%]) than in the insulin glargine group (4 [6.6%]) prematurely discontinued the 24-week study treatment. For both treatment groups, the main reason for treatment discontinuation was "other reasons" (2 [3.3%] for insulin glargine and 6 [9.4%] for NPH insulin), the most common "other reason" being unwillingness to comply with the CGM requirements.

Patient disposition – Randomised population

	Lantus (N=61)	NPH (N=64)
Randomized and treated	61 (100%)	64 (100%)
Patients who completed the study treatment	57 (93.4%)	54 (84.4%)
Patients who completed the study treatment and protocol required CGMs*	48 (78.7%)	51 (79.7%)
Patients who discontinued the study treatment prematurely	4 (6.6%)	10 (15.6%)
Family's request for treatment discontinuation	3 (4.9%)	9 (14.1%)
Reason for treatment discontinuation		
Adverse event	0	2 (3.1%)
Lack of efficacy	0	0
Poor compliance to protocol	1 (1.6%)	2 (3.1%)
Lost to follow-up	1 (1.6%)	0
Other reasons	2 (3.3%)	6 (9.4%)
Status at last study contact		
Alive	61 (100%)	64 (100%)
Dead	0	0
Unknown	0	0

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

* A patient was considered to meet the protocol required number CGMs measurements if he/she has recorded at least 6 days of CGM glucose data on at least 5 separate occasions during treatment, two of which occasions must have occurred after Week 14. A patient was considered as having recorded for at least 6 days of CGM glucose data between two consecutive visits if the number of captured CGM glucose measurements is greater or equal to 1296 between those two consecutive visits.

In twelve patients in the glargine group (19.7%) and in sixteen patients in the NPH group (25%) occurred a stratification error. In total, 14 (23%) irregularities were found in the glargine group, versus 18 (28.1%) irregularities in the NPH group.

As mentioned earlier, one patient randomised to the NPH group received insulin glargine treatment as a result of an IP dispensation error.

Protocol deviations were predefined as "important" or "other" by the clinical study team. Fifteen patients had important protocol deviations: 8 (13.1%) in the insulin glargine group and 7 (10.9%) in the NPH insulin group. Of them, 3 concerned a protocol deviation during screening (one patient had a medical history of primary seizure disorder and 2 patients did not satisfy the 6 days of useable CGM) and 12 deviations concerned the protocol procedures during the treatment period (one patient received a wrong randomisation treatment, 2 patients used different bolus insulin [insulin aspart] and 9 patients had errors for randomisation stratification in the number of low CGM excursions).

Twenty-six (13 in each group including dropouts) out of the 125 randomised patients did not fulfill the protocol-defined on-treatment CGM requirement (≥5 occasions in between-visit intervals, of which 2 occasions had to occur after Week 14; and during each of these occasions, at least 1296 usable CGM glucose values were to be recorded.). These deviations were classified as "other".

The **analysis populations**, as defined by the protocol, are summarised in table below. The efficacy and safety populations of the insulin glargine and NPH insulin groups were of a similar size.

Summary of analysis populations

	Lantus	NPH	All
Randomized/Enrolled population	61 (100%)	64 (100%)	125 (100%)
Efficacy populations			
Modified Intent-to-Treat (mITT)	61 (100%)	64 (100%)	125 (100%)
Safety population	62	63	125
Antibody population	59	55	114
PK Population	62	0	62

Note: The randomized population and mITT population patients are tabulated according to their randomized treatment. For the other populations, patients are tabulated according to treatment actually received.

Baseline characteristics

Demographic characteristics including age, gender, and race were generally comparable between the two treatment groups though small disproportions were present, see table below. Of note, more children (17 [26.6%]) aged 3 years or younger were in the NPH group than in the glargine group (10 [16.4%]), and there was a greater percentage of Asian/Oriental patients (11 [17.2%]) in the NPH group than in the insulin glargine group (4 [6.6%]).

Demographics and patient characteristics at baseline – Randomised population

	Lantus (N=61)	NPH (N=64)	All (N=125)
Age (years)			
Number	61	64	125
Mean (SD)	4.3 (0.9)	4.1 (1.0)	4.2 (1.0)
Median	5.0	4.0	4.0
Min : Max	2 : 5	1 : 6	1 : 6
Age group (years) [n (%)]			
Number	61	64	125
≤3	10 (16.4%)	17 (26.6%)	27 (21.6%)
>3	51 (83.6%)	47 (73.4%)	98 (78.4%)
Sex [n (%)]			
Number	61	64	125
Male	32 (52.5%)	30 (46.9%)	62 (49.6%)
Female	29 (47.5%)	34 (53.1%)	63 (50.4%)
Race [n (%)]			
Number	61	64	125
Caucasian/White	53 (86.9%)	48 (75.0%)	101 (80.8%)
Black	2 (3.3%)	2 (3.1%)	4 (3.2%)
Asian/Oriental	4 (6.6%)	11 (17.2%)	15 (12.0%)
Other	2 (3.3%)	3 (4.7%)	5 (4.0%)
Ethnicity [n (%)]			
Number	61	64	125
Hispanic	17 (27.9%)	13 (20.3%)	30 (24.0%)
Non Hispanic	44 (72.1%)	51 (79.7%)	95 (76.0%)

The average durations of diabetes were equal (2.12 years) in the two treatment groups. The majority of the patients (112 [89.6%]) was taking a basal-bolus multiple injection regimen with a few (13 [10.4%]) on premixed insulin prior to entering the study. The total daily mean (SD) dose of basal insulin was 7.29 (4.11) U in the insulin glargine group and 7.61 (4.77) U in the NPH insulin group. The total daily mean (SD) dose of bolus insulin was 7.14 (3.64) U in the insulin glargine group and 7.98 (7.20) U in the NPH insulin group. In the insulin glargine group, the number of multiple injections of bolus insulin was higher (21 [34.4%] patients with 2 injections and 5 [8.2%] patients with ≥3 injections) than in the NPH group (15 [23.4%] patients with 2 injections and 1 [1.6%] patient with ≥3 injections).

Baseline HbA1c levels are shown in the table below. Mean HbA1c was slightly lower in the Lantus group (8.023%), versus NPH insulin (8.248%). However, the median HbA1c was slightly higher in the Lantus group (8.10%), versus NPH group (7.95%).

Summary of baseline HbA1c – mITT population

HbA1c (%)	Lantus (N=61)	NPH (N=64)
Baseline		
Number	61	64
Mean (SD)	8.023 (1.049)	8.248 (1.429)
Median	8.100	7.950
Min : Max	6.10 : 10.90	6.00 : 12.00

After signing the informed consent, patients were requested to use CGM, perform FSBG, and report any hypoglycaemic event during the screening period. Fifty-six (91.8%) patients in the insulin glargine group and 59 (92.2%) patients in the NPH group had at least one "all hypoglycaemia" episode during the screening. The average numbers of "all hypoglycaemia" episodes per patient in each treatment group were comparable (7.66 for insulin glargine and 8.81 for NPH).

1.5.2. Efficacy Results

Primary analysis

Over the 24-week on-treatment period, nearly all individuals in each treatment group (98.4% for NPH insulin and 100% for insulin glargine) experienced hypoglycaemia (see table below). The analysis of "all hypoglycaemia" incidence rate (without any distinction of severity) was 192.75 per patient-year for insulin glargine and 168.91 per patient-year for NPH glargine, with an incidence ratio of 1.18 and 95% CI of 0.97 to 1.44.

Based on the criteria for the primary analysis, because the upper bound of the 95% CI of 1.44 was greater than the pre-specified non-inferiority margin of 1.15, daily treatment with insulin glargine over the 24-week on-treatment period did not demonstrate the pre-specified non-inferiority in the rate of "all hypoglycaemia" compared to NPH insulin, both given as basal insulin plus bolus injection with short-acting insulin.

Summary of "all hypoglycaemia" events during on-treatment period – mITT population

"All hypoglycemia"	Lantus (N=61)	NPH (N=64)
Number of patients with events (n(%))	61 (100%)	63 (98.4%)
Number of events		
Mean (SD)	85.84 (55.83)	66.27 (43.80)
Median	78.00	64.00
Min : Max	1.0 : 261.0	0.0 : 233.0
Exposure (years)		
Mean (SD)	0.44 (0.09)	0.41 (0.14)
Median	0.46	0.46
Min : Max	0.0 : 0.5	0.0 : 0.5
Event rate (events/year)		
Mean (SD)	192.75 (119.28)	168.91 (101.04)
Median	173.01	161.48
Min : Max	21.2 : 570.8	0.0 : 547.9
Ratio of mean event rates		
Estimate (SE)	1.18 (0.12)	-
95% CI	(0.97 to 1.44)	-

Note: On-treatment period for hypoglycemia is from the first dose of IP up tp 24 hours after the last dose of IP

Ratio of mean event rates between Lantus vs. NPH is estimated from GLM with fixed effect terms for randomization strata and treatment; The model used Poisson distribution with log-link function and the empirical standard error estimates by Generalized Estimating Equation (GEE) was used.

Additional analyses on hypoglycaemia

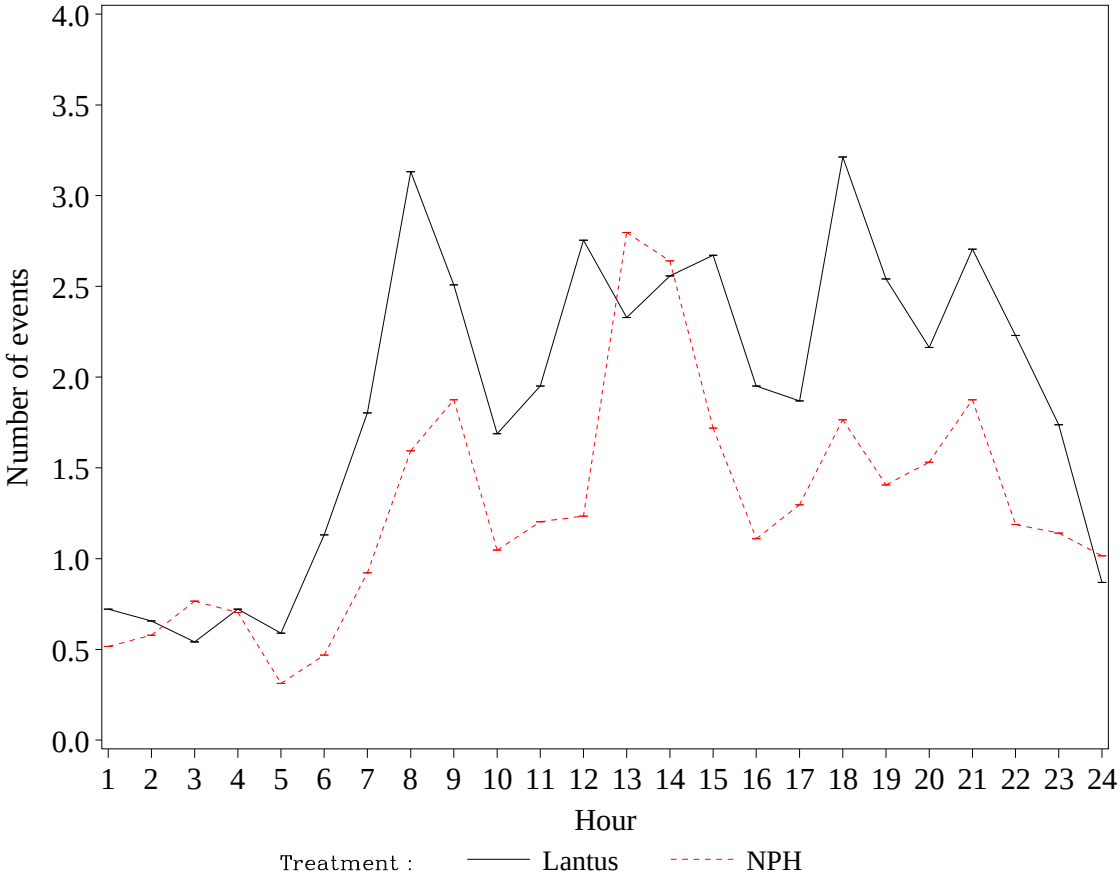
The number of bolus insulin injections per day in both treatment groups was very close to 3 (range of mean number of injections 2.93 – 3.07 in the glargine group, vs 2.84 – 3.07 in the NPH group). Therefore there is no difference in number of bolus injections per day between the glargine group and the NPH group.

The results for the primary outcome of "all hypoglycemia" were dominated (in terms of the number of events) by the third component, low fingerstick blood glucose (FSBG) values, in particular by low FSBG values that were 'sporadic' (ie did not occur at times of symptomatic hypoglycemia or low CGM [continuous glucose monitoring] excursions). These low sporadic FSBG values tended to cluster at mealtimes, as Figure below shows. They did not occur more often at the noon meal in the glargine group.

There were more FSBG values performed overall (ie, both low and not low) in the glargine group than in the NPH group, and on average CGM glucoses trended lower in the glargine group during daytime hours than in the NPH group, both factors which would tend to generate more "low" FSBG values in the glargine group than in the NPH group. The occurrence of these low peri-mealtime asymptomatic FSBGs was certainly influenced by the bolus insulin doses given for the meal before the one at which the low FSBG value was recorded, and, as above, the evidence points to the fact that in both groups, an injection of bolus insulin was generally given with each meal.

On the other hand, symptomatic hypoglycemia events did not show the same mealtime peak incidence that "low FSBG"s did. Symptomatic hypoglycemia episodes occurred most commonly peri-midday in both groups.

Plot of "low sporadic" FSBG readings by time of day – mITT population



Variability in insulin dose is best reflected by the standard deviation (SD) of the dose in U/kg. The dose range of 0.13 – 1.19 U/kg referred to simply reflects the greatest and least glargine doses given during the trial. The high and low extremes of dose can be related to many factors, such as age, diet, proportion of total daily insulin dose taken as bolus vs basal, and insulin resistance. In the 125-patient PRESCHOOL study the SD of glargine doses was 0.15 – 0.18 U/kg (CSR Table 42), as compared to NPH (0.16 – 0.21 U/kg). This compares favorably with the SDs of the total insulin doses in Study HOE901/3003 conducted in 349 older T1DM children (glargine 0.30 – 0.32 U/kg, NPH 0.32 – 0.34 U/kg). In this study, the age range was 5 – 16 (median 12.0, mean 11.7 years).

The MAH performed correlations between basal insulin dose and:

- "all hypoglycemia", the primary outcome variable
- Symptomatic hypoglycemia
- Body weight,

The tables below show the results:

Correlation between the average basal insulin dose by body weight (U/kg) over all on-treatment visits, and the parameter shown

Correlation [coefficent(P value)]	Lantus	NPH
Basal insulin (U/kg) with		
All hypoglycemia	0.1521(0.2378)	-0.0049(0.9698)
Symptomatic hypoglycemia	0.1417(0.2718)	-0.1102(0.3901)
Body weight	0.3223(0.0106)	0.1439(0.2604)

PGM=DEVOPS/HOE901/EFC11202/CSR_01/REPORT/PGM/__chmp_corr.sas
OUT=REPORT/OUTPUT/__chmp_corr_ontreat_i.rtf (20MAR2012 - 4:39)

Correlation between the average basal insulin dose (U) over all on-treatment visits, and the parameters shown

Correlation [coefficent(P value)]	Lantus	NPH
Basal insulin (U) with		
All hypoglycemia	0.1365(0.2902)	0.0196(0.8786)
Symptomatic hypoglycemia	0.1211(0.3485)	-0.0172(0.8934)
Body weight	0.5854(<.0001)	0.5747(<.0001)

PGM=DEVOPS/HOE901/EFC11202/CSR_01/REPORT/PGM/__chmp_corr.sas
OUT=REPORT/OUTPUT/__chmp_corr_u_ontreat_i.rtf (20MAR2012 - 4:40)

No correlation between basal insulin dose and hypoglycemia of either type is significant, however in both groups there is a very significant correlation between basal insulin dose and body weight, and for Lantus, this is observed even after the dose is normalized for body weight. These are growing children with a wide variability in their body weights over the age range for inclusion, more so than adults and probably more so than older children.

The distribution of insulin dose is tabulated below for both treatment groups.

The distribution of the average basal insulin by body weight (U/Kg) over all on-treatment visits

	Lantus (N=62)	NPH (N=63)
Basal insulin (U/Kg)		
Number	62	63
Mean (SEM)	0.363 (0.0205)	0.439 (0.0232)
SD	0.161	0.184
Median	0.326	0.409
Min : Max	0.11 : 0.87	0.03 : 0.88
Q1 : Q3	0.262 : 0.438	0.300 : 0.523
Geometric mean	0.331	0.391
Coefficient of variation	44.4339	41.9981

PGM=DEVOPS/HOE901/EFC11202/CSR_01/REPORT/PGM/__chmp_corr_dist.sas
OUT=REPORT/OUTPUT/__chmp_corr_dist_ontreat_i.rtf (20MAR2012 - 4:57)

The mean dose of NPH over the entire study is somewhat higher than the mean dose of glargine (as reported in the CSR), but the standard deviations and standard errors of the basal insulin dose in the two arms, the best measure of variability, are quite similar, although slightly greater in the NPH group.

There were 2 episodes of "Headache" reported in the glargine group (in patients 71002004 and 76002001) versus none in the NPH group, and one episode of "Somnolence" in glargine patient 76002004. These symptoms were apparently related to low blood glucose

Secondary analyses

The components of the primary outcome of "all hypoglycaemia" were analysed individually. Table below shows the *symptomatic hypoglycaemia events*. The symptomatic hypoglycaemia events were more common in the NPH group than in the Lantus group. Mean (SD) number of events: 11.52 (16.86) in the Lantus group, versus 13.42 (20.62) in the NPH group. The median was 3 events in the Lantus group, versus 4 events in the NPH group. Resulting in an estimate ratio of mean event rates of 0.76 with 95% CI= (0.46; 1.25).

The symptomatic hypoglycaemia events comprised approximately 15% of the overall primary outcome. They tended to cluster around midday in the NPH group, with a smaller peak between midnight and 5 AM. In the insulin glargine group, symptomatic hypoglycaemia was also more common in the late morning and early afternoon, but not as prominently as in the NPH group.

Summary of symptomatic hypoglycaemia events during on-treatment period – mITT population

Symptomatic hypoglycemia	Lantus (N=61)	NPH (N=64)
Number of patients with events (n(%))	40 (65.6%)	44 (68.8%)
Number of events		
Mean (SD)	11.52 (16.86)	13.42 (20.62)
Median	3.00	4.00
Min : Max	0.0 : 69.0	0.0 : 79.0
Exposure (years)		
Mean (SD)	0.44 (0.09)	0.41 (0.14)
Median	0.46	0.46
Min : Max	0.0 : 0.5	0.0 : 0.5
Event rate (events/year)		
Mean (SD)	25.54 (37.25)	33.02 (47.95)
Median	6.52	10.56
Min : Max	0.0 : 150.0	0.0 : 165.2
Ratio of mean event rates		
Estimate (SE)	0.76 (0.19)	-
95% CI	(0.46 to 1.25)	-

Note: On-treatment period for hypoglycemia is from the first dose of IP up to 24 hours after the last dose of IP

Ratio of mean event rates between Lantus vs. NPH is estimated from GLM with fixed effect terms for randomization strata and treatment; The model used Poisson distribution with log-link function and the empirical standard error estimates by Generalized Estimating Equation (GEE) was used.

Part of the second primary outcome component was *confirmed low CGM excursions* <70 mg/dL (3.9 mmol/L), confirmed by a concomitant FSBG measurement. The occurrence of these events was similar

between the treatments, as shown in the table below. There was a clustering of events around mealtimes.

Summary of all confirmed low CGMS excursions during on-treatment period – mITT population

All confirmed low CGMS excursions	Lantus (N=61)	NPH (N=64)
Number of patients with events (n(%))	60 (98.4%)	61 (95.3%)
Number of events		
Mean (SD)	33.61 (32.40)	28.98 (23.97)
Median	23.00	25.00
Min : Max	0.0 : 144.0	0.0 : 99.0
Exposure (years)		
Mean (SD)	0.44 (0.09)	0.41 (0.14)
Median	0.46	0.46
Min : Max	0.0 : 0.5	0.0 : 0.5
Event rate (events/year)		
Mean (SD)	74.61 (74.09)	71.60 (53.20)
Median	50.00	57.49
Min : Max	0.0 : 398.5	0.0 : 221.0
Ratio of mean event rates		
Estimate (SE)	1.06 (0.16)	-
95% CI	(0.79 to 1.42)	-

Note: On-treatment period for confirmed CGMs excursion is from the first dose of IP up to 24 hours after the last dose of IP

Ratio of mean event rates between Lantus vs. NPH is estimated from GLM with fixed effect terms for randomization strata and treatment; The model used Poisson distribution with log-link function and the empirical standard error estimates by Generalized Estimating Equation (GEE) was used.

The third component, any FSBG <70 mg/dL, is shown in the table below. The mean number of all low FSBG events was higher in the Lantus group, compared to the NPH group, 85.87 versus 66.27 events respectively. The estimate (SE) ratio of mean event rates between Lantus and NPH was 1.18 (0.12), with 95% CI: 0.96; 1.45.

The MAH explains this disproportion between insulin glargine and NPH insulin in low FSBG to greater performance of FSBG monitoring in the insulin glargine group, compared to the NPH group. In the insulin glargine group more FSBGs were performed, and thus more FSBGs <70 mg/dL could be detected.

Summary of all low FSBG events during on-treatment period – mITT population

All low FSBG	Lantus (N=61)	NPH (N=64)
Number of patients with events (n(%))	61 (100%)	63 (98.4%)
Number of events		
Mean (SD)	85.87 (56.89)	66.27 (44.56)
Median	78.00	63.00
Min : Max	1.0 : 268.0	0.0 : 235.0
Exposure (years)		
Mean (SD)	0.44 (0.09)	0.41 (0.14)
Median	0.46	0.46
Min : Max	0.0 : 0.5	0.0 : 0.5
Event rate (events/year)		
Mean (SD)	192.69 (121.78)	168.24 (101.21)
Median	174.78	161.70
Min : Max	21.2 : 586.1	0.0 : 547.9
Ratio of mean event rates		
Estimate (SE)	1.18 (0.12)	-
95% CI	(0.96 to 1.45)	-

Note: On-treatment period for hypoglycemia is from the first dose of IP up to 24 hours after the last dose of IP

Ratio of mean event rates between Lantus vs. NPH is estimated from GLM with fixed effect terms for randomization strata and treatment; The model used Poisson distribution with log-link function and the empirical standard error estimates by Generalized Estimating Equation (GEE) was used.

According to the MAH, the primary outcome was driven by the disproportion in low FSBG values. Overall, the ratio of events between insulin glargine and NPH insulin that were either symptomatic hypoglycaemia events or confirmed low CGM excursions was 1.06 (0.81 – 1.38). This small insulin glargine to NPH insulin disproportion may have been in part due to the greater mean number of days the CGM devices were worn in the insulin glargine group (82.6 days, versus 76.2 days for NPH, ratio 1.08).

The MAH states that the FSBG values <70 mg/dL that occurred at other times, ie the "sporadic" low FSBG values, were more numerous in the insulin glargine group than in the NPH group, and are displayed in the table below.

As events of either symptomatic hypoglycaemia or low CGM excursions were relatively balanced between treatments, and were triggered by hypoglycaemic stimuli rather than captured sporadically, it is evident that the disproportion in FSBG monitoring performance did not impact these components of the primary outcome. Rather the insulin glargine to NPH insulin disproportion in total FSBG monitoring (ratio 1.16) would have been expected to principally affect the third component of the primary outcome, low sporadic FSBG readings.

Summary of "low sporadic" FSBG during on-treatment period – mITT population

All "low sporadic" FSBG	Lantus (N=61)	NPH (N=64)
Number of patients with events (n(%))	60 (98.4%)	62 (96.9%)
Number of events		
Mean (SD)	45.03 (42.68)	30.70 (24.84)
Median	29.00	26.50
Min : Max	0.0 : 195.0	0.0 : 108.0
Exposure (years)		
Mean (SD)	0.44 (0.09)	0.41 (0.14)
Median	0.46	0.46
Min : Max	0.0 : 0.5	0.0 : 0.5
Event rate (events/year)		
Mean (SD)	102.23 (92.48)	80.64 (79.72)
Median	72.18	65.53
Min : Max	0.0 : 424.0	0.0 : 547.9
Ratio of mean event rates		
Estimate (SE)	1.34 (0.20)	-
95% CI	(1.01 to 1.79)	-

Note: On-treatment period for hypoglycemia is from the first dose of IP up to 24 hours after the last dose of IP

Ratio of mean event rates between Lantus vs. NPH is estimated from GLM with fixed effect terms for randomization strata and treatment; The model used Poisson distribution with log-link function and the empirical standard error estimates by Generalized Estimating Equation (GEE) was used.

HbA1c levels

Mean HbA1c in the two treatment groups at the various time points is shown in the table below.

The observed changes were not statistically significant, and on average HbA1c values were the same at the end of the study as they were at the start. This is true despite an increase in the mean dose of NPH insulin, from 0.37 IU/kg at baseline to 0.46 IU/kg at Week 24. Insulin glargine doses remained stable over the course of the study – mean dose at baseline was 0.35 U/kg, and at endpoint was 0.38 U/kg – as did bolus insulin doses in both arms, both in terms of number of injections and total units. Only 22 – 23% of patients in either treatment group achieved an HbA1c in the target range (≤7.5%) by the end of treatment.

Summary of HbA1c at end-of-treatment (ANCOVA-LOCF) – mITT population

HbA1c (%)	Lantus (N=61)	NPH (N=64)
Baseline		
Number	61	64
Mean (SD)	8.023 (1.049)	8.248 (1.429)
Median	8.100	7.950
Min : Max	6.10 : 10.90	6.00 : 12.00
End of treatment		
Number	59	57
Mean (SD)	8.071 (0.884)	8.344 (1.161)
Median	8.100	8.100
Min : Max	6.40 : 11.10	6.00 : 12.70
LS Mean (SE)[a]	8.139(0.1065)	8.232(0.1134)
LS Mean Difference(SE)[a]	-0.093(0.1523)	-
95% CI[a]	(-0.3948 to 0.2087)	-
Change from baseline		
Number	59	57
Mean (SD)	0.036 (0.979)	-0.000 (1.035)
Median	0.000	0.100
Min : Max	-2.50 : 2.60	-3.20 : 2.30
LS Mean (SE)[a]	-0.048(0.1065)	0.045(0.1134)
LS Mean Difference(SE)[a]	-0.093(0.1523)	-
95% CI[a]	(-0.3948 to 0.2087)	-

LOCF = Last observation carry forward.

[a]Analysis of covariance (ANCOVA) model with treatment, and randomization strata (baseline number of CGM hypoglycemic excursions <0.5 events/24hours or ≥0.5 events/24 hours, and baseline HbA1c <8.5% or ≥8.5%) as fixed effects, and using the baseline value as covariate.

Blood glucose variability

"Average (blood) glucose" was the average of all available CGM interstitial glucose values for the patient.

As might be expected from the plot of average CGM glucose by time of day, the variability of CGM glucose (the standard deviation of all these values over the trial) was high, and similar between treatments (see table below.

Summary of blood glucose variability based on CGMS values over the entire study – mITT population

Parameter	Lantus (N=61)	NPH (N=64)
Blood glucose variability (mmol/L)		
Number	60	63
Mean (SD)	4.954 (0.826)	5.089 (0.731)
Median	5.097	4.999
Min : Max	3.04 : 6.55	3.60 : 6.78

Several observations are apparent from this data:
• Mean CGM values were above the recommended target of 10 mmol/L during the whole day in both groups.
• There was variability in mean CGM values over the course of the day, with troughs corresponding to post-meal effects of bolus injections, and peaks following the meals.
• For most of the day (all non-nocturnal hours), the mean CGM values in the insulin glargine group were lower than the corresponding values in the NPH group. In particular, the mean CGM glucose level was lower in the insulin glargine group between 13:00 and 22:00 hours, which was the time when there were greater numbers of FSBG readings <70 mg/dL in the insulin glargine group.
• Between midnight and 05:00 hours, mean CGM glucose was lower in the NPH group than in the insulin glargine group, perhaps related to the evening NPH doses, given in most patients in that treatment group, on most days.
• Fasting glucose levels seem lower on average in the insulin glargine group than in the NPH group.
• HbA1c results reflected an averaging of BG differences (as judged by average of CMGS values) during the day and evening – somewhat lower during the day for insulin glargine, somewhat lower overnight in the NPH group – that may have cancelled each other out in the overall assessment of average glycaemia.

1.5.3. Discussion

In support of the Application one clinical trial was submitted (Study EFC11202). The study design was according to the agreements made during the PIP procedure. However, no child aged below the age of 2 years was included in the glargine group, thus no clinical data on the efficacy below this age is available and this is now appropriately reflected in the SmPC.

There were some differences between treatment groups in the patient disposition. In the glargine group, 57/61 (93.4%) completed the study, while a lower number 54/64 (84.4%) of participants in the NPH insulin group completed the trial. Discontinuation in the NPH group was higher in the following categories: Family's request (14.1% versus 4.9%); Adverse events (3.1% versus none); poor compliance to protocol (3.1% versus 1.6%); and "other reasons" (9.4% versus 3.3%). Since the number of patients who discontinued during the study was small (4 versus 10 subjects), influence on efficacy or safety results is not expected.

Furthermore, the proportion of "any randomisation or drug allocation irregularities" was quite substantial in both treatment groups. In the glargine group, 14 events (23%) and in the NPH group 18 (28.1%) of irregularities occurred. These events were mainly categorised as stratification errors [12 (19.7%) in the glargine group, versus 16 (25%) in the NPH group]. Since the baseline characteristics regarding HbA1c and rate of hypoglycaemic events were comparable between groups, it is not expected that this misclassification (stratification errors) will have a large influence on the efficacy results.

Lastly, a substantial percentage of important protocol deviations were noted. Since the number of subjects involved was limited (8 and 7 patients per treatment group), influence on the efficacy results is not expected to be substantial.

Baseline characteristics were comparable between groups.

Mean HbA1c levels were slightly lower in the glargine group, while the median HbA1c levels were slightly lower in the NPH group. There was a greater variation in values in the NPH group, versus the glargine group. HbA1c values at baseline were around 8%, this is higher than the recommended (<7.5%) for children with diabetes, but comparable to levels found in practice.

The mean basal insulin dosage at baseline was slightly smaller in the glargine group, however no difference was found in the median basal insulin dosage (6 U in both groups). The mean daily dose of bolus insulin was slightly higher in the NPH group, while the median daily dose was lower compared to the glargine group. In conclusion, the two treatment groups were comparable with regard the baseline daily insulin dose.

The number of "all hypoglycaemia" events at baseline was slightly lower in the glargine group. The mean (SD); and median number of events were 7.66 (6.02); 6.00 in the glargine group, versus 8.81 (13.25); 7.00 in the NPH group. There was a rather large variation in each study group, with some patients reporting no hypoglycaemic events [5 (8.2%) subjects in the glargine group, versus 5 (7.8%) in the NPH group], while the maximum number of reported hypoglycaemic events was 25 in the glargine group, versus 101 events in the NPH group.

The children in the glargine group were slightly older [mean (SD) age; median age; number (%) ≤3 years old: 4.3 (0.9) yrs; 5 yrs; 10 (16.4%) in the glargine group, versus 4.1 (1.0) yrs; 4 yrs; 17 (26.6%)].

It is not expected that any of these small differences will have an impact on the efficacy or safety results.

Primary objective was the effect of both insulins on hypoglycaemia. During treatment more hypoglycaemic events were seen in the Lantus group compared to the NPH insulin group but the difference between groups was small, and the variation rather large: mean 193 versus 169 events/year, with a ratio (95% CI) of 1.18 (0.97 to 1.14). According to the Applicant the difference might be due to the higher number of FSBG measurements performed in the Lantus group, which increases the chance of detecting low glucose levels. However, the reason(s) why there were more FSBG measurements in the Lantus group is unknown. It may be partly explained by the longer time of exposure observed in the glargine group. Maybe more measurements were made because of the more frequent insulin dose changes in this group or it could be that care takers expected more often a low blood glucose level. Therefore, the higher number of FSBG measurements has not fully been explained.

Furthermore, indeed the differences between the confirmed CGMs, and symptomatic hypoglycaemia were relatively small between the two treatment groups. Therefore the "low sporadic FSBG" probably drove the primary efficacy outcome, as stated by the MAH.

Since the CGMs were only used for a limited period of time, and symptomatic hypoglycaemia is difficult to detect in pediatrics 1 to less than 6 years old, these two variables might have had limitations in detecting hypoglycaemia during the study. It should also be noted that the time with CGMS did not differ when the longer exposure time in the glargine groups is taken into consideration.

It is stated that the difference seen in *confirmed low CGM excursions* between the two treatment groups might be due to the greater mean number of days the CGM devices were worn in the insulin glargine group (82.6 days, versus 76.2 days for NPH, ratio 1.08). However, this disproportion is almost identical to the disproportion in mean exposure (0.44 vs. 0.41 years, ratio 1.07) which means that the ratio of *events per day with CGM device* would be very close to the ratio of *events per exposure year*. I.e. the number of days the CGM devices were worn does not explain the (slightly) higher event rate in the insulin glargine group.

In the same way, the number of FSBG measurements does not differ that much between the groups when controlling for the different exposure times. The ratio of *number of FSBG measures per exposure year* 1.03.

The third variable used to detect hypoglycaemia, FSBG measurements, was used often (2 – 2018 times per patients during the 24 weeks treatment). Although this method could not continuously track the glucose level, and the number of measurements was variable between patients, this efficacy variable is important in the study to compare the differences in hypoglycaemic events between the two treatment groups. This efficacy variable could be used during the whole study duration, and this variable is independent of the hypoglycaemic awareness of the 1 to less than 6 years old pediatrics.

There are peaks in the primary outcome for both groups around the times of meals (and bolus insulin injections), more pronounced in the insulin glargine group. The largest peak for the NPH group occurs around the time of the noon meal, which coincided with the peak action of the morning dose of NPH insulin. A smaller peak for NPH can be seen in the hours following midnight. It is evident that there are more events in the insulin glargine group over the course of the 24 hours than in the NPH group.

The median number of bolus injections in both the Lantus group and the NPH insulin group in most weeks during the PRESCHOOL study was around 3 times daily without significant differences between the two treatment arms; only at week 24 the number was lower (see Table 45). The median number of bolus injections taken, is the number you would expect from a physiological point of view, assuming that three meals are taken every day. This is not suggestive for any possible specific Lantus related problems such as increases in hypoglycemia or patient's related problems (e.g. skipping meals, not willing to take injections). The peak of the NPH insulin was apparently not sufficient to cover the lunch meal and most patients (80%) received NPH insulin twice daily vs. 10% insulin glargine. This could explain the lack of difference regarding number of insulin bolus between the two treatment groups.

The large variability in individual glargine doses is not totally unexpected considering that children in a rather large age and weight span were included in the study. Further, the SD of the dose in U/kg did not differ between the glargine and the NPH dose. Thus, the basal insulin doses do not explain the difference in hypoglycaemia.

The MAH performed correlations between basal insulin dose and the primary endpoint "all hypoglycemia". The correlation coefficient for the average basal insulin dose by body weight (U/kg) over all on-treatment visits and the variable "all hypoglycaemia" was 0.1521, (P-value 0.2378). This suggests that there is some correlation between higher dosage of Lantus and incidence of hypoglycaemic events, but not statistically significant. It is to be expected that insulin lowers blood glucose levels. Therefore, a positive correlation coefficient between insulin dose and hypoglycaemia is not unexpected. This effect was not seen in the NPH insulin group, but this may have been related to the higher HbA1C levels before and at the end of the study and the twice daily dosing that occurred in most patients.

The data do not really contribute to the discussion why non-inferiority in terms of hypoglycaemia in the PRE-SCHOOL study was not met. The increase in hypoglycaemic events could be caused by the slightly better glucose levels, and lower HbA1c levels in the glargine treatment group. The increase in hypoglycaemic events was small, and the standard deviation in both treatment groups rather large. This information is sufficiently covered in the SmPC.

The MAH performed also correlation tests between basal insulin dose and symptomatic hypoglycaemia; and basal insulin dose and body weight. This information is not considered meaningful. The correlation between insulin dose and body weight has been well known for years, and symptomatic hypoglycaemic events is not a reliable parameter in young children age 2 to less than 6 years.

The three cases of somnolence and headaches which were reported in the glargine group were described by the MAH. These symptoms were indeed related to hypoglycaemic events (however not late or passed events), therefore all three events were included in the efficacy parameters as

symptomatic hypoglycaemic events. Both hypoglycemic seizures of Pt 76002001 and Pt 76002004 were listed as a SAE.

The mean HbA1c at end of study was slightly lower in the glargine group (8.07%) versus the NPH group (8.34%). This is in line with the higher number of hypoglycaemic events found in the glargine group.

It can be concluded that Lantus was shown to be at least as effective as NPH insulin in controlling blood glucose in paediatric patients with T1DM, aged 2-6 years with a small and variable increase in incidence of hypoglycaemia that might be related to the somewhat stricter regulation of the diabetes mellitus in the Lantus group.

In conclusion, insulin glargine can only be authorized in adults, adolescents and children aged 2 years and above.

1.6. Clinical Safety aspects

1.6.1. Methods – analysis of data submitted and Results

1.6.1.1. Patient exposure

The mean treatment exposure was similar between the two treatment groups, with a slightly longer exposure to insulin glargine (161.5 days for insulin glargine versus 150.3 days for NPH, see table below) and a greater percentage of patients on insulin glargine treatment having completed the study (57 [93.4%] patients on insulin glargine versus 54 [84.4%] patients on NPH). As different from the insulin glargine group, dropouts in the NPH group continued to occur after the first month of the trial. Overall, the majority of the patients were exposed to the investigational product for 141 days or longer.

Exposure to investigational product – Safety population

	Lantus (N=62)	NPH (N=63)
Duration of study treatment (days)		
Number	62	63
Mean (SD)	161.53 (33.41)	150.29 (51.31)
Median	168.00	169.00
Min : Max	13.0 : 187.0	1.0 : 192.0
Duration of study treatment by category [n (%)]		
Missing duration	0	0
1-14 days	1 (1.6%)	4 (6.3%)
15-28 days	2 (3.2%)	1 (1.6%)
29-56 days	0	2 (3.2%)
57-84 days	0	2 (3.2%)
85-112 days	0	0
113-140 days	1 (1.6%)	1 (1.6%)
141-168 days	28 (45.2%)	17 (27.0%)
>168 days	30 (48.4%)	36 (57.1%)

Note: Patients are considered in the treatment group they actually received at randomization(if any patient received both treatments, the patient is included in both treatment groups for safety population)

The average daily basal insulin dose per kilogram body weight for insulin glargine was stable over the 24-week treatment period (0.35 U/kg at Week 1 versus 0.38 U/kg at Week 24) while the average daily dose of NPH insulin increased from 0.37 U/kg at baseline of Week 1 to 0.46 U/kg at Week 24.

Almost all patients in both groups received either insulin lispro or regular human insulin, with a few on both. A smaller proportion of patients in the insulin glargine group (36 [58.1%]) than in the NPH group (46 [73.0%]) used lispro as bolus insulin. However, the fact that insulin glargine-treated patients used more regular insulin as bolus insulin is unlikely to have played a role in the primary outcome result.

The average daily doses per kilogram body weight of bolus insulin in the two treatment groups were similar at Week 1 (0.41 U/kg for insulin glargine versus 0.42 U/kg for NPH insulin) and remained practically unchanged at Week 24 (0.41 U/kg for insulin glargine versus 0.40 U/kg for NPH insulin).

1.6.1.2. Adverse events

An overview of the AEs observed during the 24 weeks of on-treatment period is provided in the table below. The proportions of patients with TEAEs were generally comparable between the two treatment groups (40 [64.5%] for insulin glargine versus 43 [68.3%] for NPH insulin). No fatal TEAE occurred in the study. Two patients on NPH insulin prematurely discontinued the study treatment due to TEAEs of drug hypersensitivity (allergic reaction to NPH) and diabetic ketoacidosis. Most AEs in both treatment groups were of mild or moderate severity.

Overview of adverse event profile: treatment-emergent adverse events – Safety population

n(%)	Lantus (N=62)	NPH (N=63)
Patients with any TEAE	40 (64.5%)	43 (68.3%)
Patients with any treatment emergent SAE	8 (12.9%)	2 (3.2%)
Patients with any TEAE leading to death	0	0
Patients with any TEAE leading to permanent treatment discontinuation	0	2 (3.2%)

TEAE: Treatment emergent adverse event
SAE: Serious adverse event

Table below presents the number of patients with TEAs by SOC. Most TEAs were classified in the SOC infections and infestations, with 33 (53.2%) in the glargine group, versus 30 (47.6%) in the NPH group. The most commonly reported TEAEs by PT were gastroenteritis, nasopharyngitis, and pharyngitis (each affecting 6 [9.7%] patients) in the insulin glargine group and pyrexia (7 [11.1%] patients) and gastroenteritis and upper respiratory tract infection (each affecting 6 [9.5%] patients) in the NPH group. These are common AEs in this age group.

Number (%) of patients with TEAE(s) by SOC – Safety population

PRIMARY SYSTEM ORGAN CLASS HLGT: High Level Group Term HLT: High Level Term Preferred Term n(%)	Lantus (N=62)	NPH (N=63)
Any class	40 (64.5%)	43 (68.3%)
INFECTIONS AND INFESTATIONS	33 (53.2%)	30 (47.6%)
BLOOD AND LYMPHATIC SYSTEM DISORDERS	0	1 (1.6%)
IMMUNE SYSTEM DISORDERS	0	1 (1.6%)
METABOLISM AND NUTRITION DISORDERS	5 (8.1%)	1 (1.6%)
PSYCHIATRIC DISORDERS	1 (1.6%)	0
NERVOUS SYSTEM DISORDERS	3 (4.8%)	0
EYE DISORDERS	2 (3.2%)	1 (1.6%)
EAR AND LABYRINTH DISORDERS	0	2 (3.2%)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	6 (9.7%)	6 (9.5%)
GASTROINTESTINAL DISORDERS	12 (19.4%)	11 (17.5%)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	4 (6.5%)	7 (11.1%)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	1 (1.6%)	0
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	10 (16.1%)	10 (15.9%)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	3 (4.8%)	3 (4.8%)
SURGICAL AND MEDICAL PROCEDURES	0	1 (1.6%)

For non-hypoglycaemia AEs, there was no prominent pattern of AEs in either treatment group. Metabolism and Nutrition Disorders occurred more often in the insulin glargine group (5 [8.1%] patients, including 1 diabetic ketoacidosis and 2 hypoglycaemic seizures) than in the NPH group (1 [1.6%] patient). Nervous System Disorders were reported only for the insulin glargine group (3 [4.8%] patients: 2 headaches, 1 somnolence). Skin and Subcutaneous Tissue Disorders were reported more often for the NPH group (7 [11.1%] patients of whom 4 had dermatitis) than for the insulin glargine group (4 [6.5%] patients). In general these AEs are very common in this childhood age group, are not related to insulin treatment, and were generally balanced between the treatment groups.

Special interest

Blood pressure and heart rate

For the vital signs parameters (blood pressure and heart rate), there were no clinically important differences between the two groups in the mean parameter values or in the mean changes from baseline.

Body weight

Body weight was measured at baseline (randomisation) and at Weeks 12 and 24 during the study. Mean body weights were similar at baseline in both the treatment groups (19.4 kg for insulin glargine and 19.7 kg for NPH insulin). Over the 24-week on-treatment period, patients in both treatment groups gained weight appropriately for their age. At both Week 12 and Week 24, on average, a slightly lower increase in body weight was observed in the patients treated with insulin glargine (0.7 kg at

Week 12 and 1.3 kg at Week 24) compared to those treated with NPH (0.8 kg at Week 12 and 1.6 kg at Week 24).

Anti-insulin antibodies

AIA were measured in patients treated with NPH and insulin glargine. For both treatment groups the percentage of AIA-positive patients was similar at screening visit (baseline), Week 4 and Week 24 with about 75% positive patients in the insulin glargine and about 80% positive patients in the NPH cohort. Analysis of individual data revealed that overall, patients with AIA negative status at baseline remained AIA negative throughout the study. For 5 individual patients in the insulin glargine treatment group and 3 in the NPH treatment group, the AIA status changed from negative to positive, and, according to the MAH, this can be mainly related to the assay sensitivity as binding values for all these patients were very low and just around the cut-off point.

For both treatment groups, there was no indication for any correlation between AIA titre/binding level and the analyzed efficacy parameters of HbA1c change, daily insulin dose, and cumulative "all hypoglycaemia". Also the data distribution pattern was similar for NPH and insulin glargine treatment group.

Neoplasms

There were no cases of cancer recorded during this trial.

1.6.1.3. Serious adverse events and deaths

There were no death events in the study.

The percentage of patients who experienced serious TEAEs was higher in the insulin glargine group (8 [12.9%] patients) than in the NPH group (2 [3.2%] patients). The differences between groups were mainly due to the imbalanced occurrence of SAEs in the SOCs of Metabolism and Nutrition Disorders.

Four (6.5%) subjects in the glargine group experienced a SAE in the SOC Metabolism and nutrician disorders, of which 2 hypoglycaemic seizures (both SAEs occurred after injection of the short-acting insulin lispro with a skipped or delayed meals and patients fully recovered without any permanent sequelae), 1 diabetic ketoacidosis (moderate intensity, patient recovered on the day of onset), and 1 dehydration (mild intensity, patient recovered one day after onset). In the NPH group 1 (1.6%) event was reported, a diabetic ketoacidosis (severe intensity; patient recovered one day after onset; NPH insulin was discontinued, patient was withdrawn from study).

Three (4.8%) subjects in the glargine group experienced a SAE in the SOC Gastrointestinal Disorders, while no patients in the NPH group reported this SAE. In two cases, a gastritis was diagnosed, and in one case abdominal pain.

The two SAEs reported in the SOC Infections and infestations concerned one patient in the glargine group who experienced viral infection of mild intensity, and one patient in the NPH group who recorded lower respiratory tract infection.

All 8 serious TEAEs in the insulin glargine group recovered and were assessed as not related to IP by the Investigator.

Other significant adverse events

Seven patients (5 [8.1%] in the insulin glargine group and 2 [3.2%] in the NPH group) experienced 9 TEAEs of device lead damage (CGM sensor fracture) when a CGM device was in use. The TEAEs occurred either during the sensor replacement, which was required for every 6-day consecutive use with the CGM device or while the child was wearing the device and physically active. The TEAEs were

of mild or moderate intensity, without any associated AE of infection or local reaction reported. All 7 of the patients continued using the CGM device as per the protocol requirement after the AE occurrence.

1.6.1.4. Laboratory findings

Hematology, clinical chemistry, and urinalysis tests were performed only at screening, to rule out major systemic disease. No clinically relevant laboratory findings were noted according the MAH.

1.6.1.5. Safety in special populations

N/A

1.6.1.6. Post marketing data

Lantus has been marketed in adult and paediatric patients with T1DM for the past 10 years in almost all countries of the world. Although this study is the first formal, sponsor assessment of the use of insulin glargine in preschool children with T1DM, and to date there are no approvals for the use of insulin glargine in the preschool population in any country, some children entering the trial were already taking insulin glargine (Lantus) off label.
Based on Reports of post-marketing experience (cut-off date 21 April 2011), after review of spontaneous AEs, it can be concluded that the AEs reported for the age group of 1 less than 6 years are similar to the AEs observed for the age group of 6-17 years, and are primarily related to dysglycaemia and injection site events. The lower percentage of SAEs in the younger age group (approximately 11% versus approximately 18% in the older pediatric age group) indicates that the impact of those AEs on patient safety is not worse than that in the older age group.
No significant signal has been seen with regard to patient safety in the population of patients aged 1to less than 6 years.

1.6.2. Discussion

There was no prominent pattern of AEs in either treatment group. The proportions of patients with TEAEs were generally comparable between the two treatment groups (40 [64.5%] for insulin glargine versus 43 [68.3%] for NPH insulin). No fatal TEAE occurred in the study. Two patients on NPH insulin prematurely discontinued the study treatment due to TEAEs of drug hypersensitivity (allergic reaction to NPH) and diabetic ketoacidosis, whereas none did on insulin glargine treatment. Most AEs in both treatment groups were of mild or moderate severity.
The most commonly reported TEAEs by PT were gastroenteritis, nasopharyngitis, and pharyngitis (each affecting 6 [9.7%] patients) in the insulin glargine group and pyrexia (7 [11.1%] patients) and gastroenteritis and upper respiratory tract infection (each affecting 6 [9.5%] patients) in the NPH group. These are common AEs in this age group.
No clinically relevant differences were noticed between the two treatment groups, regarding vital signs (blood pressure and pulse); body weight or anti insulin antibodies. No clinically relevant laboratory findings were found, however no measurements were made during the study. This is acceptable.
There were no cases of cancer recorded during this trial.
The percentage of patients who experienced serious TEAEs was higher in the insulin glargine group (8 [12.9%] patients) than in the NPH group (2 [3.2%] patients). The differences between groups were mainly due to the imbalanced occurrence of SAEs in the SOCs of Metabolism and Nutrition Disorders. The SAEs events in the glargine group were not assessed to be related to basal insulin, more specifically the two cases of hypoglycemia were related to the injection of short-acting insulin with a skipped or delayed meal.

Regarding to the use of CGM devices, the nine "CGM sensor fracture" events are noted. Use of CGMD is challenging, and the observed AEs are therefore acceptable.
Based on post-marketing off-label experience in children 1 to less than 6 years old, no new safety concerns for this age group was found.
In conclusion, there is no evidence that the safety profile of insulin glargine in young children, age 1-6 years old, with T1DM differs notably from NPH insulin.

1.7. Risk management plan

The MAH submitted an updated Risk Management Plan within this variation procedure

Based on the safety conclusions, the CHMP requested the submission of an updated Risk Management Plan within this procedure in which the data related to malignancies in children in relocated to Part I – Safety Specifications.

Table 1. Summary of the risk management plan (including the changes related to the application presented highlighted). New text is presented in green, and deleted text is in strikethrough.

Safety concern	Proposed pharmacovigilance activities (routine and additional)	Proposed risk minimization activities (routine and additional)
Important Identified risks		
Hypoglycaemia	For the paediatric and adult populations Routine pharmacovigilance, special attention in PSURs	***Routine minimization (labelling information)*** SmPC Section *4.4 Special warnings and precautions for use* *ANNEX 2A* , warns about the possible occurrence of hypoglycaemia. It reminds the adherence of the patient to the dose and to the dietary regimen, to the correct insulin administration and awareness of hypoglycaemic symptoms to reduce the risk of hypoglycaemia. SmPC Section ~~4.~~*4.5 Interaction with other medicinal products ...* *ANNEX 2A* ~~(interactions),~~ refers to the possible interaction with other medicinal products that may enhance the blood-glucose-lowering effect and increase susceptibility to hypoglycaemia. SmPC Section *4.8 Undesirable effects* *ANNEX 2A* , lists hypoglycaemia as the most frequent adverse reaction of insulin therapy
Injection site reactions	For the paediatric and adult populations Routine pharmacovigilance, special attention in PSURs	***Routine minimization (labelling information)*** SmPC Section *4.2 Posology and method of administration* *ANNEX 2A* , indicates the method of administration SmPC Section *4.8 Undesirable effects* *ANNEX 2A* , lists the injection site reactions as a common undesirable effect
Hypersensitivity reactions	For the paediatric and adult populations Routine pharmacovigilance, special attention in PSURs	***Routine minimization (labelling information)*** SmPC Section *4.3 Contraindications* *ANNEX 2A* : known hypersensitivity to insulin glargine or to any of the excipients is a contraindication to its use. SmPC Section *4.8 Undesirable effects* *ANNEX 2A* ,lists the allergic reactions as a rare undesirable effect
Medication errors (insulin mix-ups)	For the paediatric and adult populations Routine pharmacovigilance, special attention in PSUR, ~~Cumulative reports on mix-up at the time of each PSUR to identify all insulin glargine cases reporting mix-ups with other insulins~~	Medical devices issues are being handled in the SmPC of the relevant presentations. ***Routine minimization (labelling information)*** SmPC section *6.6 Special precautions for disposal and other handling* *ANNEX 2A* states that: ~~"Insulin label must always be checked before each injection to avoid medication errors between insulin glargine and other insulins. (see section 4.4)"~~ "Lantus® must not be mixed with any other insulin or diluted. Mixing or diluting

Safety concern	Proposed pharmacovigilance activities (routine and additional)	Proposed risk minimization activities (routine and additional)
		can change its time/action profile and mixing can cause precipitation. Insulin pen; The cartridges are to be used in conjunction with an insulin pen such as OptiPen and other pens suitable for Lantus® cartridges, and as recommended in the information provided by the device manufacturer. The manufacturer's instructions for using the pen must followed carefully for loading the cartridge, attaching the needle, and administering the insulin injection. If the insulin pen is damaged or not working properly (due to mechanical defects) it has to be discarded and a new insulin pen has to be used. If the pen malfunctions (see instruction for using pen), the solution may be drawn from the cartridge into a syringe (suitable for insulin with 100 units/ml) and injected". Cartridge; Before insertion into the pen, the cartridge must be stored at room temperature for 1 to 2 hours. Inspect the cartridge before use. It must only be used if the solution is clear, colourless, with no solid particles visible, and if it is of water-like consistency. Since Lantus® is a solution, it does not require resuspension before use. Air bubbles must be removed from the cartridge before injection (see instructions for using the pen). Empty cartridges must not be refilled". SmPC section *4.4 Special warnings and precautions for use ANNEX 2A* Medication errors have been reported in which other insulins, particularly short-acting insulins, have been accidentally administered instead of insulin glargine. Insulin label must always be checked before each injection to avoid medication errors between insulin glargine and other insulins. It warns also about the fact that insulin glargine "…is not the insulin of choice for treatment of diabetes ketoacidosis…In case of insufficient glucose control or a tendency to hyper- or hypoglycaemic episodes, the patient's adherence to the prescribed treatment regimen, injection sites and proper injection technique and all other relevant factors should be reviewed before dose adjustment is considered. Transferring a patient to another type or brand of insulin should be done under strict medical supervision."

Safety concern	Proposed pharmacovigilance activities (routine and additional)	Proposed risk minimization activities (routine and additional)
		~~*Additional minimization*~~ ~~Training guides are provided for all insulin pen delivery devices (re-usable and disposable) used with insulin glargine~~
Important Potential Risks		
Malignancies	For the adult and paediatric population: Routine pharmacovigilance, special attention in PSURs, recording and analysis of spontaneous reporting (post marketing surveillance) For the adult population specifically: One RCT: Study HOE901/4032 / LTS6035/The ORIGIN trial Three~~Three~~ epidemiological studies	***Routine minimization (labelling information)*** Theoretical risk only, not described in the SmPC.
Antigenicity	For the paediatric and adult populations: Routine pharmacovigilance, special attention in PSURs	***Routine minimization (labelling information)*** SmPC Section *4.4 Special warnings and precautions for use* *ANNEX 2A*, indicates that insulin administration may cause antibodies to form
Important missing information		
Use in pregnancy	Routine pharmacovigilance	***For the adult population*** ***Routine minimization (labelling information)*** SmPC section *4.6 Fertility, pregnancy and lactation* *ANNEX 2A*: informs about the lack of adequate data in pregnancy, and that caution should be exercised when prescribing to pregnant women, careful monitoring of glucose control being essential.

The CHMP, having considered the data submitted, was of the opinion that routine pharmacovigilance was adequate to monitor the safety of the product.

No additional risk minimisation activities were required beyond those included in the product information.

1.8. Changes to the Product Information

The MAH proposed to update Product Information in order to reflect Lantus use in children aged 1 to less than 6 years old.

During the procedure, based on scientific assessment the CHMP concluded that Lantus use can be authorised only to children aged 2 to less than 6 years old. The MAH was requested to update PI accordingly.

The following changes to the Product Information (PI) were endorsed by the CHMP (new text in bold and underlined and deleted text marked as strikethrough):

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of **diabetes mellitus in** adults, adolescents and children **aged ~~of 6~~ 2** years **and** ~~or~~ above ~~with diabetes mellitus, where treatment with insulin is required~~.

4.2 Posology and method of administration

[...]

Paediatric population
Safety and efficacy of Lantus have been established in adolescents and children **aged** ~~of 6~~ **2** years and **older** ~~above~~. **(see section 5.1). Lantus has not been studied in children below the age of 2 years.**
~~In children, efficacy and safety of Lantus have only been demonstrated when given in the evening. Due to limited experience on the efficacy and safety of Lantus in children below the age of 6 years, Lantus should only be used in this age group under careful medical supervision.~~

4.8 Undesirable effects

[...]

Paediatric population

In general, the safety profile for children and adolescents (≤ 18 years of age) is similar to the safety profile for adults.
The adverse reaction reports received from post marketing surveillance included relatively more frequent injection site reactions (injection site pain, injection site reaction) and skin reactions (rash, urticaria) in children and adolescents (≤ 18 years of age) than in adults.
~~No c~~ Clinical study safety data are **not** available **for**~~in~~ children **under ~~below 6~~ 2** years ~~of age~~.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

[...]

A 24-week parallel group study was conducted in 125 children with type 1 diabetes mellitus aged 2 to 6 years, comparing insulin glargine given once daily in the morning to NPH insulin given once or twice daily as basal insulin. Both groups received bolus insulin before meals. The primary aim of demonstrating non-inferiority of insulin glargine to NPH in all hypoglycaemia was not met and there was a trend to an increase of hypoglycemic events with insulin glargine [insulin glargine: NPH rate ratio (95% CI) = 1.18 (0.97-1.44)]. Glycohaemoglobin and glucose variabilities were comparable in both treatment groups. No new safety signals were observed in this trial.

5.2 Pharmacokinetic properties

[...]

Paediatric population

~~No specific pharmacokinetics study in children or adolescents was conducted~~ **Pharmacokinetics in children aged 2 to less than 6 years with type 1 diabetes mellitus was assessed in one clinical study (see section 5.1). Plasma "trough" levels of insulin glargine and its main M1 and M2 metabolites were measured in children treated with insulin glargine, revealing plasma concentration patterns similar to adults, and providing no evidence for accumulation of insulin glargine or its metabolites with chronic dosing.**

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

In support of the extension of indication 1 clinical study EFC11202 was submitted.

Study EFC11202 was a 24-Week multinational, multicenter, randomised, open-label, 2 parallel arms, Phase 3b study comparing the efficacy and safety of insulin glargine (Lantus) as basal insulin, administered once daily before breakfast, versus Neutral Protamine Hagedorn (NPH) insulin administered 1 or 2 times daily in children with T1DM aged at least 1 year to less than 6 years. However, no children below the age of 2 years were included in the glargine group.

Blood glucose registration was performed using a CGMS for a minimum of 6 days of useable glucose values during at least 5 occasions during treatment. This is the first study using CGM devices to study the efficacy of insulin Lantus. Furthermore, FSBG values were recorded during the whole study duration.

The primary objective was to determine the efficacy of insulin glargine compared to NPH insulin on the rate of "all hypoglycaemia", as measured by using CGMS, FSBG and reported symptomatic events. The study design was according the agreements made during the PIP-procedure.

Out of 125 randomised patients, 61 were randomised to insulin glargine and 64 to NPH insulin. A total of 111 patients completed the 24-week study treatment: 57 (93.4%) patients treated with insulin glargine compared to 54 (84.4%) patients treated with NPH. Among the completers, 99 patients (48 for insulin glargine and 51 for NPH insulin) satisfied the protocol required CGM performance.

Benefits

In the trial, baseline HbA1c levels were comparable between groups. The mean HbA1c at end of study was slightly lower in the glargine group (8.07%) versus the NPH group (8.34%). In either treatment group 22 – 23% of patients achieved an HbA1c in the target range (≤7.5%) by the end of treatment.

Furthermore, the variability in blood glucose was comparable between the treatment groups. Most of the variability in CGM glucose fluctuations appeared to depend more on bolus insulin dosing rather than basal insulin dosing. It was proposed that the age limit in the indication is set to 2 years of age due to the lack of clinical experience in children below this age.

In this study, insulin glargine was injected once daily, while most patients in the NPH insulin treatment group received two injections for basal insulin. The reduced number of injections in the glargine group, together with comparable glucose levels between the treatment groups, could be of benefit for young children.

With respect to pharmacokinetics, there is a large uncertainty in the measured Ctrough values, with coefficients of variation of more than 150% in the values of the main metabolite M1. This high variability may be due to the variability in dose, the number of clinical sites used in this study. There is no accumulation of the main metabolite (M1) of insulin glargine after multiple dosing. The comparison with data from adults demonstrates that the plasma concentration pattern in the children (2 – 6 years) is qualitatively and quantitatively similar to the adults.

Risks

The proportions of patients with TEAEs were generally comparable between the two treatment groups (40 [64.5%] patients for insulin glargine versus 43 [68.3%] patients for NPH insulin), and the majority of TEAEs were mild in severity. Most TEAEs were typical for this age range. The most commonly reported TEAEs by treatment group were gastroenteritis, nasopharyngitis, and pharyngitis (each affecting 6 [9.7%] patients) in the insulin glargine group and pyrexia (7 [11.1%] patients) and gastroenteritis and upper respiratory tract infection (each affecting 6 [9.5%] patients) in the NPH group. The TEAEs which occurred in the insulin glargine group were generally not considered related to insulin glargine, and raised no new safety concern in this age group.

The percentage of patients who experienced serious TEAEs was higher in the insulin glargine group (8 [12.9%] patients) than in the NPH group (2 [3.2%] patients), mainly due to the imbalanced occurrence of SAEs in the SOCs of Metabolism and Nutrition Disorders (2 hypoglycaemic seizures, 1 diabetic ketoacidosis, and 1 dehydration in the insulin glargine group; 1 diabetic ketoacidosis in the NPH group) and Gastrointestinal Disorders (2 gastritis and 1 abdominal pain in the insulin glargine group). All 8 serious TEAEs in the insulin glargine group were assessed as not related to basal insulin by the Investigator, and all subjects recovered.

There were no cases of cancer diagnosed in the study.

Over the 24-week on-treatment period, nearly all individuals in each treatment group (98.4% for NPH insulin and 100% for insulin glargine) experienced hypoglycaemia. The analysis of "all hypoglycaemia" incidence rate (without any distinction of severity) was 192.75 per patient-year for insulin glargine and 168.91 per patient-year for NPH glargine, with an incidence ratio of 1.18 and 95% CI = (0.97; 1.44).

Based on the criteria for the primary analysis, treatment with insulin glargine did not demonstrate the pre-specified non-inferiority in the rate of "all hypoglycaemia" compared to NPH insulin.

The separate components of the primary outcome of "all hypoglycaemia" were analysed individually. The *symptomatic hypoglycaemia* events were more common in the NPH group than in the glargine group. Mean (SD) number of events: 11.52 (16.86) in the glargine group, versus 13.42 (20.62) in the NPH group. Resulting in an estimate ratio of mean event rates of 0.76 with 95% CI= (0.46; 1.25). Symptomatic hypoglycaemia is often used as variable in studies, but is not as reliable as CGMS in tracking hypoglycaemic events. Especially in this age group, hypoglycaemia unawareness (or not able to communicate the hypoglycaemia to the care takers) could be common.

The occurrence of *confirmed low CGM excursions* <70 mg/dL (3.9 mmol/L) was similar between the treatments. The estimate ratio of mean event rates between glargine and NPH was 1.06, with 95% CI= (0.79; 1.42).

The mean number of *all low FSBG* events was higher in the glargine group, compared to the NPH group, 85.87 versus 66.27 events respectively. The estimate (SE) ratio of mean event rates between glargine and NPH was 1.18 (0.12), with 95% CI: (0.96; 1.45).

There were two severe hypoglycaemic events in the glargine group with seizure. In both cases, these events were most likely caused by other clinical circumstances, such as missed or reduced carbohydrate intake, unusual physical activity, or excessive bolus insulin dosing.

Overall, no specific concerns were raised with the safety observations in the study population over the 24-week treatment period. This study in paediatrics 2-6 years old demonstrated that treatment with glargine as basal insulin administered once daily was well tolerated as compared to treatment with NPH insulin. There were no new safety signals found in this young age group.

Balance

The CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.

The clinical Study EFC11202 in children aged 1 to less than 6 years with T1DM demonstrated that treatment with insulin glargine as basal insulin administered once daily in combination with multiple injections of short-acting insulin was as efficient as NPH with respect to glucose control as measured by HbA1c. According to the diabetes guideline, HbA1c should be considered as the primary endpoint also in children and this has been the basis for paediatric approval for other insulin analogues. However, in the current study the primary endpoint was "all hypoglycaemic events" and for this endpoint non-inferiority was not shown. The difference in "all hypoglycaemic events" was driven by the component FSBG which clearly clustered around meal times, indicating that this endpoint may have been driven by bolus rather than basal insulin injections. The increase in hypoglycaemic events could also have been caused by slightly better glucose levels, and lower HbA1c levels in the glargine treatment group. The increase in hypoglycaemic events was however small, and the standard deviation of hypoglycaemic events was in both treatment groups rather large. No new safety signals were discovered in the study.

The risk/benefit balance for insulin glargine in paediatrics 2 to less than 6 years old is considered positive. However, due to the lack of clinical experience and PK/PD data in children below the age of 2 years, treatment is not recommended in this group.

Most patients in the insulin glargine group received basal insulin once daily, while most paediatrics in the NPH insulin group needed two injections of basal insulin. This reduction in insulin injections in the insulin glargine group could be considered to be an advantage in this age group.

In this study glargine was shown to be as effective as NPH insulin in controlling blood glucose in pediatrics with T1DM. However, due to the lack of clinical experience in children below the age of 2 years, treatment is not recommended in this group. The risk/benefit balance for insulin glargine in pediatrics 2 to less than 6 years old is considered positive.

In addition, the CHMP considered that future PSURs will provide separate analysis on cases reported in the paediatric and the adult population.

3. Recommendations

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 changes:

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

Extension of indication for the use of Lantus in children aged 2 to less than 6 years affecting sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC. The Package Leaflet was proposed to be updated in accordance.

In addition, the MAH took the opportunity to update the list of local representatives in the Package Leaflet.

The requested variation proposed amendments to the Update of Summary of Product Characteristics and Package Leaflet.

Conditions and requirements of the marketing authorisation

Risk management system and PSUR cycle

The MAH must ensure that the system of pharmacovigilance, presented in Module 1.8.1 of the marketing authorisation, is in place and functioning before and whilst the product is on the market.

The MAH shall perform the pharmacovigilance activities detailed in the Pharmacovigilance Plan, as agreed in 2.1 of the Risk Management Plan (RMP) presented in Module 1.8.2 of the marketing authorisation and any subsequent updates of the RMP agreed by the CHMP.

As per the CHMP Guideline on Risk Management Systems for medicinal products for human use, the updated RMP should be submitted at the same time as the next Periodic Safety Update Report (PSUR).

In addition, an updated RMP should be submitted:

- When new information is received that may impact on the current Safety Specification, Pharmacovigilance Plan or risk minimisation activities
- Within 60 days of an important (pharmacovigilance or risk minimisation) milestone being reached
- at the request of the EMA

Paediatric Data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/133/2009 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.