22 September 2011
EMA/CHMP/521798/2011
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Levemir

insulin detemir

Procedure No.: EMEA/H/C/000528/II/0051

Note

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

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1. Scientific discussion

1.1. Introduction

Insulin detemir (Levemir) received marketing authorisation from the European Commission on 1 June 2004 and by the Food and Drug Agency (FDA) on 16 June 2005, and has since been marketed in more than 60 countries worldwide. It was originally approved for use in the treatment of diabetes mellitus as a long-acting basal insulin in combination with meal-related insulin and subsequently also in combination with oral antidiabetic drugs. Insulin detemir is to be administered s.c. once or twice daily, and the dose is to be adjusted individually, depending on the subjects' needs.

In the EU, the indication was subsequently extended to include paediatric subjects ≥ 6 years of age on 29 March 2005 (Commission Decision) based on the results of a confirmatory clinical efficacy and safety trial in children and adolescents aged 6-17 years (NN304-1379).

In the US, Levemir was initially approved for once- or twice-daily subcutaneous administration for the treatment of adult and paediatric patients with type 1 diabetes mellitus or adult patients with type 2 diabetes mellitus who require basal (long acting) insulin for the control of hyperglycaemia. As with the EU label, the indication for paediatric subjects between ages 6-17 years was also based on clinical trial NN304-1379.

The paediatric clinical development programme for the use of insulin detemir consists of four trials: One completed clinical pharmacology trial (NN304-1222), one completed phase 3a clinical efficacy and safety trial (NN304-1379), one completed phase 3b clinical efficacy and safety trial (NN304-1689) and a phase 3b clinical efficacy and safety trial (NN304-1690), which is an extension trial to Trial NN304-1689.

The long-term safety trial (NN304-1689) was performed with children and adolescents with type 1 diabetes to investigate the long-term safety of the product in paediatric subjects including the development of insulin antibodies in children during at least 52 weeks of treatment. Since the time for peaking of insulin antibodies in children was not known, an extension trial of a further 52 weeks (Trial NN304-1690) was performed. Children with Type 1 diabetes in the insulin detemir treatment group were followed for the development in insulin antibodies for a total of 104 weeks of treatment.

The present application for extension of the indication to include children 2-5 years of age is based on these 2 trials NN304-1689 and NN304-1690. The studies were discussed with the EMA through scientific advice as part of a post-approval commitment. Consequently, both trials have been submitted as part of a FUM and the paediatric article 46, where the Agency has assessed the trials and found them adequate to fulfill the FUM. In addition, the 2 trials are included in the PIP that was approved by PDCO and verified for compliance.

The application implies changes in section 4.1, 4.2 and 5.1 of the SPC, a minor change in the RMP and changes in section 1 and 3 of the Package leaflet.

The variation submitted is the following:

Variation(s) requested		**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 Levemir in children aged 2-5 years affecting sections 4.1, 4.2 and 5.1 of the SmPC. Package Leaflet has been updated accordingly. Also Annex II has been updated to reflect new version number of the Risk Management Plan.

Information on Paediatric requirements

Pursuant to Article 8 of Regulation (EC) N° 1901/2006 as amended, the application included an EMA decision P/269/2010 for the following conditions:

- Treatment of Type 1 Diabetes Mellitus
- Treatment of Type 2 Diabetes Mellitus

On the agreement of a paediatric investigation plan (PIP).

The PIP is not yet completed.

1.2. Clinical pharmacology

No new data.

Discussion on clinical pharmacology

PK and PD data in the population below six years are needed, as agreed on with the PDCO. Study NN1250-3561, a 6 + 6 months multi-national, open-label, randomised trial to investigate (among other objectives) the pharmacokinetics of insulin detemir in different age groups using a sparse sampling approach and population PK modelling will be performed. Results are awaited.

1.3. Clinical efficacy

1.3.1. Dose response study

N/A

1.3.2. Main studies

Trial NN304-1689 was a 52-week open-label randomised, multi-national, controlled trial designed both to confirm the efficacy and safety of insulin detemir treatment in children and adolescents aged 2-16 years diagnosed with type 1 diabetes, and to evaluate the potential effects of long-term insulin antibody development. Young children aged 2-5 years were included in this long-term trial in order to obtain clinical data in this age group. Subjects were treated with either insulin detemir or Neutral Protamine Hagedorn (NPH) insulin in a basal-bolus regimen with rapid acting insulin aspart (NovoRapid) at meals. Parameters were both efficacy (glycaemic control) and safety including development of insulin antibodies. The trial included 10 visits at the clinical trial site.

Trial NN304-1690 was an open-label, multi-national, multi-centre, single arm, 52-week extension of Trial NN304-1689 of insulin detemir administered once or twice daily to children and adolescents (3-17 years) diagnosed with type 1 diabetes. At entry to this trial the subjects had finalised 52-week treatment with insulin detemir in NN304-1689. Subjects treated with NPH insulin in Trial NN304-1689 were not offered to continue in the extension, due to the fact that the primary endpoint of the extension trial was to study the development of insulin detemir-insulin aspart cross-reacting antibodies following a 104-week period (52 weeks in NN304-1689 and 52 weeks in NN304-1690) of insulin detemir treatment. All subjects in the insulin detemir arm who continued their insulin detemir treatment also received insulin aspart as bolus insulin before main meals and larger snacks. The key

efficacy and safety parameters were the same as in Trial NN304-1689. The trial included a total of 5 visits to the clinical trial sites, of which the first was at the same time as the last visit in Trial NN304-1689.

1.3.2.1. Methods

The table below gives an overview of the two trials

Trial Country	Treatment	Dosing	Design	Objectives	Exposure
NN304-1689 35 sites in 11 countries (BG, DK, CZ, FI, FR, HU, MK, PL, RU, TR, UK)	IDet+IAsp versus NPH+IAsp Basal insulin once or twice daily Bolus insulin with meals	Basal-bolus adjusted to individual requirements	52-week, multi-centre, open-label, randomised, parallel Efficacy endpoints: • HbA_{1c} • FPG • 9-point SMPG profiles • With-in subject variation • Nocturnal SMPG	Efficacy and Safety	347 children and adolescents: • Young children 2–5 yrs: IDet: 42; NPH: 40 • Children 6–12 yrs: IDet: 79; NPH: 88 • Adolescents 13–16 yrs: IDet: 56; NPH: 42
NN304-1690 29 sites in 11 countries: (BG, DK, CZ, FI, FR, HU, MK, PL, RU, TR, UK)	IDet+IAsp Basal insulin once or twice daily Bolus insulin with meals	Basal-bolus adjusted to individual requirements	52-week, multi-centre, open-label, single arm Efficacy endpoints: • HbA_{1c} • FPG	Efficacy and Safety	146 children and adolescents: • Young children 2–5 yrs: IDet:37 • Children 6–12 yrs: IDet: 59 • Adolescents 13–16 yrs: IDet: 50

IDet: insulin detemir; IAsp: insulin aspart; NPH: NPH insulin; yrs: years; HbA_{1c}: glycosylated haemoglobin; FPG: fasting plasma glucose; SMPG: self-measured plasma glucose

Treatments

Insulin detemir or NPH insulin were to be administered once or twice daily at the same time as the basal insulin was given prior to randomisation. The insulin detemir and NPH insulin injections administered s.c. in the thigh using the NovoPenJunior Green injection device. The injection area was to remain unchanged throughout the trial even if a single dose was delivered as more than one injection. Subjects were instructed to rotate the site of injection within the area chosen in order to prevent lipohypertrophy. Subjects on a previous once-daily basal insulin regimen were to continue on a once-daily regimen. Likewise, subjects on previous twice-daily or more frequent basal insulin regimens were to continue on a twice-daily regimen. However, subjects were permitted to switch from a once-daily to a twice-daily regimen (and vice versa) based on the investigators' judgement in relation to titration targets.

All subjects received insulin aspart as bolus insulin immediately before or after main meals. Insulin aspart was administered s.c. in the abdomen preprandially 2-4 times a day, in connection with main meals using the NovoPenJunior Yellow injection device. Extra doses were permitted in connection with larger snacks. Subjects taking bolus insulin postprandially before randomisation were to continue to do so. All subjects were switched from their previous insulin regimen to randomly allocated trial treatment with insulin detemir or NPH insulin on a unit-to-unit basis. If subjects were on a mixed insulin regimen (once or twice daily), the corresponding basal insulin dose was calculated and used as the initial dose. If mixed insulin was used three times daily, the basal component was calculated, and the equivalent dose was administered as one third in the morning and two thirds in the evening.

All subjects were to be individually titrated on a continual basis according to pre-specified plasma glucose (PG) targets adopted from the International Society for Paediatric and Adolescent Diabetes (ISPAD) Guidelines (see Table below).

The table below shows Plasma Glucose Targets for Glycaemic Control

Fasting/preprandial PG	Postprandial PG: 1–3 hours after a meal	Nocturnal PG
4.0–7.0 mmol/L (72–126 mg/dL)	5.0–11.0 mmol/L (90–198mg/dL)	≥ 3.6 mmol/L (65 mg/dL)

PG: plasma glucose

Comparator:

In Trial N304-1689, NPH insulin was chosen as the comparator because it is conventionally used as basal insulin in children and adolescents on a basal-bolus regimen, and because NPH insulin has a well established efficacy and safety profile. As one of the secondary objectives of this trial was to investigate antibody development during long-term treatment, a comparator with a well-known safety profile was considered important. No comparator was included in NN304-1690 as only insulin detemir treated subjects were offered to continue in the extension trial.

In both Trial NN304-1689 and NN304-1690 insulin aspart was chosen as the bolus component of a basal-bolus regimen. The rapid-acting property of insulin aspart is a particular advantage in this trial population due to a more variable and unpredictable life style pattern in children and adolescents. Furthermore, insulin detemir is most likely to be used together with a fast-acting insulin analogue in clinical practice.

The algorithm used for basal insulin doses is shown in Table below and indicates the suggested increase in the basal insulin dose based on the average of the three PG values measured before breakfast and dinner. If a subject had only measured PG values on 2 of the last 3 days prior to the contact, titration of the basal insulin dose was to be based on these values. If only one measurement was available, this was used to assess the need for insulin dose adjustment at the discretion of the investigator. The algorithm was only to be used if there had been no major hypoglycaemic episodes and/or PG values ≤4.0 mmol/L (≤72 mg/dL) without obvious explanations between two consecutive contacts.

Algorithm for Titration of Basal Insulin Dose

Current dose		< 5U	5-15U	> 15U
FPG or pre-dinner PG		Adjustment (U)		
< 4.0 mmol/L	< 72 mg/dL	Reduce according to local practice	Reduce according to local practice	Reduce according to local practice
4.1-7.0 mmol/L	72-126 mg/dL	0	0	0
7.1-10.0 mmol/L	126-180 mg/dL	+ ½	+ 1	+ 2
10.1-15.0 mmol/L	181-270 mg/dL	+ 1	+ 2	+ 4
> 15.0 mmol/L	> 270 mg/dL	+ 1½	+ 3	+ 5

FPG: fasting plasma glucose; PG: plasma glucose

A similar algorithm was used for the titration of bolus insulin doses.

Endpoints

Endpoint	Description
Primary endpoint	
HbA_{1c}	• Analysed at a central laboratory using a High Performance Liquid Chromatography method.
Secondary endpoints	
Fasting plasma glucose (FPG)	• Subjects were instructed in how to use the home blood sampling kit provided by Novo Nordisk at the screening visit, • Subjects were asked to take blood samples for assessing FPG in the mornings prior to visits to the trial site at baseline, at approximately 3-months during the trial, and at the final visit. FPG was analysed at a central laboratory using the hexokinase method.
SMPG [a.]	• Subjects were asked to measure plasma glucose on the last 3 days before each scheduled visit or telephone contact throughout the trial • Timing of SMPG ▪ Before breakfast ▪ Before dinner
9-point SMPG profile[a.b.]	• Subjects were asked to record 9-point profiles on a normal weekday 4-7 days prior to visits (baseline, 26 weeks, and 52 weeks). • Timing of 9-point SMPG Profiles: ▪ Before breakfast ▪ 90 minutes after start of breakfast ▪ Before lunch ▪ 90 minutes after start of lunch ▪ Before dinner ▪ 90 minutes after start of dinner ▪ At bedtime ▪ At 3 a.m. ▪ Before breakfast the following day
Within-subject variation of SMPG [b.]	• Calculated based on a combination of SMPG values measured during the last 7 days prior to last visit (52 weeks) ▪ Latest 3 SMPG values before breakfast and before dinner ▪ Two SMPG values before breakfast and one before dinner from the 9-point SMPG profile
Nocturnal SMPG [b.]	• Taken from the 9-point SMPG profile value at 3 a.m. at 52 weeks

a. SMPG measurements and 9-point profile were not to be performed on the same days

b. 9-point SMPG profiles, within-subject variation and Nocturnal SMPG were not efficacy endpoint in NN304-1690.

Selection criteria:

<table>
<tr><th>Selection Criteria[a]</th><th>Specifications</th></tr>
<tr><td>Subjects</td><td>Boys and girls diagnosed with type 1 diabetes ≥ 12 months prior to inclusion</td></tr>
<tr><td>Age</td><td>Between 2–16 years at randomisation</td></tr>
<tr><td>HbA_{1c}</td><td>≤ 11%</td></tr>
<tr><td>BMI</td><td>Maximum BMI according to Age and Sex
<table>
<tr><th>Sex</th><th>2–7 years</th><th>8–9 years</th><th>10–11 years</th><th>12–13 years</th><th>14–16 years</th></tr>
<tr><td>Boys</td><td>≤ 20 kg/m^2</td><td>≤ 20 kg/m^2</td><td>≤ 22 kg/m^2</td><td>≤ 24 kg/m^2</td><td>≤ 25 kg/m^2</td></tr>
<tr><td>Girls</td><td>≤ 20 kg/m^2</td><td>≤ 21 kg/m^2</td><td>≤ 23 kg/m^2</td><td>≤ 25 kg/m^2</td><td>≤ 27 kg/m^2</td></tr>
</table></td></tr>
<tr><td>Current therapy</td><td>• Insulin detemir naïve (all other insulins and insulin regimens were allowed)
• Total daily dose of insulin ≤ 2 Units (U)/kg</td></tr>
<tr><td>Exclusion criteria</td><td>• Known or suspected allergy to trial product(s) or related products
• Significant concomitant disease such as endocrine, hepatic, renal, cardiac, respiratory, neurological, gastrointestinal, malignant or pancreatic diseases as judged by the investigator
• Mental incapacity, unwillingness or language barriers, precluding adequate understanding or co-operation (child and parent should be evaluated as a unit)
• The receipt of any investigational drug within 1 month prior to this trial
• Known hypoglycaemic unawareness as judged by the investigator or recurrent major hypoglycaemic events
• Any disease or condition that the investigator feels will interfere with the trial (e.g., highly variable eating habits, employment as a shift worker, etc.)</td></tr>
</table>

Statistical Methods

Sample size

The primary objective of Trial NN304-1689 was to confirm efficacy of insulin detemir in combination insulin aspart in terms of glycaemic control. This was done by showing that insulin detemir + insulin aspart is non-inferior to NPH + insulin aspart in terms of glucose lowering effect as assessed by mean change from baseline in HbA1c after 52 weeks of treatment using a non-inferiority margin of 0.4% (absolute). Sample size was determined based on this primary objective.

The non-inferiority margin of 0.4% (absolute) was chosen in accordance with the FDA guidance. Let D be the mean treatment difference for change in HbA1c (insulin detemir + insulin aspart minus NPH + insulin aspart). The null-hypothesis was tested against the alternative hypothesis of noninferiority as given by H_0: D > 0.4% against H_A: D ≤ 0.4%

Operationally the null-hypothesis was rejected and non-inferiority considered confirmed if the upper bound of the two-sided 95% confidence interval for the mean HbA1c treatment difference was below or equal to 0.4%. This is equivalent to using a one-sided test of size 2.5%.

Sample size is determined using a t-statistic under the assumption of a one-sided test of size 2.5% and a zero mean treatment difference (i.e. D=0%). Based on experience from previous insulin detemir trial with children and adolescents (aged 6-17 years) a conservative estimate for the standard deviation (SD) of 1.1% for HbA1c was used in the sample size calculation.

As NN304-1689 is a non-inferiority trial sample size was determined such that the anticipated power is at least 85% in the evaluation of the PP analysis set. The number of subjects excluded from the PP analysis set is dependent on the trial design. In this trial an estimate of 20% was used and sample size was ceiled in the FAS to have integer sample size for each group that adheres exactly to the group allocation weights (1:1). Hence the total number of subjects to be randomised was 344 subjects in order to have at least 85% power in the evaluation of the PP analysis set.

A total sample size of 344 subjects and a drop-out rate of 20% would yield 274 subjects for evaluation of HbA1c. No separate sample size was calculated for young children between 2–5 years, since it was considered very difficult to include enough young children in the trial to have sufficient statistical power for statistical analysis, due to the low prevalence of diabetes in young children below 6 years.

Since the primary endpoint in Trial NN304-1690 was a safety endpoint, only secondary efficacy endpoints were included in this trial. The secondary efficacy endpoints in this trial were HbA1c and FPG at end of the trial (after 104 weeks of treatment). As NN304-1690 was an extension to trial NN304-1689, no sample size calculation has been made for this trial. However, assuming that 120 were treated with insulin detemir in the trial with a drop out rate of 15%, it would be possible to detect, with more than 80% power, a slope of 0.06 in cross-reacting antibody reduction over time at a 5% significance level. Standard deviation for the cross-reacting antibody measurements was estimated to 23%.

Efficacy Analysis Sets

In **Trial NN304-1689** two efficacy analysis sets were defined:

1. Full analysis set (FAS) implemented according to the intention to treat principle, used for efficacy analyses: All randomised subjects exposed to at least one dose of trial product with a post baseline observation, classified according to randomised treatment.
2. Per-protocol analysis set (PP): All exposed subjects who completed the trial without significantly violating the inclusion/exclusion criteria or other aspects of the protocol considered to potentially affect the efficacy results and who fulfilled the prespecified criteria for being included in the PP analysis set.

The primary efficacy analysis was based on both the FAS and the PP analysis set. All secondary efficacy analyses were based on the FAS.

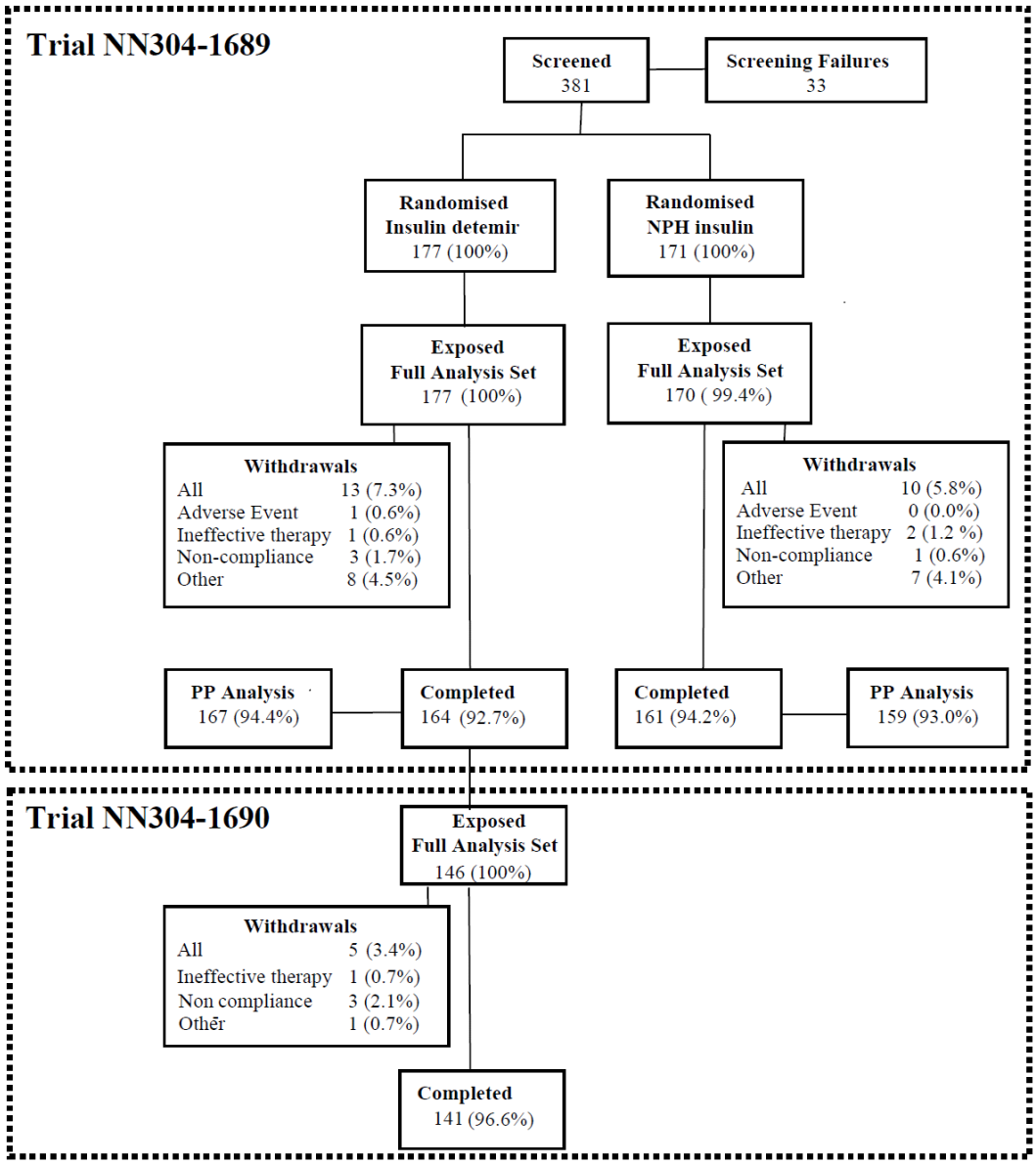
In **Trial NN304-1690** one efficacy analysis set was defined:

- Full analysis set (FAS**,** NN304-1690) implemented according to the intention to treat principle. The FAS is normally defined as all randomised subjects exposed to at least one dose of trial product with a post observation, classified according to randomised treatment. In Trial NN304-1690, the specific definition of FAS is different, since the subjects are not randomised, namely subjects with signed informed consent who are exposed to trial drug in the extension period. Since the NN304-1690 trial is an extension to the NN304-1689 trial, the FAS in NN304-1690 is a subset of the FAS in NN304-1689.

Results

Subject Disposition

A total of 381 children and adolescents were screened for inclusion in NN304-1689 (see figure below). Thirty-three of these were excluded because of failure to meet all the selection criteria. The main reason for exclusion was failure to meet the inclusion criterion of HbA1c ≤ 11%.



Subject disposition for Trial NN304-1689 and Extension Trial NN304-1690

In total, 348 children and adolescents were enrolled in the trial and randomly allocated to treatment with either insulin detemir or neutral protamine Hagedorn (NPH) insulin, in a basal-bolus regimen with insulin aspart as the bolus insulin. One subject allocated to the NPH insulin treatment arm withdrew consent prior to initiating treatment. Thus, 347 subjects were exposed to trial products and therefore included in the FAS. Both the proportion of subjects withdrawn and reasons for withdrawal were similar in the two treatment arms. The primary reason for withdrawal in both treatment arms was 'other' which included unspecified unwillingness to continue (14 subjects).

The proportion of subjects completing the trial was similar with both treatments, as was the proportion of subjects who completed the trial without significantly deviating from the protocol in ways that could potentially affect the efficacy results (i.e., the PP analysis set).

Subject disposition by Age Group, NN304-1689

Age Group 2–5 Years	Detemir	NPH	Total	% trial pop.
Randomised	42 (100.0%)	40 (100.0%)	82 (100.0%)	23.6%
Exposed	42 (100.0%)	40 (100.0%)	82 (100.0%)	
Withdrawals	1 (2.4%)	1 (2.5%)	2 (2.4%)	
Adverse event	1 (2.4%)	0 (0.0%)	1 (1.2%)	
Inefficient therapy	0 (0.0%)	1 (2.5%)	1 (1.2%)	
Completed	41 (97.6%)	39 (97.5%)	80 (97.6%)	
Age Group 6–12 Years				
Randomised	79 (100.0%)	88 (100.0%)	167 (100.0%)	48.1%
Exposed	79 (100.0%)	88 (100.0%)	167 (100.0%)	
Withdrawals	8 (10.1%)	5 (5.7%)	13 (7.8%)	
Inefficient therapy	1 (1.3%)	0 (0.0%)	1 (0.6%)	
Non-Compliance	2 (2.5%)	1 (1.1%)	3 (1.8%)	
Other	5 (6.3%)	4 (4.5%)	9 (5.4%)	
Completed	71 (89.9%)	83 (94.3%)	154 (92.2%)	
Age Group 13–16 Years				
Randomised	56 (100.0%)	43 (100.0%)	99 (100.0%)	28.2%
Exposed	56 (100.0%)	42 (97.7%)	98 (99.0%)	
Withdrawals	4 (7.1%)	4 (9.3%)	8 (8.1%)	
Inefficient therapy	0 (0.0%)	1 (2.3%)	1 (1.0%)	
Non-Compliance	1 (1.8%)	0 (0.0%)	1 (1.0%)	
Other	3 (5.4%)	3 (7.0%)	6 (6.1%)	
Completed	52 (92.9%)	39 (90.7%)	91 (91.9%)	

In total 146 out of 164 insulin detemir treated subjects, who completed Trial NN304-1689, were included in Trial NN304-1690. Only subjects who were treated with insulin detemir in Trial NN304-1689 were offered participation in the extension Trial NN304-1690. The majority of the 18 subjects who did not wish to participate in Trial NN304-1690 were in the age group 6-12 years.

The subjects were distributed between the three age groups with 37 young children (2-5 years), 59 children (6-12 years) and 50 adolescents (13-16 years).

Five subjects were withdrawn during the extension trial NN304-1690, of these one subject from the 2-5 years age group (other reasons: Parents decision), one subject from the 6-12 years age group (inefficient therapy) and three subjects from the 13-16 years age group (non-compliance). No subjects were withdrawn from the extension trial due to adverse events.

Subject disposition by Age Group, NN304-1690

	2-5 Years	6-12 Years	13-16 Years	Total
Included	37 (100.0%)	59 (100.0%)	50 (100.0%)	146 (100.0%)
Exposed	37 (100.0%)	59 (100.0%)	50 (100.0%)	146 (100.0%)
Withdrawals	1 (2.7%)	1 (1.7%)	3 (6.0%)	5 (3.4%)
Inefficient therapy	0 (0.0%)	1 (1.7%)	0 (0.0%)	1 (0.7%)
Non-Compliance	0 (0.0%)	0 (0.0%)	3 (6.0%)	3 (2.1%)
Other	1 (2.7%)	0 (0.0%)	0 (0.0%)	1 (0.7%)
Completed	36 (97.3%)	58 (98.3%)	47 (94.0%)	141 (96.6%)
Full analysis set	37 (100.0%)	59 (100.0%)	50 (100.0%)	146 (100.0%)
Safety analysis set	37 (100.0%)	59 (100.0%)	50 (100.0%)	146 (100.0%)

Demographic and Other Baseline Characteristics

The table below shows the demographic and other baseline characteristics for the children included in study NN304-1689 by age group:

	2-5 years		6-12 years		13-16 years	
	Insulin Detemir	Insulin NPH	Insulin Detemir	Insulin NPH	Insulin Detemir	Insulin NPH
Number of subjects	42	40	79	88	56	42
Age (years)						
Mean (SD)	4.3 (1.19)	4.5 (1.03)	9.8 (1.90)	9.8 (2.07)	14.6 (1.02)	14.6 (0.92)
Median	4	5	10	10	14	15
Min ; Max	2 ; 5	2 ; 5	6 ; 12	6 ; 12	13 ; 16	13 ; 16
Gender						
Female	24 (57.1%)	19 (47.5%)	43 (54.4%)	36 (40.9%)	27 (48.2%)	18 (42.9%)
Male	18 (42.9%)	21 (52.5%)	36 (45.6%)	52 (59.1%)	29 (51.8%)	24 (57.1%)
Race						
White	40 (95.2%)	37 (92.5%)	79 (100%)	87 (98.9%)	55 (98.2%)	41 (97.6%)
Other				1 (1.1%)		1 (2.4%)
Unknown (*)	2 (4.8%)	3 (7.5%)			1 (1.8%)	
Pubertal status						
Tanner Grade 1	42 (100%)	40 (100%)	58 (73.4%)	62 (70.5%)	4 (7.1%)	2 (4.8%)
Tanner Grade 2 Or More			21 (26.6%)	26 (29.5%)	52 (92.9%)	40 (95.2%)
Height (m)						
Mean (SD)	1.05 (0.09)	1.07 (0.09)	1.39 (0.14)	1.39 (0.15)	1.64 (0.10)	1.65 (0.09)
Median	1.05	1.07	1.39	1.39	1.64	1.65
Min ; Max	0.84 ; 1.24	0.87 ; 1.27	1.10 ; 1.65	1.11 ; 1.72	1.41 ; 1.89	1.44 ; 1.84
Body weight (kg)						
Mean (SD)	17.2 (2.47)	18.5 (3.00)	35.5 (9.81)	34.9 (10.8)	54.2 (11.1)	55.8 (10.6)
Median	17	19	34	33	55	55
Min ; Max	13.0 ; 21.9	11.7 ; 26.2	19.8 ; 62.0	18.2 ; 60.4	31.5 ; 77.0	38.0 ; 83.0
BMI (kg/m2)						
Mean (SD)	15.73 (1.27)	16.18 (1.24)	17.88 (2.18)	17.64 (2.27	19.88 (2.91)	20.44 (2.62)
Median	15	16	18	18	20	20
Min ; Max	13.10 ; 19.1	13.36 ; 19.2	13.48 ; 23.4	13.66 ; 23.1	14.58 ; 27.0	15.74 ; 25.4
HbA1c (%)						
Mean (SD)	8.16 (1.12)	8.14 (1.17)	8.52 (1.15)	8.59 (0.99)	8.45 (1.05)	8.25 (1.19)
Median	8	8	9	9	8	8
Min ; Max	6.60 ; 10.9	6.10 ; 11.0	5.60 ; 10.8	6.40 ; 10.8	6.50 ; 11.2	6.30 ; 10.8
FPG (mmol/L)						
Mean (SD)	8.44 (4.86)	8.56 (4.09)	8.39 (4.13)	8.94 (4.58)	8.25 (4.41)	8.32 (5.12)
Median	7	7	8	8	8	7
Min ; Max	2.22 ; 18.3	2.50 ; 19.2	1.61 ; 19.3	2.28 ; 20.4	1.89 ; 20.8	1.33 ; 20.2
Diabetes history (years)						
Mean (SD)	2.20 (1.01)	2.08 (0.82)	3.83 (2.36)	3.89 (2.27)	4.65 (3.37)	4.78 (3.24)
Median	2	2	3	3	4	4
Min ; Max	1.03 ; 5.04	1.03 ; 4.28	1.01 ; 9.72	1.04 ; 11.7	1.09 ; 14.3	1.04 ; 15.5

*: Race not known for French subjects. BMI: body mass index; SD: standard deviation; SAS: safety analysis set

Primary Endpoint – HbA1c, End of Trial

The primary objective in Trial NN304-1689 was to compare the glycaemic control after 12 months of treatment with insulin detemir or NPH insulin administered once or twice daily in combination with mealtime insulin aspart in children and adolescents with type 1 diabetes.Treatment with insulin detemir was shown to be non-inferior to NPH insulin as measured by HbA1c after 52 weeks. The upper confidence interval for the estimated treatment differences in HbA1c was less than the prespecified criterion of 0.4%. The estimated mean absolute change in HbA1c was 0.34% with insulin detemir and 0.22% with NPH insulin, Table below. These results were consistent with the corresponding analysis for the PP analysis set.

Comparison of HbA1c (%) and Change in HbA1c after 52 Weeks, NN304-1689

Insulin Detemir N	Mean (SE)	NPH insulin N	Mean (SE)	Detemir-NPH Diff (95% CI)	Non-inferiority	Superiority
FAS						
HbA1c						
171	8.75 (0.11)	168	8.64 (0.11)	0.12 (-0.12; 0.36)	Yes	No
Change in HbA1c from baseline						
171	0.34 (0.11)	168	0.22 (0.11)	0.12 (-0.12; 0.36)	Yes	No
PP analysis set						
HbA1c						
167	8.75 (0.11)	159	8.62 (0.11)	0.13 (-0.12; 0.37)	Yes	No
Change in HbA1c from baseline						
167	0.35 (0.11)	159	0.22 (0.11)	0.13 (-0.12; 0.37)	Yes	No

The estimated means, mean difference, and the confidence intervals (CI) are based on an analysis of covariance (ANCOVA) model including adjustment for HbA1c at baseline, pubertal status at baseline, country and age stratification at randomisation

Note: Model includes adjustment for HbA_{1c} at Baseline, pubertal status at baseline.

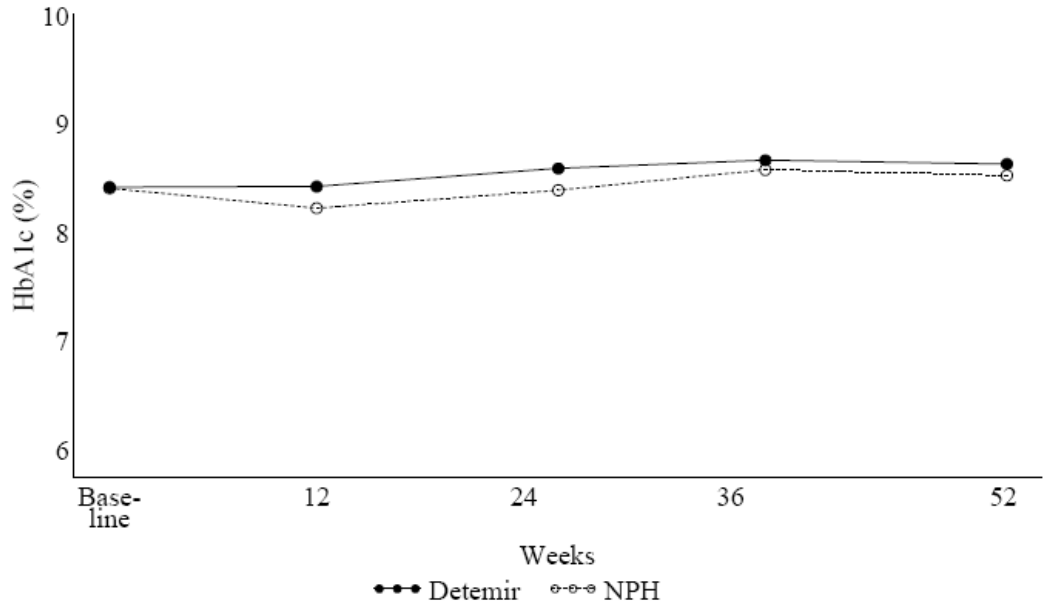
FAS: full analysis set; HbA_{1c}: glycosylated haemoglobin; N: number of subjects; NPH: Neutral Protamine Hagedorn; PP: per protocol; SE: standard error

Country and age stratification at randomisation

Mean: Estimated change from baseline to end of trial

Diff: Estimated difference in change between treatments

Mean HbA1c increased over 52 weeks in both treatment arms, Figure below. Although HbA1c decreased initially with NPH insulin over the first 12 weeks of treatment, the mean level was similar to that with insulin detemir after 52 weeks. The initial decrease in HbA1c in the NPH insulin treatment arm observed over the first 12 weeks of treatment was not sustained. Similar observations were made for the PP analysis set.



FAS: full analysis set; LOCF: last observation carried forward

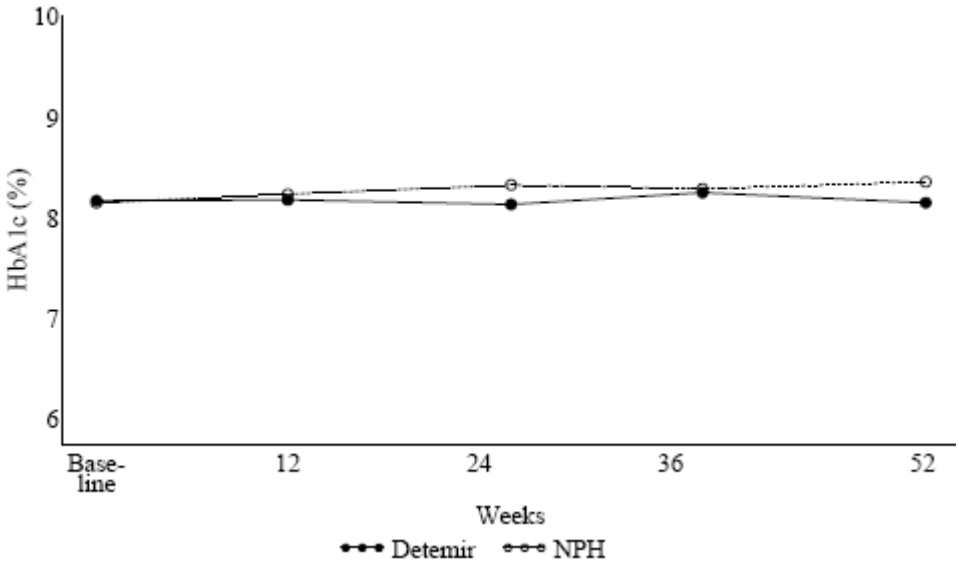
Observed Mean HbA1c (%) over Time (LOCF), FAS, NN304-1689

The table below provides an overview of HbA1c levels in all subjects, and a summary of the young children category. Mean and median HbA1c levels were numerically lower in the young children group, in comparison with all subjects (including the young children). There was a wide distribution in HbA1c levels in all groups.

Overview HbA1c levels in young children and all subjects (FAS) in Study NN304-1689

NN304-1689		**Young Children (2-5 years old)**		**All subjects (2-16 years old)**	
	HbA1c (%)	**Insulin detemir**	**NPH insulin**	**Insulin detemir**	**NPH insulin**
Baseline	n	42	40	177	170
	Mean (SD)	8.16 (1.1)	8.14 (1.2)	8.41 (1.1)	8.42 (1.1)
	Median	8.2	8.2	8.3	8.4
	Min ; Max	6.6 ; 10.9	6.1 ; 11.0	5.6 ; 11.2	6.1 ; 11.0
Week 52	n	41	39	170	168
	Mean (SD)	8.1 (1.2)	8.3 (1.1)	8.6 (1.5)	8.5 (1.2)
	Median	8.0	8.1	8.4	8.3
	Min ; Max	5.7 ; 10.7	6.8 ; 12.4	5.7 ; 15.1	6.0 ; 12.6
Change from baseline to Week 52	Mean (SD)	0.0 (1.0)	0.2 (0.9)	0.2 (1.3)	0.1 (1.1)
	Median	-0.2	0.4	0.0	0.1
	Min ; Max	-1.8 ; 2.4	-1.7 ; 2.4	-2.0 ; 6.1	-2.8 ; 4.3

The slight increase in HbA1c observed with both insulin detemir and NPH insulin described for the total group is largely attributable to suboptimal glycaemic control in the subgroup of adolescents (13-16 years). The figure below shows the mean HbA1c over time for age-group 2-5 years (full analysis set):



As for subjects who continued insulin detemir treatment in the extension trial NN304-1690 for a total of 104 weeks, glycaemic control measured as mean HbA1c was relatively stable during the whole treatment period with a slight increase in observed mean HbA1c from 8.4% at baseline of Trial NN304-1689 to 8.7% by the end of Trial NN304-1690. Mean HbA1c was lowest for the young children (2-5 year) and highest for the adolescents (13-16 year) throughout the whole treatment period of 104 weeks.

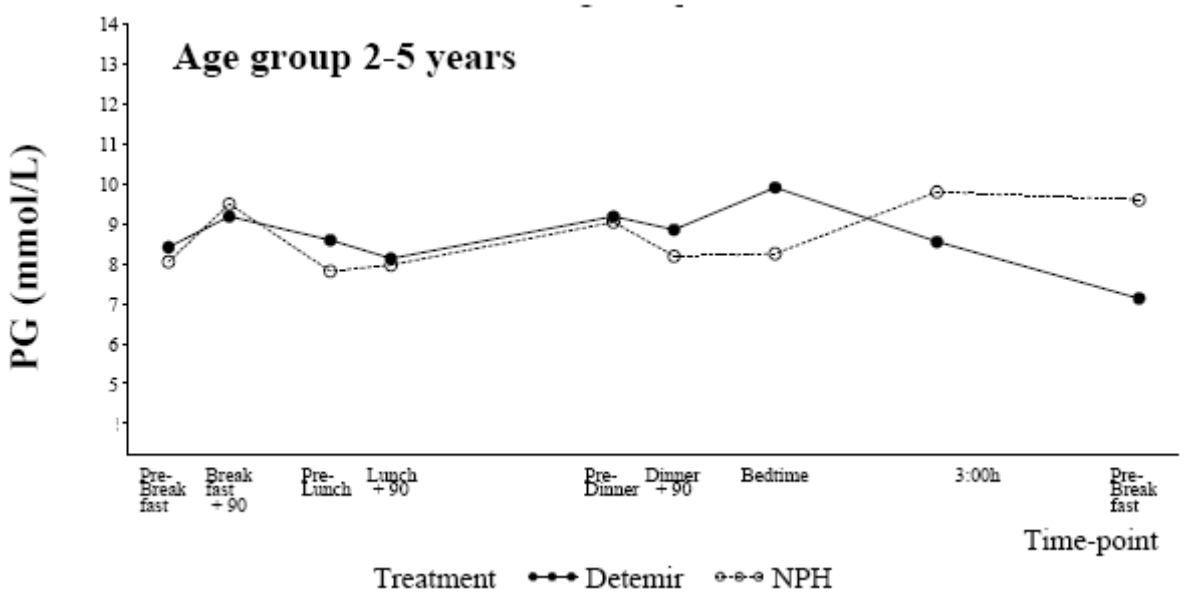
Secondary Endpoint – Fasting Plasma Glucose

Mean FPG varied over time for all age groups and treatment. There was a consistent trend towards lower mean FPG values after 52 weeks with insulin detemir compared to NPH insulin in all three age groups.

When looking at mean FPG for the insulin detemir group throughout the whole treatment period of 104 weeks, mean FPG was highest for the children (6-12 year), whereas mean FPG was lowest for the young children (2-5 year) except at end of trial where mean FPG for subjects in the young children was similar to the mean FPG for the total group and lowest for the adolescents (13-16 year).

Secondary Endpoint – Nine-point Self-measured Plasma Glucose Profiles by Age Groups

The mean 9-point SMPG profiles appeared similar after 52 weeks of treatment with insulin detemir or NPH insulin. The mean pre-breakfast SMPG level at the end of the profile tended to be lower with insulin detemir than with NPH insulin in young children aged 2-5 years Figure below, but this trend was not evident in older children or adolescents.



Observed Mean 9-point SMPG profiles after 52 weeks in children 2-5 years, Study NN304-1689.

Secondary Endpoint – Nocturnal Self-measured Plasma Glucose

Although there were some differences between treatments over time, particularly in young children (2-5 years) and children (6-12 years), mean nocturnal SMPG levels remained similar to baseline after 52 weeks with insulin detemir.

Target Plasma Glucose by Age Groups

Based on the latest 9-point SMPG profile in the trial, the proportion of subjects who achieved the target pre-breakfast and pre-dinner plasma glucose concentration of 4.0–7.0 mmol/L (72–126 mg/dL) and the nocturnal plasma glucose concentration of ≥ 3.6 mmol/L (≥65 mg/dL) after 52 weeks is shown in Table below. The percentage of subjects reaching the targets varied somewhat between the age groups, but in general, young children aged 2–5 years and children aged 6-12 years were more successful at achieving the target pre-breakfast PG values with insulin detemir than with NPH insulin after 52 weeks, whereas more subjects treated with NPH insulin reached pre-dinner target.

Subjects having reached targeted glucose values at end of 52 weeks treatment by age group, FAS, NN304-1689

	Detemir	NPH	Total
All subjects			
Total in FAS	177	170	347
4.0< Pre-breakfast PG <7.0	70 (39.5)	53 (31.2)	123 (35.4)
4.0< Pre-dinner PG <7.0	42 (23.7)	49 (28.8)	91 (26.2)
3.6<= Nocturnal PG	144 (81.4)	138 (81.2)	282 (81.3)
All Three Targets	18 (10.2)	13 (7.6)	31 (8.9)
Age Group 2-5			
Total in FAS	42	40	82
4.0< Pre-breakfast PG <7.0	20 (47.6)	14 (35.0)	34 (41.5)
4.0< Pre-dinner PG <7.0	9 (21.4)	9 (22.5)	18 (22.0)
3.6<= Nocturnal PG	38 (90.5)	34 (85.0)	72 (87.8)
All Three Targets	4 (9.5)	1 (2.5)	5 (6.1)
Age Group 6-12			
Total in FAS	79	88	167
4.0< Pre-breakfast PG <7.0	32 (40.5)	25 (28.4)	57 (34.1)
4.0< Pre-dinner PG <7.0	17 (21.5)	25 (28.4)	42 (25.1)
3.6<= Nocturnal PG	62 (78.5)	72 (81.8)	134 (80.2)
All Three Targets	9 (11.4)	7 (8.0)	16 (9.6)
Age Group 13-16			
Total in FAS	56	42	98
4.0< Pre-breakfast PG <7.0	18 (32.1)	14 (33.3)	32 (32.7)
4.0< Pre-dinner PG <7.0	16 (28.6)	15 (35.7)	31 (31.6)
3.6<= Nocturnal PG	44 (78.6)	32 (76.2)	76 (77.6)
All Three Targets	5 (8.9)	5 (11.9)	10 (10.2)

FAS: Full analysis set; PG: Plasma glucose

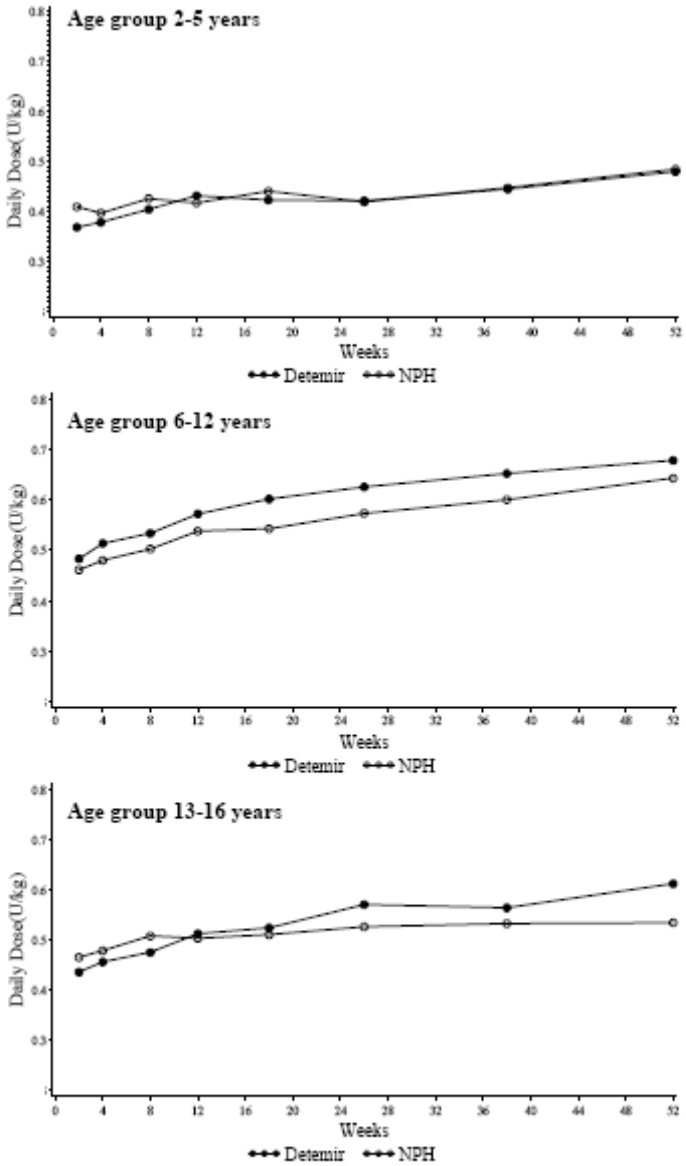
With regard to the target plasma glucose values after 104 weeks of treatment 45.9% of the subjects in the youngest age-group reached the pre-breakfast plasma glucose target, whereas approximately one third of the children and adolescents reached the pre-breakfast and approximately one third of all subjects reached the pre-dinner SMPG targets of plasma glucose levels between 4.0 and 7.0 mmol/L. Between 6.8% and 14% of the subjects in the three age groups reached both plasma glucose targets.

Results analysed by sex

The overall observed mean change in HbA1c from baseline to 52 weeks differed slightly for boys and girls in both treatment groups: females 0.10 (SD 1.18), males 0.35 (SD 1.37). By the end of 104 weeks of treatment the change in mean HbA1c for insulin detemir treated girls was 0.33% and 0.40% for insulin detemir treated boys.

Dose Development by Age Group

The development of mean daily basal insulin doses for the young children (2-5 years), the children (6-12 years) and adolescents (13-16 years) was generally consistent with that observed with the total group.



Mean Daily Basal Insulin Dose over time by age group, SAS, NN304-1689

Discussion on efficacy

The persistence of efficacy in young children, children and adolescents was evaluated over a period of 52 weeks in Trial NN304-1689 and for a subset of insulin detemir treated children over a period of 104 weeks in Trial NN304-1690.

The trial NN304-1689 populations in the two treatment arms were generally well matched, with the exception of differences for sex and fasting plasma glucose (FPG). The proportion of girls allocated to insulin detemir (53%) was higher than in the NPH insulin treatment arm (43%) - and this was true for all age groups. Also, a slightly lower mean FPG was reported at baseline in the insulin detemir arm (8.36 mmol/L) compared with the NPH insulin arm (8.70 mmol/L). Both of these imbalances might be "favourable" for the detemir treatment evaluation; however it is shown to be without significance.

The subjects included in the extension study NN304-1690 did not differ significantly with regard to any of the baseline characteristics from the population in the detemir arm of study NN304-1689. A higher percentage of girls was included in the two lowest age groups (young children 2-5 years and children 6-12 years), while the opposite was observed for adolescents 13-16 years).

Mean HbA1c developed similarly in both treatment arms, increasing slightly from 8.4% to 8.5-8.6% by the end of 52 weeks of treatment. For subjects treated with insulin detemir mean HbA1c remained relatively stable during the additional 52 weeks of treatment. By the end of 104 weeks of treatment mean HbA1c in the insulin detemir arm was 8.7%. When entering the extension period, HbA1c was lower for the young children (8.15%) than for the children (8.52%) and adolescents (8.93%).

Mean daily basal and bolus insulin doses were similar with insulin detemir treatment and NPH insulin treatment throughout the trial. Mean daily doses of insulin detemir and NPH insulin increased most markedly during the first 12 weeks of treatment, possibly reflecting dose titration at the beginning of the trial. The mean daily basal insulin doses continued to increase at a lower but steady rate for the remaining 40 weeks of the trial. This might be related to the normal growth of the children.

In both detemir and NPH insulin treatment groups, HbA1c levels increased during the 52 weeks of the study. Detemir was non-inferior to NPH insulin in HbA1c values, using a non-inferiority margin of 0.4%. Numerically, the HbA1c values were lower in the NPH insulin group, compared to the detemir treatment group. The efficacy of insulin detemir in the young age subset of 2-5 years was comparable with the total group (including young children). In this subgroup, insulin detemir showed numerically lower HbA1c levels over time in comparison with NPH insulin group.

In Study NN304-1689 the secondary endpoint FPG in the detemir group was similar to the FPG in the NPH insulin group. In young subject, age 2-5 years old, the same trend was seen in FPG-values.

In Study NN304-1689 the secondary endpoint 9-point SMPG in the detemir group was similar to the 9-point SMPG in the NPH insulin group. In the young subject group, age 2-5 years old, the same trend was seen in 9-point SMPG profiles.

There were no evident differences in the overall persistence of efficacy among the three age groups, and no notable differences in insulin dosing or HbA1c development between insulin detemir and NPH insulin for young children (2-5 years), children (6-12 years) or adolescents (13-16 years). Similarly when looking at HbA1c and insulin dosing for the insulin detemir treated subjects of 104 weeks overall persistence of efficacy was preserved in all three age groups. No statistical tests were performed due to the relatively small number of subjects in the subpopulations.

1.4. Clinical safety

In this efficacy and safety Trial NN304-1689 347 patients were included, eligible subjects were insulin detemir naïve, 2-16 years of age and diagnosed with type 1 diabetes for a minimum of 12 months prior to inclusion in this trial. Furthermore, the subjects were to have a total daily insulin dose ≤ 2.00 units (U)/kg and the screening HbA1c was to be ≤ 11%. Criteria set for maximum BMI correlated to age were to be fulfilled. Subjects with clinically significant concomitant diseases, including impaired renal and hepatic function, were not to be included in this trial. Since a stable diabetes treatment for at least 1 year was wanted in this trial, children below the age of 2 years were not included. Since Trial NN304-1689, plus the extension trial (Trial NN304-1690) were to run for a total of 2 years, subjects above 16 years were excluded to avoid having adult subjects in the trial.

The key safety parameters were insulin antibodies, incidence of hypoglycaemia, standard deviation (SD) score for weight, adverse events (AEs), incidence of ketoacidosis requiring hospitalisation, safety laboratory parameters and insulin dose. Trial NN304-1689 included a total of 10 visits to the clinical trial sites and 8 telephone contacts during the treatment period. At the final visit, subjects in the insulin detemir treatment arm were offered to continue in the 52-week extension efficacy and safety trial in which the treatment and the key efficacy and safety parameters were the same as in Trial NN304-1689. The trial included a total of 5 visits to the clinical trial sites, of which the first was at the

same time as the last visit in Trial NN304-1689. Safety surveillance was performed on an ongoing basis by an internal safety committee in Novo Nordisk A/S, headed by Global Safety.

1.4.1. Patient exposure

In Trial NN304-1689 the number of subject years of exposure and the mean number of treatment days were similar in the two treatment groups for the total group as well as for the three age subgroups (see table below).

Exposure by Age Group (Mean Values), SAS, NN304-1689.

	Insulin detemir		NPH insulin	
	Subject years of exposure (years)	Duration of treatment (days)	Subject years of exposure (years)	Duration of treatment (days)
Total group	168.4	347.4	163.5	351.3
2-5 years	41.0	356.8	39.1	356.9
6-12 years	74.2	343.0	84.1	349.1
13-16 years	53.1	346.5	40.3	350.5

SAS: Safety analysis set

A summary of exposure for the subjects continuing in the extension trial NN304-1690 is presented in table below.

Exposure by Age Group (Mean Values), SAS, Insulin Detemir Treated Subjects in Trial NN304-1690 Whole treatment period.

	Insulin detemir	
	Subject years of exposure (years)	Duration of treatment (days)
Total group	289.2	723.5
2-5 years	73.2	722.9
6-12 years	117.5	727.6
13-16 years	98.4	719.0

SAS: Safety analysis set

Insulin dose

The ratio of insulin detemir/NPH insulin mean daily insulin doses at end of trial was close to 1 for both basal and bolus insulin, meaning that mean doses were similar in the two treatment groups.

Mean daily insulin detemir doses per kg body weight continued to increase throughout the whole treatment period, whereas the mean daily insulin aspart doses were relatively stable throughout the trial.

1.4.2. Adverse events

In Trial NN304-1689 the overall percentage of subjects with events and the event rates of all AEs and of non-serious AEs were similar in the two treatment groups, while the percent of subjects with events and the event rate (events per 100 years of exposure) of SAEs were lower with insulin detemir (8% and 9.5, respectively) than with NPH insulin (12% and 14.7, respectively). Few of the AEs in either treatment group were severe, and the event rate of severe AEs was lower with insulin detemir (4.2)

than with NPH insulin (9.2). The event rate of AEs possibly or probably related to trial product was similar in the two treatment groups.

Throughout the whole treatment period of 104 weeks, 116 (79.5%) of the 146 subjects experienced 714 AEs and 12 (8.2%) subjects experienced 17 SAE; 4 of the SAEs were assessed as being possible or probable related to insulin detemir and 1 SAE as being probable related to insulin aspart. No SAEs were assessed as possible for insulin aspart.

In the age groups 2-5 years and 13-16 years the rate of AEs per 100 years of exposure with insulin detemir (294.9 and 207.0, respectively) was lower than with NPH insulin (432.4 and 357.2), while the rate of AEs was higher with insulin detemir (412.4) than with NPH insulin (286.5) in the age group 6-12 years. For subjects continuing insulin detemir treatment in the extension trial NN304-1690 the rate of AEs were also higher in the young children and children age subgroups (243.1 and 325.9, respectively) than in the adolescent age subgroup (155.4).

Table below shows that injection site disorders, skin disorders and metabolic disorders were the most frequently reported AEs considered possibly or probably related to basal insulin with more injection site erythema in the insulin detemir group and more hypoglycaemia in the NPH insulin group. The display of AE by relation to basal insulin was similar for subjects continuing insulin detemir treatment in the extension Trial NN304-1690 for up to 104 weeks.

Adverse Events Probably or Possibly Related to Basal Insulin by MedDRA System Organ Class, SAS, NN304-1689

	Detemir			NPH		
	N (%)	E	R	N (%)	E	R
Subjects	177			170		
Total Exposure(year)	168.4			163.5		
Events	18 (10.2)	19	11.3	16 (9.4)	19	11.6
General disorders and administration site conditions	8 (4.5)	8	4.8	5 (2.9)	6	3.7
Injection Site Erythema	5 (2.8)	5	3.0	1 (0.6)	1	0.6
Injection Site Hypertrophy	0			3 (1.8)	3	1.8
Application Site Nodule	1 (0.6)	1	0.6	0		
Injection Site Mass	0			1 (0.6)	1	0.6
Injection Site Pain	1 (0.6)	1	0.6	0		
Injection Site Pruritus	1 (0.6)	1	0.6	0		
Injection Site Swelling	0			1 (0.6)	1	0.6
Skin and subcutaneous tissue disorders	7 (4.0)	8	4.8	4 (2.4)	4	2.4
Lipodystrophy Acquired	2 (1.1)	2	1.2	3 (1.8)	3	1.8
Pruritus	3 (1.7)	4	2.4	0		
Lipohypertrophy	1 (0.6)	1	0.6	1 (0.6)	1	0.6
Urticaria	1 (0.6)	1	0.6	0		
Metabolism and nutrition disorders	1 (0.6)	1	0.6	6 (3.5)	6	3.7
Hypoglycaemia	1 (0.6)	1	0.6	3 (1.8)	3	1.8
Hypoglycaemic Unconsciousness	0			2 (1.2)	2	1.2
Diabetic Ketoacidosis	0			1 (0.6)	1	0.6
Injury, poisoning and procedural complications	1 (0.6)	1	0.6	1 (0.6)	1	0.6
Contusion	1 (0.6)	1	0.6	0		
Medication Error	0			1 (0.6)	1	0.6
Gastrointestinal disorders	0			1 (0.6)	1	0.6
Abdominal Pain	0			1 (0.6)	1	0.6
Investigations	1 (0.6)	1	0.6	0		
Weight Decreased	1 (0.6)	1	0.6	0		
Nervous system disorders	0			1 (0.6)	1	0.6
Convulsion	0			1 (0.6)	1	0.6

N: Number of subjects; %: Percentage of subjects; E: Number of events
R: Ratio - Number of events per 100 exposure years; SAS: Safety analysis set

The most common AEs in both treatment groups of Trial NN304-1689 and in the insulin detemir treated subjects continuing treatment for 104 weeks were upper respiratory tract infections (including nasopharyngitis and pharyngitis), headache and gastroenteritis.

1.4.2.1. Serious adverse events and deaths

The rate of SAEs decreased with increasing age in the age subgroups, with the adolescents having the lowest events rates, (see tables below):

Serious Adverse Events (SAEs) by Age Group, SAS, Trial NN304-1689

	Insulin detemir					NPH				
	Subjects	N	%	E	R	Subjects	N	%	E	R
Total group	177	14	7.9	16	9.5	170	20	11.8	24	14.7
Children 2–5 years	42	5	11.9	5	12.2	40	6	15.0	7	17.9
Children 6–12 years	79	8	10.1	10	13.5	88	10	11.4	12	14.3
Children 13–16 years	56	1	1.8	1	1.9	42	4	9.5	5	12.4

Subjects: Subjects exposed; N: Number of subjects with an event; %: Percentage of subjects; E: Number of events; R: Ratio - Number of events per 100 exposure years; SAS: Safety analysis set

Serious Adverse Events (SAEs) by Age Group, SAS, Insulin Detemir Tre Subjects in Trial NN304-1690 Whole Treatment Period

	Insulin detemir				
	Subjects	N	%	E	R
Total group	146	12	8.2	17	5.9
Children 2–5 years	37	3	8.1	4	5.5
Children 6–12 years	59	6	10.2	9	7.7
Children 13–16 years	50	3	6.0	4	4.1

Subjects: Subjects exposed; N: Number of subjects with an event; %: Percentage of subjects; E: Number of events; R: Ratio - Number of events per 100 exposure years; SAS: Safety analysis set

The most common SAEs were within infections, gastrointestinal disorders and metabolic disorders in both treatment groups and age subgroups.

No deaths were reported in any of the 2 trials.

Body weight

In Trial NN304-1689 the mean change in body weight from baseline to 52 weeks of treatment was lower with insulin detemir (3.2 kg) than with NPH insulin (4.1 kg).

To be able to compare weight between the two treatment groups in the various age groups of children, weight SD scores were used. The SD score is a standardisation by age and sex of a reference population to show the variation of a measured value from the mean value of the reference population for the relevant age and sex. An SD score of '0' represents the mean value for the relevant age group of the chosen reference population, and a score of '-2' represents a value being 2 SDs below the mean value for the relevant age group of the chosen reference population.

The weight SD score was planned to be based on local standard growth curves, since there are differences between the participating countries in the trial, but in several countries, these data were not available to use for this purpose. The central derivation of the SD scores based on standard growth curves from the UK is therefore an approximation with a certain amount of uncertainty included.

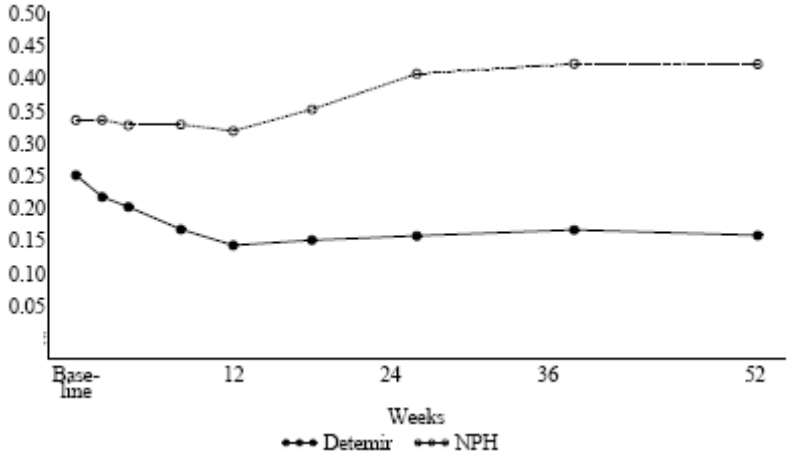
Mean Body Weight and Mean Standard Deviation Score of Weight by Age Group, SAS, NN304-1689

		Insulin detemir			NPH insulin	
	N	Body Weight (kg)	Weight SD score	N	Body Weight (kg)	Weight SD score
Total group	177			170		
Baseline (Visit 2)		37.3	0.25		36.5	0.34
At 52 weeks (Visit 10)		40.4	0.16		40.8	0.42
Change from baseline		3.2	-0.07		4.1	0.07
2–5 years	42			40		
Baseline (Visit 2)		17.3	0.09		18.6	0.46
At 52 weeks (Visit 10)		19.0	-0.08		21.2	0.51
Change from baseline		1.7	-0.17		2.5	0.03
6–12 years	79			88		
Baseline (Visit 2)		35.8	0.46		35.1	0.30
At 52 weeks (Visit 10)		40.0	0.42		40.0	0.41
Change from baseline		4.2	-0.01		4.8	0.11
13–16 years	56			42		
Baseline (Visit 2)		54.4	0.08		56.4	0.30
At 52 weeks (Visit 10)		57.4	-0.02		61.2	0.36
Change from baseline		2.9	-0.09		4.4	0.03

SAS: Safety analysis set

The mean change in weight SD score from baseline to 52 weeks of treatment was -0.07 with insulin detemir and 0.07 with NPH insulin. This means that the mean weight with insulin detemir decreased towards the standard mean value, while the mean weight with NPH insulin increased during the trial.

As for subjects treated with insulin detemir continuing treatment for 104 weeks the mean body weight increased 6.8 kg from baseline (Visit 2) and the mean change in weight SD score from baseline to 104 weeks was -0.07.



Mean Standard Deviation Score of Body Weight by Visit, SAS, Trial NN304-1689

The mean difference between the two treatment groups in estimated weight SD score at the end of the Trial NN304-1689 was statistically significant: insulin detemir – NPH insulin was -0.15, 95% C.I.: [-0.23; -0.07].

Hypoglycaemic Episodes

In Trial NN304-1689 the percentage of subjects who experienced hypoglycaemic episodes during the treatment period was lower with insulin detemir (95) than with NPH insulin (98), and the rate (number of episodes divided by the number of subject years of exposure) was also lower with insulin detemir than with NPH insulin, Table below.

Summary of All Hypoglycaemic Episodes, SAS, NN304-1689

	Insulin detemir				NPH insulin			
	N	(%)	E	R	N	(%)	E	R
All 24h episodes	168	95	9448	56.3	166	98	11576	71.0
Severe 24 h	3	2	3	0.0	12	7	15	0.1
Moderate 24h	30	17	370	2.2	28	16	947	5.8
Mild 24h	148	84	5956	35.5	151	89	7189	44.1
Biochemical 24h	135	76	3119	18.6	128	75	3425	21.0
All nocturnal	131	74	1379	8.2	141	83	2141	13.1
Severe nocturnal	0	0	0	0.0	5	3	6	0.0
Moderate nocturnal	15	8	59	0.4	14	8	112	0.7
Mild nocturnal	100	56	712	4.2	111	65	1139	7.0
Biochem. nocturnal	83	47	608	3.6	85	50	884	5.4
All diurnal	167	94	8069	48.1	166	98	9435	57.9
Severe diurnal	3	2	3	0.0	8	5	9	0.0
Moderate diurnal	27	15	311	1.9	27	16	835	5.1
Mild diurnal	146	82	5244	31.2	150	88	6050	37.1
Biochem. diurnal	128	72	2511	15.0	123	72	2541	15.6

N: Number of subjects; %: Percentage of subjects; E: Number of episodes; R: Rate (number of episodes per subject year of exposure); SAS: Safety analysis set

Of the subjects continuing insulin detemir treatment for 104 weeks, 99.3% experienced one or more hypoglycaemic episodes. In total 16074 hypoglycaemic episodes, corresponding to a rate of 55.6 episodes per exposure year, were reported during the whole insulin detemir treatment period. The majority of the hypoglycaemic episodes occurred during the day (diurnal) and were mild in severity or were biochemical hypoglycaemic episodes (PG<3.6mmol/L with no signs or symptoms). A total of 6 subjects reported 7 severe hypoglycaemic episodes of which 4 were nocturnal events:

Young children: Two severe hypoglycaemic episodes in two subjects: Subject 202002 experienced one severe event of hypoglycaemic unconsciousness after 545 days of treatment. Subject 352010 experienced one nocturnal event of severe hypoglycaemic unconsciousness after 406 days of treatment.

Children: Two severe hypoglycaemic episodes in two subjects: Subject 152002 experienced one nocturnal event of severe hypoglycaemia after 459 days of treatment and Subject 603007 experienced one event of severe hypoglycaemia after 63 days of treatment.

Adolescents: Three severe hypoglycaemic episodes in two subjects: Subject 403006 experienced two nocturnal events of severe hypoglycaemia after 493 and 503 days treatment. Both events were reported as SAEs and assessed as being possibly related to insulin detemir and unlikely related to insulin aspart treatment. The subject recovered from the events on the same day. Subject 301005 experienced one event of severe hypoglycaemia after 250 days of treatment.

The rate of hypoglycaemic episodes was lower with insulin detemir than with NPH insulin in all three age subgroups, Table below.

Summary of All Hypoglycaemic Episodes by age group, SAS, NN304-1689

	Detemir				NPH			
	N	(%)	E	R	N	(%)	E	R
Age Group 2-5 years								
Subjects in SAS	42				40			
All events	40	(95)	2072	5064.2	39	(98)	3050	7825.9
Diurnal	40	(95)	1743	4260.1	39	(98)	2373	6088.8
Nocturnal	29	(69)	329	804.1	33	(83)	677	1737.1
Age Group 6-12 years								
Subjects in SAS	79				88			
All events	73	(92)	4918	6648.0	85	(97)	6164	7349.8
Diurnal	72	(91)	4284	5791.0	85	(97)	5159	6151.5
Nocturnal	60	(76)	634	857.0	71	(81)	1005	1198.3
Age Group 13-16 years								
Subjects in SAS	56				42			
All events	55	(98)	2458	4640.0	42	(100)	2362	5876.4
Diurnal	55	(98)	2042	3854.7	42	(100)	1903	4734.5
Nocturnal	42	(75)	416	785.3	37	(88)	459	1142.0

N: Number of subjects; %: Percentage of subjects; E: Number of events; R: Events per 100 exposure years; SAS: Safety analysis set

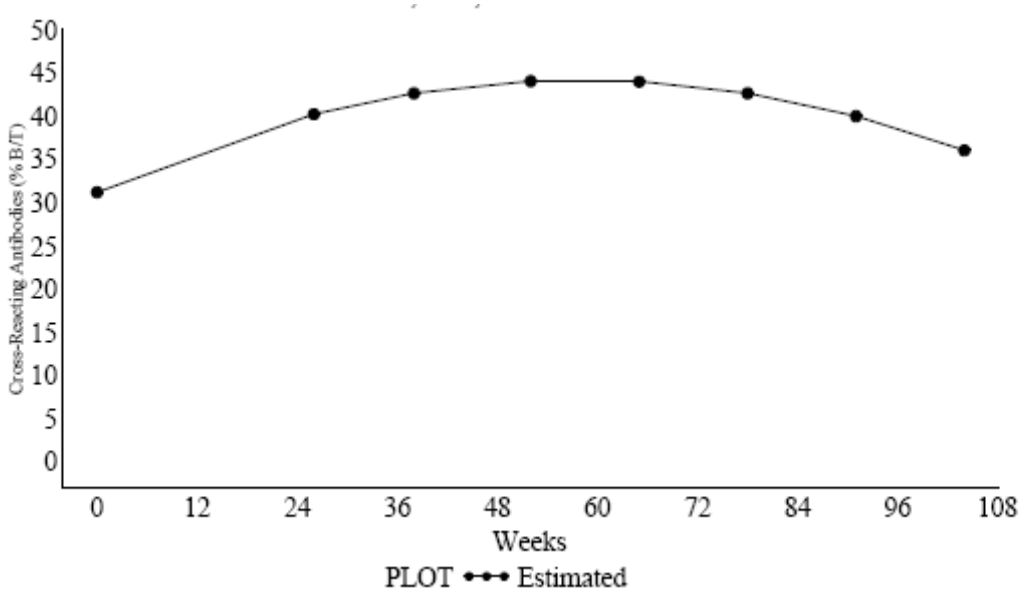
The number of treatment emergent hypoglycaemic episodes for subjects treated with insulin detemir for 104 weeks, were slightly higher in the children (6-12 year age group) compared with the young children (2-5 year age group) and the adolescents (13-16 year age group).

Laboratory findings

There were no significant findings among haematology and biochemistry tests.

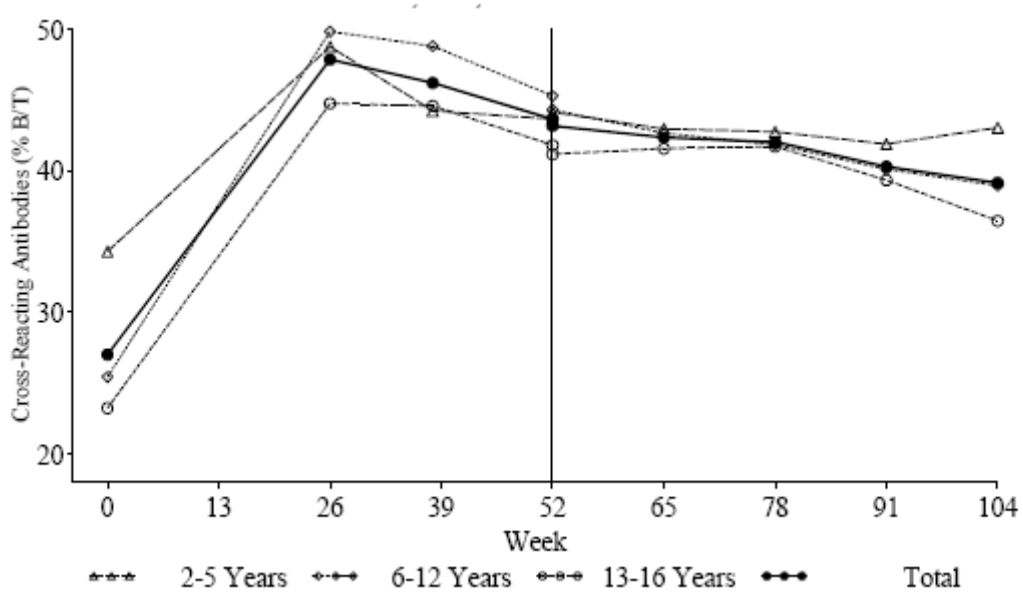
Antibodies

Estimated cross-reacting antibodies over 104 weeks of treatment with insulin detemir are presented in figure below. As illustrated, the development of antibodies over 104 weeks could be modelled by a parabola, with a positive slope of the parabola during the first year, maximum observed after 52-weeks and then a negative slope of the parabola during the extension period. In other words, the estimated level of cross-reacting antibodies increased during the first year of treatment with insulin detemir and insulin aspart, peaked after 1 year and then decreased during the second year of treatment.

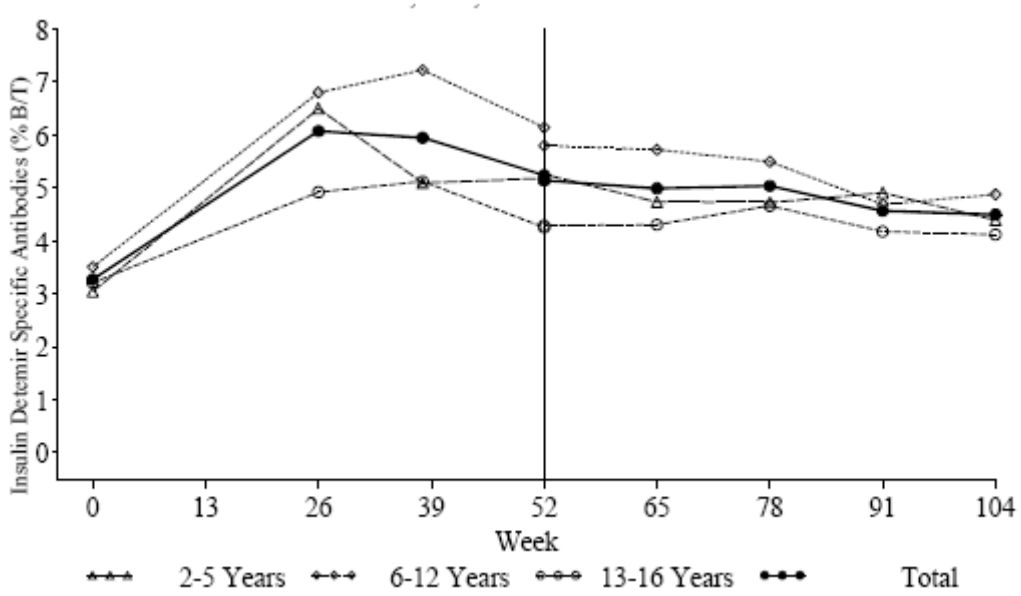


Estimated Cross-Reacting Antibodies (% B/T) over time, Time interval 3h, Corrected Data, SAS, Insulin Detemir Treated Subjects in Trial NN304-1690 Whole Treatment Period

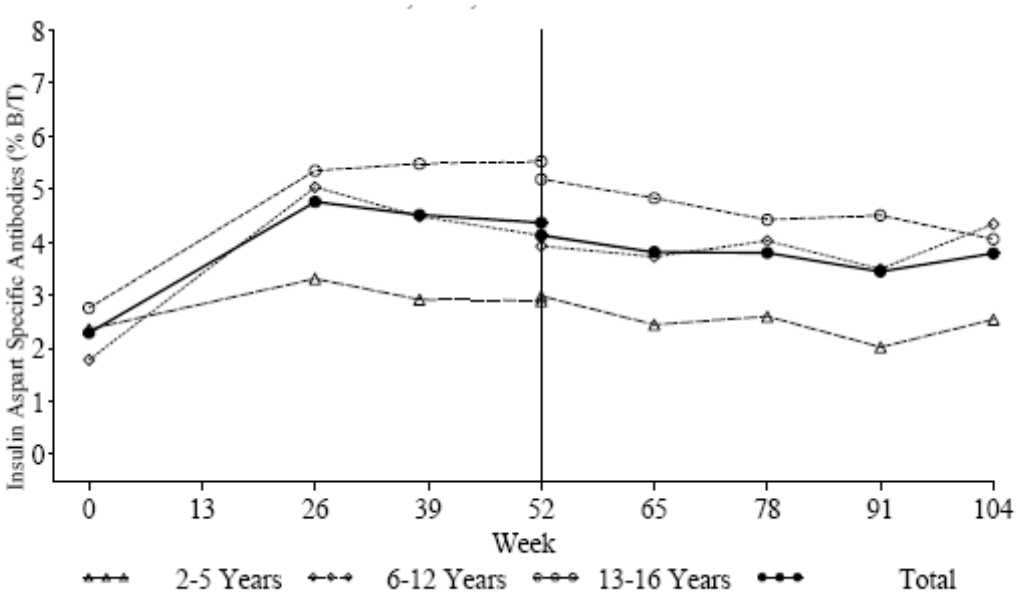
Mean cross-reacting antibodies, mean insulin detemir and mean insulin aspart antibodies over time by age group for subjects in both trials are presented in figures below. The development of mean cross-reacting antibodies was similar for all three age groups during the trial. A slight increase in mean cross-reacting antibodies for the young children and a slight decrease for the adolescents was observed towards the end of the trial. Mean insulin detemir specific antibody levels were slightly higher for the children (6-12 year age group) compared to the total mean level, whereas the mean insulin detemir specific antibody levels in adolescents (13-16 year age group) were slightly lower. Mean insulin aspart specific antibody levels were slightly higher for the adolescents compared to the total mean level, whereas the mean insulin aspart specific antibody levels in the young children (2-5 year age group) were slightly lower.



Mean Cross-Reacting Antibodies (% B/T) over time by Age Group, Corrected Data, SAS, Insulin Detemir Treated Subjects in Trial NN304-1690 Whole Treatment Period



Mean Insulin Detemir Specific Antibodies (% B/T) over time by Age Group, Corrected Data, SAS, Insulin Detemir Treated Subjects in Trial NN304-1690 Whole Treatment Period



Mean Insulin Aspart Specific Antibodies (% B/T) over time by Age Group, Corrected Data, SAS, Insulin Detemir Treated Subjects in Trial NN304-1690 Whole Treatment Period

1.4.2.2. Safety in special populations

N/A

1.4.2.3. Safety related to drug-drug interactions and other interactions

No drug interactions have been studied in Trial NN304-1689 and NN304-1690.

1.4.2.4. Discontinuation due to adverse events

There was no difference between the treatment groups in AEs leading to a change in insulin dose.

1.4.2.5. Post marketing experience

The post-marketing safety information for insulin detemir received by Novo Nordisk A/S is reported in Periodic Safety Update Reports according to the regulatory requirements.

Discussion on safety

The safety profile of insulin detemir was in the 2 studies included in this application in agreement with the safety profile shown in previous insulin detemir studies.

The estimated weight SD score at the end of the trial was statistically significantly lower with insulin detemir than with NPH insulin, which means that the weight returned towards the mean value for the reference population instead of continuing towards relatively higher levels with increasing risk of obesity. The lower weight SD score with insulin detemir corresponds to the lower BMI reported in the previous children trial. The central derivation of the SD scores based on standard growth curves from the UK was used, since in several countries standard growth curves were not available. Therefore, an approximation with a certain amount of bias was included in this measurement.

The estimated level of cross-reacting antibodies increased during the first year of treatment with insulin detemir and insulin aspart, peaked after 1 year and then decreased during the second year of treatment. The development of cross-reacting antibodies was similar for all 3 age-groups.

The overall percentage of subjects with adverse events were similar among children treated with insulin detemir and NPH insulin, and in the age-group 2-5 years the rate of AEs per 100 years of exposure with insulin detemir was lower than with NPH insulin.

During both studies, most subjects experienced hypoglycaemic events. Percentages of subjects who experienced hypoglycaemic events and their overall rates were lower for subjects treated with insulin detemir in comparison with the NPH insulin treated children, in study NN304-1689. Seven severe hypoglycaemic events occurred during the 104 weeks period in the detemir insulin treated children. In the children aged 2-5 years, the rate of hypoglycaemic events was comparable with the whole group and the detemir group experienced less hypoglycemic events, compared to young children in the NPH treatment group.

The current data suggests that insulin detemir has a numerically lower, although not statistically significant, rate of all nocturnal hypoglycaemic episodes. As discussed in the PDCO, the collection of nocturnal hypoglycaemic events is not considered optimal. Many children are not symptomatic and may sleep apparently calmly, while in hypoglycaemia. However, this phenomenon is only detectable by multiple (2-3) time points or by using CGM devices.

Furthermore the rate of hypoglycaemic episodes was lower with insulin detemir than with NPH insulin in all three age groups and within the insulin detemir arm the number of treatment emergent hypoglycaemic episodes was lower in the young children than in children 6-12 years.

In the longer term there have been associations and concerns raised by an increased prevalence of cancers in those receiving long acting insulin analogues. These are appropriately addressed in the Risk Management plan.

Significance of paediatric studies

This application was based on two studies:

Study **NN304-1689** was a 52-week, Multinational, Multi-Centre, Open-Labelled, Randomised, Parallel, Efficacy and Safety Comparison of Insulin Detemir and NPH Insulin in Children and Adolescents 2-16 years with Type 1 Diabetes on a Basal-Bolus Regimen with Insulin Aspart as Bolus Insulin. Young children aged 2-5 years were included in this long-term trial in order to obtain clinical data in this age group.

Study **NN304-1690** was a 52-Week, Multinational, Multi-Centre, Open-Labelled Extension to trial NN304-1689 of Insulin Detemir in Children and Adolescents 3-17 years with Type 1 Diabetes on a Basal-Bolus Regimen with Insulin Aspart as Bolus Insulin. Subjects treated with NPH insulin in Trial NN304-1689 were not offered to continue in the extension.

The persistence of **efficacy** in young children, children and adolescents was evaluated over a period of 52 weeks in Trial NN304-1689 and for a subset of insulin detemir treated children over a period of 104 weeks in Trial NN304-1690.

The **effect** of insulin detemir on HbA1C was similar when compared to NPH; HbA1c increased slightly from 8.4% to 8.5-8.6% by the end of 52 weeks of treatment. For subjects treated with insulin detemir mean HbA1c remained relatively stable during the additional 52 weeks of treatment. Mean daily basal and bolus insulin doses were similar in between the two groups throughout the trial. There were no evident differences in the overall persistence of efficacy, in insulin dosing or HbA1c development between insulin detemir and NPH insulin for young children (2-5 years), children (6-12 years) or adolescents (13-16 years).

The **safety** profile of insulin detemir was similar to that observed in previous insulin detemir studies. The overall percentage of subjects with adverse events was similar among children treated with insulin detemir and NPH insulin. In the age-group 2-5 years the rate of AEs per 100 years of exposure with insulin detemir was lower than with NPH insulin. Furthermore the rate of hypoglycaemic episodes was lower with insulin detemir than with NPH insulin in all three age groups (2-5, 6-12 and 13-16 years) and within the insulin detemir arm the number of treatment emergent hypoglycaemic episodes was lower in the young children than in children 6-12 years. The estimated level of cross-reacting antibodies increased during the first year of treatment with insulin detemir and insulin aspart, peaked after 1 year and then decreased during the second year of treatment. The development of cross-reacting antibodies was similar for all 3 age-groups.

Based on the results described above the efficacy and safety data for the 2-5 years old and safety data for the 6-16 years old generated from studies **NN304-1689** and **NN304-1690** (completed after the entry into force of the paediatric regulation) are considered of importance and clinical relevance for the paediatric population (Guideline on the format and content of applications for agreement or modification of a paediatric investigation plan and requests for waivers or deferrals and concerning the operation of the compliance check and on criteria for assessing significant studies (2008/C 243/01)). It has to be noted that insulin detemir is already authorised for treatment of diabetes mellitus in adults, adolescents and children aged 6–17 years.

The CHMP is of the opinion that **NN304-1689**, which is contained in the agreed Paediatric Investigation Plan and has been completed after 26 January 2007, is considered significant.

1.4.3. Pharmacovigilance aspects

1.4.3.1. Detailed description of the Pharmacovigilance system

N/A

1.4.4. Risk management plan

The applicant has submitted a Risk Management Plan (RMP). The RMP is written in accordance with the current guidelines.

Summary of the risk management plan

Safety Concern	Proposed Pharmacovigilance Activities	Proposed Risk Minimisation Activities
Identified Risks		
Hypoglycaemia	Ongoing routine pharmacovigilance (single case reporting, PSURs, ASRs/DSURs)	Addressed in the SmPC, Sections 4.4, 4.5, 4.7 and 4.8. **Section 4.4 Special warnings and precautions for use:** Omission of a meal or unplanned, strenuous physical exercise may lead to hypoglycaemia. Hypoglycaemia may occur if the insulin dose is too high in relation to the insulin requirement. Patients, whose blood glucose control is greatly improved, e.g. by intensified insulin therapy, may experience a change in their usual warning symptoms of hypoglycaemia, and should be advised accordingly. Usual warning symptoms may disappear in patients with longstanding diabetes. Concomitant illness, especially infections and feverish conditions, usually increases the patient's insulin requirements. Concomitant diseases in the kidney, liver or affecting the adrenal, pituitary or thyroid gland can require changes in insulin dose. When patients are transferred between different types of insulin medicinal products, the early warning symptoms of hypoglycaemia may change or become less pronounced than those experienced with their previous insulin. **Section 4.5 Interaction with other medicinal products and other forms of interaction:** Beta-blocking agents may mask the symptoms of hypoglycaemia. Alcohol may intensify or reduce the hypoglycaemic effect of insulin. **Section 4.7 Effects on ability to drive and use machines**: The patient's ability to concentrate and react may be impaired as a result of hypoglycaemia. This may constitute a risk in situations where these abilities are of special importance (e.g. driving a car or operating machinery). Patients should be advised to take precautions to avoid hypoglycaemia while driving. This is particularly important in those who have reduced or absent awareness of the warning signs of hypoglycaemia or have frequent episodes of hypoglycaemia. The advisability of driving should be considered in these circumstances. **Section 4.8 Undesirable effects:** The most frequently reported adverse reaction is hypoglycaemia. It may occur if the insulin dose is too high in relation to the insulin requirement. Severe hypoglycaemia may lead to unconsciousness and/or convulsions and may result in temporary or permanent impairment of brain function or even death. The symptoms of hypoglycaemia usually occur suddenly. They may include cold sweats, cool pale skin, fatigue, nervousness or tremor, anxiousness, unusual tiredness or weakness, confusion, difficulty in concentration, drowsiness, excessive hunger, vision changes, headache, nausea and palpitation. From clinical investigations, it is known that major hypoglycaemia, defined as requirement for third party intervention, occurs in approximately 6% of the patients treated with Levemir. Hypoglycaemia is listed as very common (≥1/10) adverse reaction.

Injection site reactions	Ongoing routine pharmacovigilance (single case reporting, PSURs, ASRs/DSURs)	Addressed in the SmPC, Sections 4.4 and 4.8. **Section 4.4 Special warnings and precautions for use:** As with any insulin therapy, injection site reactions may occur and include pain, redness, hives, inflammation, bruising, swelling and itching. Continuous rotation of the injection site within a given area may help to reduce or prevent these reactions. Reactions usually resolve in a few days to a few weeks. On rare occasions, injection site reactions may require discontinuation of Levemir. **Section 4.8 Undesirable effects:** Injection site reactions are seen more frequently during treatment with Levemir than with human insulin products. These reactions include pain, redness, hives, inflammation, bruising, swelling and itching at the injection site. Most of the injection site reactions are minor and of a transitory nature, i.e. they normally disappear during continued treatment in a few days to a few weeks. Listed as common (≥1/100 to <1/10) adverse reactions.
Lipodystrophy	Ongoing routine pharmacovigilance (single case reporting, PSURs, ASRs/DSURs)	Addressed in the SmPC. **Section 4.8 Undesirable effects:** Lipodystrophy is reported as uncommon. It may occur at the injection site as a consequence of failure to rotate injection sites within an area. Listed as uncommon (≥1/1,000 to ≤1/100) adverse reaction.
Oedema	Ongoing routine pharmacovigilance (single case reporting, PSURs, ASRs/ DSURs)	Addressed in the SmPC. **Section 4.8 Undesirable effects:** At the beginning of the insulin treatment, oedema may occur; these reactions are usually of transitory nature. Listed as uncommon (≥1/1,000 to ≤1/100) adverse reaction.
Allergic reactions	Ongoing routine pharmacovigilance (single case reporting, PSURs, ASRs/DSURs and follow-up questions for allergic reactions)	Addressed in the SmPC. **Section 4.8 Undesirable effects:** Allergic reaction, potentially allergic reaction, urticaria, rash and eruptions are uncommon when Levemir is used in basal-bolus regimen. However, when used in combination with oral antidiabetic medicinal products, three clinical studies have shown a frequency of common (2.2% of allergic reactions and potentially allergic reactions have been observed). Listed as uncommon adverse reaction. The occurrence of generalised hypersensitivity reactions (including generalised skin rash, itching, sweating, gastrointestinal upset, angioneurotic oedema, difficulties in breathing, palpitation and reduction in blood pressure) is very rare but can potentially be life threatening. Anaphylactic reactions are listed as very rare (< 1/10,000) adverse reactions
Important Potential Risks		
Cardiovascular & cerebrovascular events	Ongoing routine pharmacovigilance (single case reporting, PSURs, ASRs/DSURs)	Not applicable

Antibody formation	Ongoing routine pharmacovigilance (single case reporting, PSURs, ASRs/DSURs and follow-up questions for allergic reactions)	Not applicable
Microvascular complications of the eye	Ongoing routine pharmacovigilance (single case reporting, PSURs, ASRs)	Not applicable
Medication errors	Ongoing routine pharmacovigilance (single case reporting, PSURs, ASRs/DSURs)	Not applicable
Potential anti-insulin antibody development in relation to NN729 process (allergic reactions and lack of efficacy)	Ongoing routine pharmacovigilance (single case reporting, PSURs, ASRs/DSURs and follow-up questions for allergic reactions)	Not applicable
Potential risk of malignant neoplasms following combination treatment with insulin detemir + liraglutide + metformin	• Single case reporting including targeted follow-up questionnaires • Aggregated periodic reporting- these cases will be described and evaluated in dedicated sections within the PSURs and ASRs/DSURs • Novo Nordisk A/S has initiated contact with GPRD concerning the possibility for performing a pharmacoepidemiological study The feasibility of performing subanalyses within the patient population included in the ongoing cardiovascular outcome trial for liraglutide (LEADER) upon	Not applicable

Off-label use in children below the age of 2	Ongoing routine pharmacovigilance (single case reporting - including those from NN1250-3561 - PSURs, ASRs/DSURs)	The SmPC will reflect that insulin detemir is indicated for patients above the age of 2 years.
Important Missing Information		
Elderly	Ongoing routine pharmacovigilance (single case reporting, PSURs, ASRs/DSURs)	Addressed in the SmPC, Sections 4.2 and 5.2 Special populations: **Section 4.2 Posology and method of administration**: As with all insulin medicinal products, in elderly patients, glucose monitoring should be intensified and Levemir dosage adjusted on an individual basis. **Section 5.2 Pharmacokinetic properties:** There was no clinically relevant difference in pharmacokinetics of insulin detemir between elderly and young subjects.
Patients with renal or hepatic impairment	Ongoing routine pharmacovigilance (single case reporting, PSURs, ASRs/DSURs)	Addressed in the SmPC, Sections 4.2 and 5.2, Special populations: **Section 4.2 Posology and method of administration**: As with all insulin medicinal products, in patients with renal or hepatic impairment, glucose monitoring should be intensified and the insulin detemir dosage adjusted on an individual basis. **Section 5.2 Pharmacokinetic properties:** There was no clinically relevant difference in pharmacokinetics of insulin detemir between subjects with renal or hepatic impairment and healthy subjects.
Children <2 years	Ongoing routine pharmacovigilance (single case reporting, PSURs, ASRs/DSURs).	Not applicable.
Patients with cardiac impairment	Ongoing routine pharmacovigilance (single case reporting, PSURs, ASRs/DSURs)	Not applicable.

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.

1.4.5. Changes to the Product Information

The following changes are proposed for the Product Information (deleted text strikethrough, new text in bold underlined):

4.1 Therapeutic indications

Treatment of diabetes mellitus in adults, adolescents and children aged ~~6 17~~ **2** years **and above**.

4.2 Posology and method of administration

[. . .]

Based on study results, the following titration guideline is recommended **for adult diabetes patients**:

[. . .]

Paediatric population

The efficacy and safety of Levemir were demonstrated in ~~children and~~ adolescents **and children** aged ~~6 to 17~~**2** years **and above** in studies up to ~~6~~**12** months (see section 5.1).

As with all insulin medicinal products, in children and adolescents, glucose monitoring should be intensified and the insulin detemir dose adjusted on an individual basis.

Levemir has not been studied in children below the age of 2 years.

[. . .]

5.1 Pharmacodynamic properties

[. . .]

In long-term treatment trials in patients with type 1 diabetes **receiving a basal-bolus insulin therapy**, fasting plasma glucose was improved with Levemir compared with NPH insulin ~~when given as basal/bolus therapy including in children and adolescents aged 6 to 17 years~~. Glycaemic control (HbA_{1c}) with Levemir **was** ~~is~~ comparable to NPH insulin, with a lower risk of nocturnal hypoglycaemia and no associated weight gain.

In clinical trials using basal bolus insulin therapy, the overall rates of hypoglycaemia with Levemir and NPH insulin were similar. Analyses of nocturnal hypoglycaemia in patients with type 1 diabetes showed a significantly lower risk of minor nocturnal hypoglycaemia (able to self-treat and confirmed by capillary blood glucose less than 2.8 mmol/l or 3.1 mmol/l if expressed as plasma glucose) than with NPH insulin, whereas no difference was seen in type 2 diabetes. ~~Furthermore, the overall risk of nocturnal hypoglycaemia in children and adolescents aged 6 to 17 years with type 1 diabetes was significantly lower with Levemir compared to NPH insulin.~~

Antibody development has been observed with the use of Levemir. However, this does not appear to have any impact on glycaemic control.

Paediatric population

The efficacy and safety of Levemir has been studied for up to 12 months, in two randomised controlled clinical trials in adolescents and children (n=694 in total); one of the studies included in total 82 children aged 2-5 years. Both trials demonstrated that glycaemic control (HbA_{1c}) with Levemir is comparable to NPH insulin when given as basal-bolus therapy, using a non-inferiority margin of 0.4%. In addition less weight gain (SD score, weight corrected for gender and age) was observed with Levemir than with NPH insulin.

The trial including children above 2 years was extended for an additional 12 months (total of 24 months treatment data) to assess antibody formation after long-term treatment with Levemir. After an increase in insulin antibodies during the first year, the insulin antibodies decreased during the second year to a level slightly higher than pre-trial level. Results indicate that antibody development had no negative effect on glycaemic control and Levemir dose.

[. . .]

The Packade Leaflet has been updated accordingly.

Also Annex II has been updated to reflect new version number of the Risk Management Plan

2. Overall discussions and benefit-risk assessment

In support of the extension of indication 2 clinical studies were submitted.

The already completed Trial NN304-1689 and ongoing extension Trial NN304-1690 at submission were agreed on, during the paediatric investigation procedure by the PDCO. The SA, provided in 2005 by the CHMP, was not followed completely. As agreed on during the PIP procedure three additional studies, including NN1250-3561, will cover the currently missing data regarding PK-data in small children and nocturnal hypoglycaemia data in children using CGM devices.

The data that were collected in the studies from the whole 2-year treatment period suggest that insulin detemir is safe and efficacious and can be used in children between 2 and 16 years of age.

In the basal-bolus treatment regimen, the efficacy and safety of insulin detemir was compared to NPH insulin when both were used once or twice daily according to pre-trial regimen, in combination with insulin aspart as mealtime insulin. Insulin detemir was as safe and efficacious as NPH insulin in treatment of children and adolescents from 2-16 years with type 1 diabetes mellitus. Children treated with insulin detemir had less hypoglycaemia, less weight gain and fewer SAEs than children treated with NPH insulin.

Potential benefits that may be expected from the use of insulin detemir compared with NPH insulin in young children (2-5 years) are related to a lower within-subject variation in fasting plasma glucose, less hypoglycaemia (both 24h and nocturnal hypoglycaemia, which was not off-set by an increase in diurnal episodes) and less inappropriate weight gain. The overall AE profile for young children was similar to that of NPH insulin.

Obtaining good glycaemic control is a challenge for children and adolescents, due to growth, variable lifestyle, hormonal changes, and the need of assistance with insulin injection. The titration of insulin doses to obtain the target plasma glucose values led to similar HbA1c and fasting plasma glucose values with similar insulin doses per kg body weight in the two treatment groups. The ratio of insulin detemir/NPH insulin mean daily insulin doses at end of trial was close to 1 for both basal and bolus insulin, meaning that mean doses were similar in the two treatment groups. For the insulin detemir treated subjects continuing treatment for the complete 2-year period mean HbA1c levels were relatively stable, with a slight increase over time (mean HbA1c for all subjects at baseline was 8.43% and at end of trial 8.74%). Throughout the 2-year period, mean HbA1c was lowest for the young children and highest for the adolescents. Overall, children in the 2-5 years of age group maintained better glycaemic control, compared to the older children.

The increase in HbA1c seen in both treatment groups may, as suggested by the MAH, reflect the general difficulties in treating children for whom many factors, including: fear of hypoglycaemia, social status, different country distribution, available help in day care or school and highly variable lifestyle, influence the glycaemic control. It might be speculated whether the titration of the insulin doses was sufficient or whether further intensification of the insulin treatment was hindered by hypoglycaemia or fear of, especially nocturnal, hypoglycaemia.

The observed changes in the insulin antibodies of children with type 1 diabetes treated with insulin detemir in a basal-bolus regimen with insulin aspart as mealtime insulin over two years do not seem to present a safety concern. The estimated antibody profile based on data from the whole 2-year treatment period showed that after an increase in insulin antibodies during the first year, the insulin antibodies decreased during the second year to a level slightly higher than pre-trial level.

In conclusion, although the number of children 2-5 years of age exposed to detemir was only 41 the data from Trial NN304-1689 and NN304-1690 support the extension of the current indication for

insulin detemir to include the use of insulin detemir in children 2-5 years. The number was in agreement with the agreed Paediatric Investigation Plan saying: "In the insulin detemir group, at least 40 between 2 and 5 years …. at randomisation". These young children, irrespective of gender, did as well as the older children ≥ 6 years for whom insulin detemir was approved in EU in 2005. Insulin detemir was as safe and efficacious as NPH insulin in treatment of children and adolescents from 2-16 years with diabetes mellitus. Children treated with insulin detemir had similar glycaemic control, less hypoglycaemia, few severe nocturnal hypoglycaemia episodes, less weight gain and fewer serious adverse events than children treated with NPH insulin. The longer duration of action, the lower within-subject variation in fasting blood glucose, the lower risk of hypoglycaemia and the lower body weight gain of s.c. insulin detemir compared to NPH insulin may offer advantages for the treatment of young children with diabetes mellitus. The proposed indication for Levemir use is children aged 2-5 years is therefore considered as approvable.

3. Conclusion

On 21 September 2011 the CHMP considered this Type II variation to be acceptable and agreed on the amendments to be introduced in the Summary of Product Characteristics, Annex II and Package Leaflet.

Furthermore, the CHMP reviewed the available paediatric data 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.

In accordance with Article 45(3) of Regulation EC(No)1901/2006 as amended, significant studies in the agreed paediatric investigation plan have been completed after the entry into force of that Regulation.

Follow-up measures undertaken by the marketing authorisation holder

As requested by the CHMP, the MAH agreed to submit the follow-up measures as listed below and to submit any variation application which would be necessary in the light of compliance with these commitments (see Letter of Undertaking attached to this report):

Medicinal product:	International non-proprietary name:	Presentations:
Levemir	insulin detemir	See Annex A

Area[1]	Description	Due date[2]
Clinical	PK-data of insulin detemir in young children is lacking. Study results from NN1250-3561 and a PK modelling study are awaited. The MAH should provide these data.	31 July 2014
Clinical	Collection of nocturnal hypoglycaemic events was not optimal, especially in the young children age group. The MAH should provide this data from study NN1250-3561.	31 July 2014

[1] Areas: Quality, Non-clinical, Clinical, Pharmacovigilance.
[2] Due date for the follow-up measure or for the first interim report if a precise date cannot be committed to.