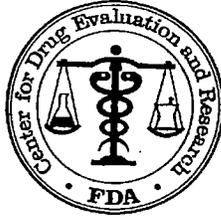


**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**21-878**

**STATISTICAL REVIEW(S)**



Department of Health and Human Services  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Biostatistics

## Statistical Review and Evaluation

### CLINICAL STUDIES

NDA: 21-878

Name of drug: Insulin detemir

Applicant: Novo Nordisk

Indication: Treatment of Diabetes Mellitus in Pediatric Populations

Documents reviewed: Vos. 1.1 33-46

Project manager: Julie Rhee (HFD-510)

Clinical reviewer: Robert Misbin, M.D. (HFD-510)

Dates: Received 12/20/04; goal date 10/20/05

Statistical reviewer: Lee-Ping Pian, Ph.D. (HFD-715)

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Keywords: NDA review, clinical studies, noninferiority trials

Statistical Review and Evaluation

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Study NN314-1379 was a 26-week, multinational, multi-center, open-labeled, 2:1 (detemir:NPH) randomized efficacy and safety comparison of insulin detemir and NPH insulin once or twice daily in children and adolescents with type 1 diabetes on a basal-bolus (insulin aspart) regimen to support an indication of detemir in pediatric populations. The study included a screening visit, a randomization visit, a 6-week titration period and a 20-week maintenance period.

Study population

Patients included males and females 6 to 17 years of age who were treated with insulin for at least 12 months for type 1 diabetes, and an HbA<sub>1c</sub> ≤12% and a BMI ≤19, ≤20, ≤22, ≤24, and ≤27 kg/m<sup>2</sup> for patients 6-7, 8-9, 10-11, 12-13, and 14-17 years, respectively.

Treatment regimen

The initial dose of both insulin detemir and NPH insulin was to be 70% of the pre-trial NPH insulin dose as measured in units (2.8 times detemir to NPH in molar concentration). Patients received once daily (at bedtime) or twice daily (morning and bedtime) basal insulin according to their pre-trial insulin regimen. Patients were to remain on the same treatment regimen but changes were allowed in order to reach glucose target. During the 6-week titration period, the investigator adjusted the insulin dose according to targeted pre-breakfast and pre-dinner values (81-140 mg/L) and severity of hypoglycemia.

Efficacy and safety variables

The primary efficacy variable was HbA<sub>1c</sub> after 26 weeks of treatment. Secondary endpoints were home-measured fasting plasma glucose, 8-point plasma glucose profile, fasting plasma glucose and nocturnal plasma glucose. The safety variables included hypoglycemia, adverse events, and clinical laboratory tests. Insulin therapy data was recorded.

Table 1 displays patient disposition

*Table 1 Patient disposition*

	Completers	Adverse event	Ineffective therapy	Non-compliance	Other
Detemir (n=232)	226 (97.4%)	1 (0.4%)	1 (0.4%)	3 (1.3%)	1 (0.4%)
NPH (n=115)	109 (94.8%)	0 (0.0%)	1 (0.9%)	2 (1.7%)	3 (2.6%)

Demographic and baseline characteristics

All but 1 patient were Caucasians (99.7%). Male and female patients were evenly distributed (50%). Sixty percent of patients were pubertal and 40% were pre-pubertal with 22 patients (6%) changed pubertal status during the study. Baseline characteristics were similar between groups (Table 2). The mean age was 12 years. The mean duration of diabetes was 5 years. The mean weight was 46 kilograms and the mean BMI 19.2 kg/m<sup>2</sup>.

Table 2 Baseline characteristics of patients.

Trt	Detemir (n=232)					NPH (n=119)				
	Mean	SD	Median	Min	Max	Mean	SD	Median	Min	Max
Age (years)	11.9	(2.8)	12.0	6.0	17.0	11.7	(2.7)	12.0	6.0	17.0
Weight (kg)	46.3	(13.6)	46.2	20.2	83.0	46.2	(15.0)	43.4	20.9	87.1
Height (m)	153.4	(15.6)	155.5	114.0	185.0	153.1	(16.5)	154.0	116.0	187.0
BMI (kg/m <sup>2</sup> )	19.2	(2.8)	18.9	13.7	27.4	19.1	(2.9)	18.7	14.5	27.9
Diabetes (years)	5.1	(3.1)	4.3	0.9	14.5	4.8	(2.8)	4.7	0.9	13.5
Hba1c (%)	8.8	(1.2)	8.8	5.5	11.4	8.8	(1.2)	8.8	5.9	11.8

Mean daily basal and bolus insulin dose

Table 3 displays the descriptive statistics of daily total dose for basal insulin and bolus insulin. Figure 1 displays change from the first 2 week titration (Week 0) to Week 26 daily insulin dose by basal or bolus insulin. The first 6 weeks were titration followed by 20 weeks of maintenance. At Week 26 the ratio (Detemir/NPH) of change from baseline was 1.13 (13.6/12) for basal insulin and 0.91 for bolus insulin (4.1/4.5). Figure 2 displays the change by once daily or twice daily basal insulin regimen. Approximately 60% of patients were on twice daily basal insulin regimen at baseline and approximately 70% at Week 26 for both groups. Figure 3 displays the mean basal and bolus insulin daily doses by pubertal status.

Table 3 Mean basal and bolus total daily dose

	Basal insulin (U, IU)				Bolus insulin (IU)			
	Detemir (N=228)		NPH (N=112)		Detemir (N=228)		NPH (N=112)	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Baseline	18.6	(10.5)	19.1	(10.7)	21.6	(12.6)	21.5	(13.5)
Week 26	32.2	(17.6)	31.0	(15.2)	25.7	(14.3)	25.9	(14.9)
Change	13.6	(12.2)	12.0	(9.0)	4.1	(8.4)	4.5	(7.8)

\* Insulin detemir 100U=2400 nmol, NPH 100 IU=600 nmol

Figure 1 Mean insulin dose by time

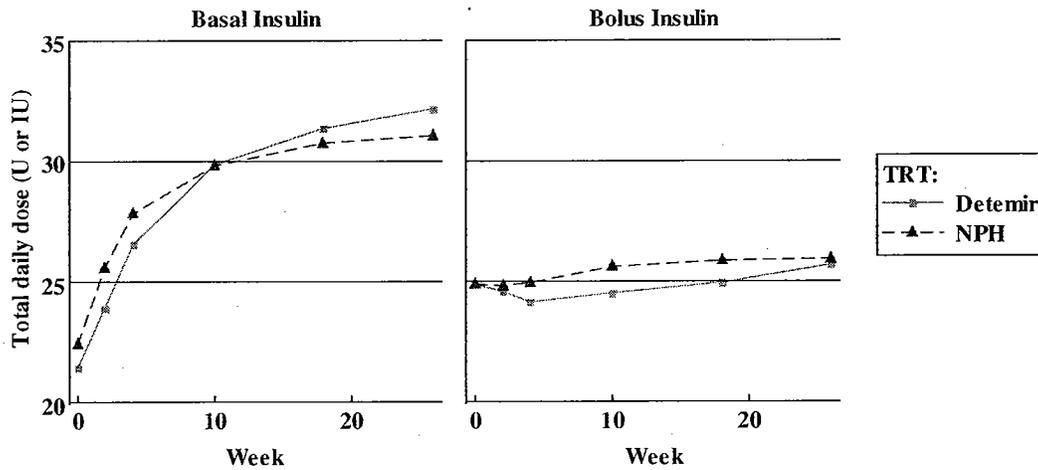


Figure 2 Mean insulin change from baseline by # of basal insulin injection

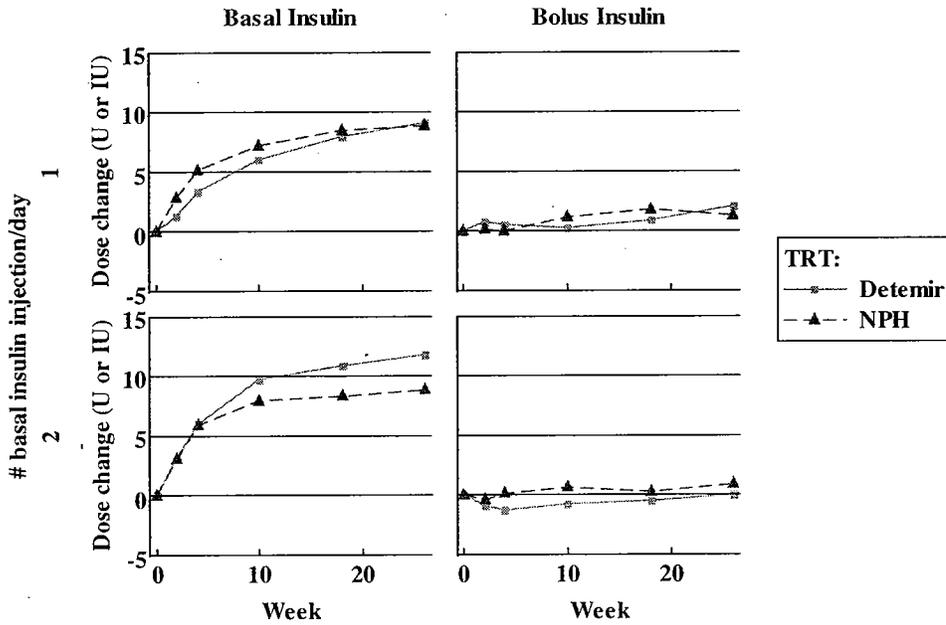
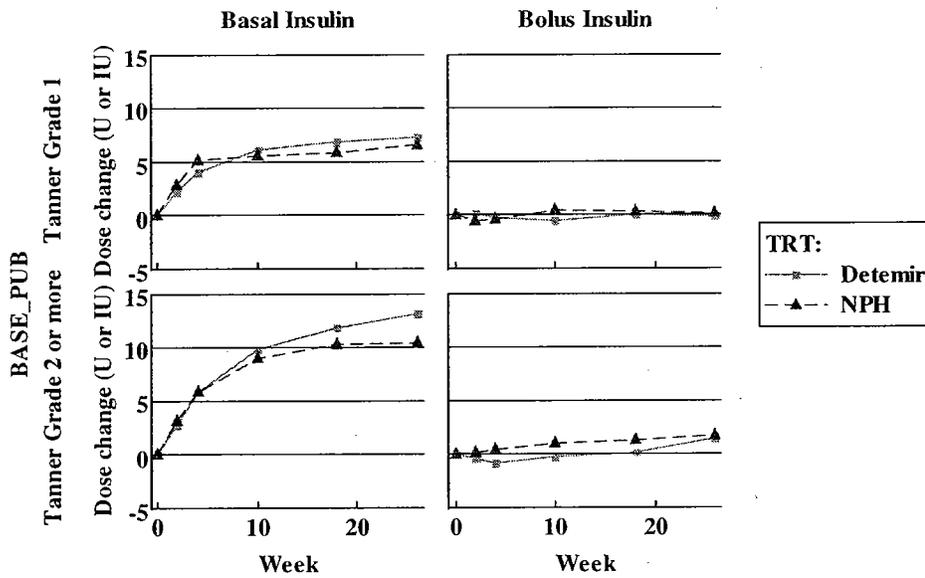


Figure 3 Mean insulin change from baseline by pubertal status



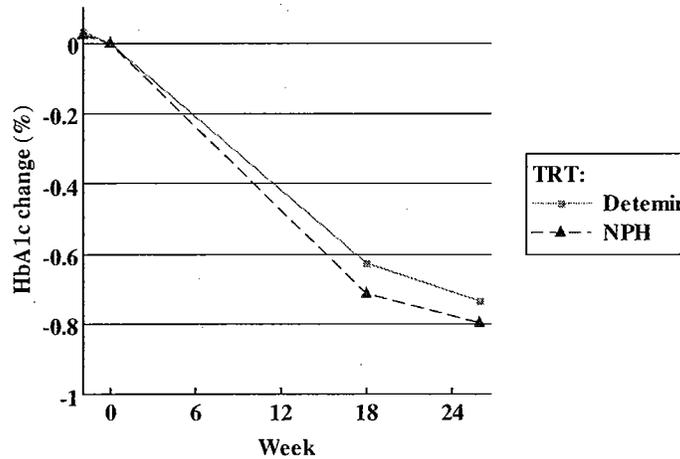
Primary efficacy analysis – HbA<sub>1c</sub> after 26 weeks

Table 4 displays the descriptive statistics for HbA<sub>1c</sub> at baseline and endpoint and change from baseline. Figure 4 displays the HbA<sub>1c</sub> change from baseline over time.

*Table 4 Descriptive statistics of HbA<sub>1c</sub> (%)*

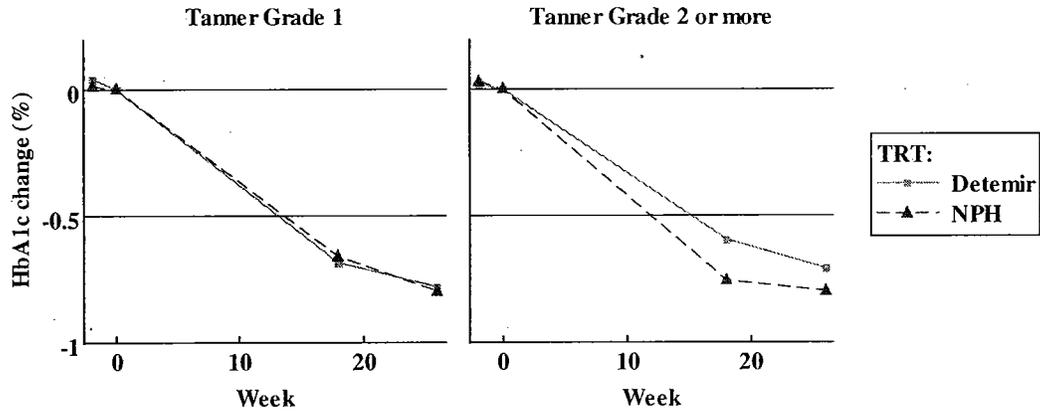
	Detemir (N=231)		NPH (N=112)	
	Mean	SD	Mean	SD
Baseline	8.76	(1.16)	8.74	(1.14)
Endpoint	8.03	(1.25)	7.95	(1.07)
Change	-0.73	(1.06)	-0.80	(1.00)

Figure 4 Mean HbA<sub>1c</sub> change from baseline by time



The analysis for the primary efficacy variable, HbA<sub>1c</sub> at endpoint, used a covariance model with treatment, group of country as fixed effects and baseline HbA<sub>1c</sub> and age as covariates. The HbA<sub>1c</sub> LSM difference of detemir and NPH was 0.09 with a 2-sided, 95% confidence interval of [-0.12, 0.30]. The 0.3% upper bound is less than the 0.4% noninferiority margin. Hence, detemir is noninferior to NPH in HbA<sub>1c</sub> at endpoint. Figure 5 displays the mean HbA<sub>1c</sub> change from baseline by the pubertal status.

Figure 5 Mean HbA<sub>1c</sub> change from baseline by pubertal status

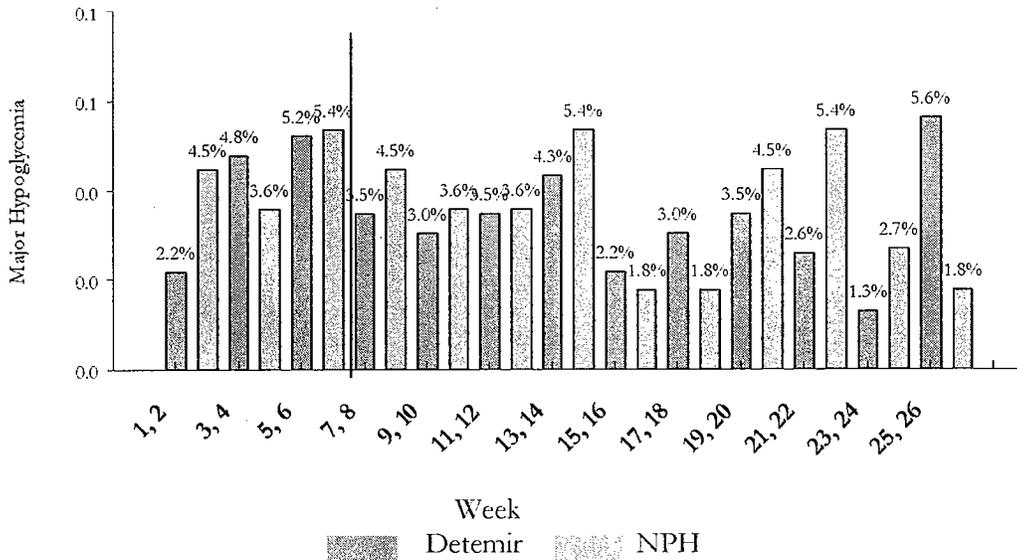


Hypoglycemia

Six patients in the detemir group and one patient in the NPH group had at least one severe hypoglycemic adverse event. Three of the 6 detemir patients and the one NPH patient experienced hypoglycemic coma.

Figure 6 displays the percentage of patients with at least one major hypoglycemia in two week intervals by treatment group during the titration phase (1<sup>st</sup> 6 weeks) and the treatment phase (20 weeks) of the study.

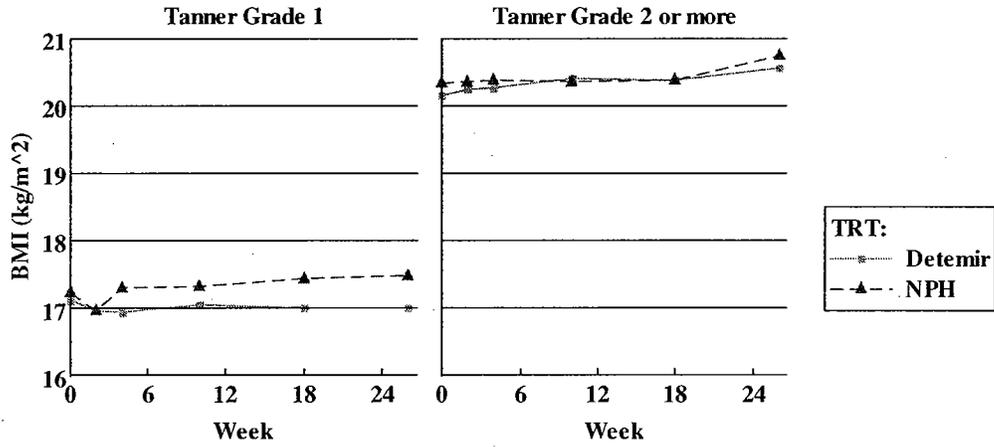
Figure 6 Percent of patients with at least one major hypoglycemia every two weeks



BMI

Figure 7 displays the median BMI at Week 26 by baseline Tanner grade.

Figure 7 Median BMI at Week 26 by pubertal status



Labeling Comments:

The 2-sided, 95% confidence interval for the mean difference of HbA<sub>1c</sub> change from baseline between Levemir and NPH should be presented.

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/s/  
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9/23/2005 02:07:55 PM  
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9/23/2005 03:42:43 PM  
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