

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
21-536

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: 21-536
Name of drug: Insulin detemir
Applicant: Novo Nordisk
Indication: Treatment of Diabetes Mellitus
Documents reviewed: Vos. 1.1 9-32, 47-62
Project manager: Julie Rhee (HFD-510)
Clinical reviewer: Robert Misbin, M.D. (HFD-510)
Dates: Received 12/20/04; goal date 6/20/05
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Keywords: NDA review, clinical studies, noninferiority trials

Statistical Review and Evaluation

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In response to the approvable letter dated October 2, 2003, the sponsor submitted 3 multinational clinical studies in type 1 diabetes (Studies 1372, 1374, 1375) and 2 clinical studies in type 2 diabetes (1385 and 1530). Among the type 1 studies; Study 1375 was a cross-over study comparing the frequency of hypoglycemia events between insulin detemir and NPH insulin. Study 1372 was a 26-week multinational, multi-center, open-label, randomized, active-controlled (Glargine) noninferiority trial in type 1 diabetes on a basal-bolus regimen with Insulin aspart as meal-related insulin and Study 1374 compared 18 weeks of treatment with twice daily insulin detemir plus bolus insulin aspart prior to meals with NPH twice daily plus human soluble insulin prior to meals for superiority.

Similar to the design of Study 1374, the two treatment groups in the type 2 superiority Study 1385, detemir and NPH, used 2 different bolus insulins, aspart and HSI, respectively. The two treatment groups in noninferiority Study 1530, also detemir and NPH, were used in combination with mono-therapy OAD or with two OADs.

Table 1 displays the demographics and baseline characteristics of the studies.

Table 1 Demographics and baseline characteristics -ITT

Study	n	Race		Gender		Age (yrs)	Weight (kg)	BMI (kg/m ²)	Diabetes duration (yrs)	HbA _{1c} (%)
		White	Other	Male	Female					
1372-Type 1										
Detemir	161	96%	4%	55%	45%	39.9(14.3)	77.5(14.9)	25.6(3.7)	17.0(11.7)	8.87(0.95)
Glargine	159	95%	5%	48%	52%	49.5(12.9)	75.1(13.5)	25.5(3.5)	16.3(9.2)	8.81(1.02)
1374-Type 1										
Detemir+Asp	298	100%	0%	61%	39%	38.8(13.5)	73.5(11.4)	24.8(3.0)	15.4(10.1)	8.48(1.12)
NPH+HSI	297	100%	0%	65%	35%	39.3(12.9)	74.2(12.2)	24.9(3.2)	15.1(10.4)	8.29(1.19)
1375-Type 1										
Detemir/NPH	66	92%	8%	52%	48%	38.5(12.3)	76.1(12.9)	25.2(3.4)	16.8(10.0)	7.96(0.63)
NPH/Detemir	64	95%	5%	56%	44%	39.9(12.4)	77.4(14.7)	25.6(3.5)	16.9(10.6)	7.88(0.69)
1385-Type 2										
Detemir+Asp	195	99%	1%	40%	60%	58.3(9.4)	82.0(13.3)	29.8(4.6)	13.7(7.5)	8.16(1.3)
NPH+HSI	199	100%	1%	44%	56%	58.2(9.2)	79.6(12.1)	28.7(4.3)	14.5(8.1)	8.08(1.2)
1530-Type 2										
Detemir+OAD	237	98%	2%	49%	51%	61.3(9.1)	82.7(13.3)	28.9(3.6)	9.6(6.6)	8.61(0.77)
NPH+OAD	238	100%	0%	57%	43%	60.4(9.3)	82.5(14.2)	29.0(3.6)	9.8(6.2)	8.51(0.76)

Tables 2 and 3 summarize the studies for type 1 and type 2 patients, respectively. Table 4 displays the reviewer's analysis on mean differences between treatment groups and corresponding 95% confidence intervals for insulin dose (U or IU).

Table 2 Summary of Type 1 diabetes Studies

Trial # center/# country	Titration & Treatment (week)	Basal+Bolus (Meal):n	HbA _{1c} (%) Mean		Insulin ratio		
			Baseline	Endpoint	Basal: nmole,	volume	Bolus:
			Endpoint Δ (C.I.)				
NN304-1372 39/3	26 (6+20)	Detemir 2x/day+IAsp: 161 Glargine 1x/day+IAsp:159	8.87	8.16	5.5 (883/161), 1.37 (37/27)	0.97 (38.5/29.3)	
			8.81	8.19			
			-0.3 (-.25, .19)				
NN304-1374 64/15	18 (6+12)	Detemir 2x/day+IAsp: 298 NPH+ 2x/day+HSI: 297	8.48(1.12)	7.88	4.6 (770/169), 1.14(32/28)	1.01 (26.4/26.3)	
			8.29(1.19)	8.11			
			-.22 (-.34, -.099)				

Table 3 Summary of Type 2 diabetes Studies

Trial # center/# country	Titration & Treatment (week)	Treatment group: n	HbA _{1c} (%) Mean		Insulin ratio		
			Baseline	Endpoint	Basal: nmole,	volume	Bolus (U)
			Endpoint Δ (C.I.)				
NN304-1530 58/10	26	Detemir 2x/day+OAD: 237 NPH 2x/day+OAD: 238	8.61 (0.78)	6.58	5.9 (1528/257), 1.5 (64/43)	NA	
			8.51 (0.76)	6.46			
			0.13 (-0.002, 0.25)				
NN304-1385 31/8	22 (6+16)	Detemir 1 or 2x/day+IAsp:195 NPH+ 1 or 2x/day+HSI: 199	8.16(1.28)	7.46	1x/day 4.03 (619/154), 1.01 (25.8/25.6)	1.08 (33.9/31.4)	
			8.08(1.23)	7.52			
			-0.062 (-0.25, 0.13)		2x/day 5.3 (1404/263), 1.34 (59/44) 1.20 (29/24)		

Table 4 Insulin Dose (U or IU) - ITT

Study	Insulin	Insulin detemir		NPH Insulin		Detemir minus NPH		
		n	Week 1	Week 24	Week 1	Week 24	Week 24 mean difference (95% CI)	
Type 2								
1385								
	Basal	188	30.6 (18.4)	48.6 (36.7)	194	28.4 (14.8)	37.5 (22.4)	11.1 (5.0, 17.3)
	Aspart or HSI	189	25.4 (13.6)	30.9 (18.8)	194	22.9 (17.2)	27.3 (17.4)	3.6 (0.01, 7.3)
1530								
	Basal	231	17.5 (4.8)	65.2 (43.1)	232	16.9 (4.7)	45.1 (26.4)	20.1 (13.6, 26.6)
Type 1								
1374								
	Basal	289	25.2 (11.1)	32.1 (15.3)	288	25.3 (10.7)	28.1 (12.3)	4.00 (1.74, 6.28)
	Aspart or HIS	289	26.2 (11.3)	26.4 (11.9)	288	25.7 (11.7)	26.1 (11.7)	0.36 (-1.57, 2.30)
1372								
			detemir (twice daily)		Glargine (once daily)			
	Basal	148	26.7 (11.2)	36.6 (18.1)	149	22.7 (8.3)	26.8 (11.9)	9.8 (6.3, 13.3)
	Aspart+other	146	29.2 (15.1)	28.6 (19.4)	150	27.8 (12.7)	29.4 (12.6)	-0.8 (-4.5, 3.0)

Hypoglycemia:

The Coma Hypoglycemia cases were from the adverse event dataset. The label stated that the overall rate of hypoglycemia were similar between patients treated with detemir and those treated with NPH human insulin.

Table 5 displays the number of Coma Hypoglycemia in the Resubmission studies.

Table 5 Number of Coma Hypoglycemia in the Resubmission - Type 1

1372		1374		1375 Cross-Over		1379 Pediatrics	
Detemir	Glargine	Detemir+Aspart	NPH+HSI	Detemir/NPH	NPH/Detemir	Detemir	NPH
2/161	2/159	2/298	1/297	2 NPH/66	0/64	3/232	1/115

For type 2 studies, the treat-to-target study (1530) had 3 cases in the NPH + OAD group and study 1385 had 1 case in NPH+HIS and none in the Detemir+Aspart group.

Table 6 displays the number of Coma Hypoglycemia in the Original NDA studies.

Table 6 Number of Coma Hypoglycemia in the Original NDA – Type 1

1181		1205		1335		1447		1448	
Detemir	NPH								
6/237	2/224	1/301	1/148	2/492	2/257	0/271	0/129	3/276	1/132

Only 1 case of Coma Hypoglycemia occurred in the detemir group in study 1166 and none in the NPH groups out of the 3 type 2 studies (1166, 1336, and 1337).

Labeling Comments:

1. The sponsor should not be allowed to _____ in the label for the following reasons. Firstly, compared to blinded studies, the open label design is more prone to confounding factors and biases that may affect the results. Secondly, the volume ratio of detemir to the controls was greater than 1. Thirdly, 2 of the studies used different bolus insulin which is another confounding factor.

2. The sponsor's claim that _____ is not valid and the finding was not consistent from study to study or time point to time point. The sponsor used the log likelihood ratio test to compare the heterogeneous variance model to a homogeneous variance model. For the self-measured fasting blood glucose, the test showed no difference in study 1372 (the within patient variability was greater for the detemir group than the glargine group), no difference in the cross over study using the first period data, and no difference for the type 2 diabetes study 1530 at week 24.

3. The sponsor should not make _____ Weight and vital signs were listed as the safety endpoints. Weight change was minimal in the studies with a mean difference less than 1 kg between treatment groups for type 1 studies.

4. The extension trial was not randomized; hence, _____

5. In the dosage and administration section the sponsor stated '_____, more Tradename may be needed relative to NPH human insulin.' The sponsor should quantify how much more detemir was needed according to the data from the clinical trials. For type 2 patients the estimate was approximately 50% more or 1.5 times in volume. For type 1 patients the estimate was approximately 18% more.

Appears This Way
On Original

Figure 1 HbA_{1c} change from baseline for Detemir (red dash) vs. control (solid) from screening (-1), randomization (0) to endpoint

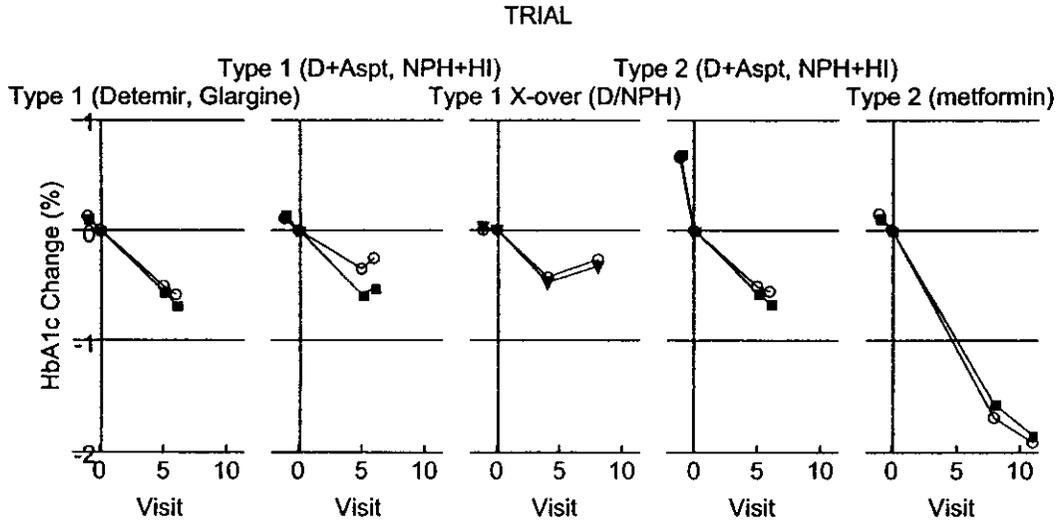
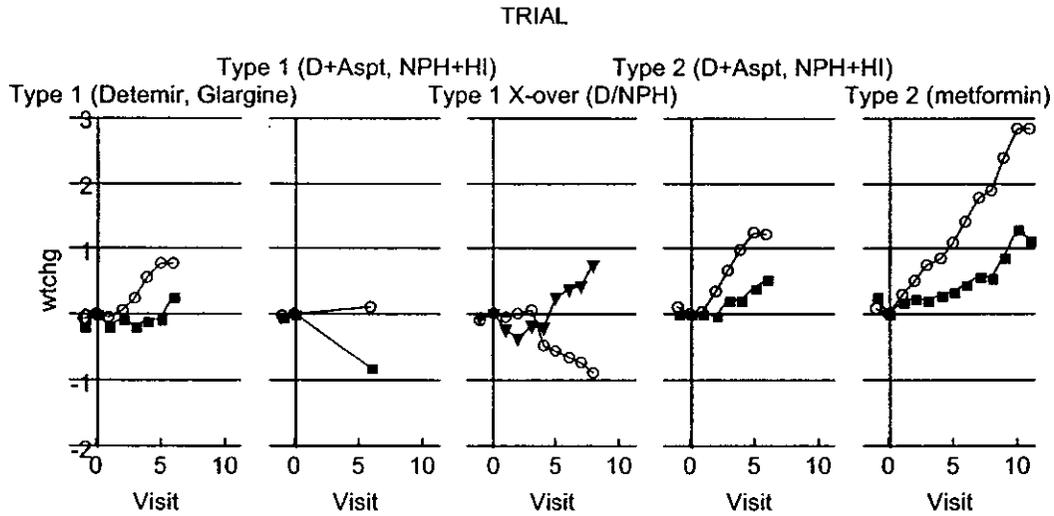


Figure 2 Weight change from baseline for Detemir (red dash)* vs. control (solid) from screening (-1), randomization (0) to endpoint



* For the 1st period of cross-over study, for the 2nd red dash for NPH

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/s/

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Concur with review.



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1 EXECUTIVE SUMMARY OF STATISTICAL FINDINGS

1.1 CONCLUSIONS

Insulin detemir as a basal insulin was noninferior to NPH in the type 1 diabetes patients based on the noninferiority margin of 0.4% for the difference between groups in the HbA_{1c} change from baseline. However, both the bolus insulin and basal insulin were administered at greater mean (molar) doses in the insulin detemir patients than in the NPH patients. For the 2 superiority studies in Type 1 diabetes comparing different timing of the basal insulin dose (morning and night vs. morning and dinner time, 12 hrs interval), HbA_{1c} change from baseline was not statistically significant different among treatment groups.

Two of the 3 studies in Type 2 diabetes failed the noninferiority criteria. The study with an upper confidence limit of 0.3% for the treatment difference between insulin detemir and NPH insulin satisfied the 0.4% noninferiority margin; however, assay sensitivity might have been compromised by the low baseline HbA_{1c} (7.8%) and a greater bolus insulin dose for the insulin detemir group. Therefore, it is concluded that insulin detemir is inferior to NPH insulin in the treatment of type 2 diabetes.

The difference in insulin use in both Type 1 and Type 2 studies poses considerable problems in interpreting the results; in a randomized trial the 2 treatment groups should be comparable with respect to all factors that might affect response. The unequal insulin dose, especially the bolus insulin, might bias the analysis toward the conclusion of no difference. However, the relevancy of the asymmetrical insulin dose in the treatment groups is a clinical decision.

2 STATISTICAL REVIEW AND EVALUATION OF EVIDENCE

2.1 INTRODUCTION AND BACKGROUND

Insulin detemir (NN304) is a new molecular entity with a recombinant DNA origin. This long-acting soluble human insulin analog differs from regular human insulin in its prolonged duration of action. This submission included 8 randomized, open label, parallel, active controlled (NPH insulin) phase 3 studies. Five of the 8 studies were in type 1 diabetes and 3 were in type 2 diabetes. Three studies (2 type 1 and 1 type 2) conducted before year 2001 used a 1200 nmol/ml formulation and the remaining studies used the 2400 nmol/ml formulation. The insulin detemir dose rationale also changed from twice the NPH insulin molar dose of 600 nmol/ml to 4 times the NPH insulin molar dose.

Six studies with a duration of 6 months were designed to show noninferiority of detemir insulin to NPH insulin and two 16-week studies were designed to show superiority of different timing of injection in the primary efficacy variable HbA_{1c}. Three of the six 6-month noninferiority trials were conducted in Type 1 diabetes and 3 were conducted in Type 2 diabetes. Both of the superiority trials were conducted in Type 1 diabetes with patients in the

third arm injecting insulin detemir at morning and dinnertime or 12 hour interval for the 2 respective studies other than the traditional bedtime injection. Patients in the type 1 studies were on a basal-bolus (meal insulin) regimen. All of the type 1 diabetes patients administrated the basal insulin twice daily except patients in one of the studies administered basal insulin once daily. The dosing regimen in the 3 studies in type 2 diabetes patients were basal insulin twice daily without bolus insulin, basal insulin twice daily plus bolus insulin and basal insulin once daily plus oral metformin.

Tables 1 and 2 summarize the studies in type 1 diabetes patients and in type 2 diabetes patients, respectively.

Table 1 Summary of 5 NPH active controlled Phase III studies – Type 1 diabetes

Trial # Place center #	Detemir nm/ml	Study design	Bolus insulin	Basal x/day duration	Treatment: n randomized	HbA _{1c} (%)		Insulin Molar ratio	
						Baseline	6 mons	Basal: nmole, volume	Bolus
1181 Eu, Aus 55	1200	NInf	HSI	2x 6 mons	Detemir: 237 NPH: 224	7.63 (1.18) 7.69 (1.23) 0.10 (-0.03, 0.23)	7.67 (1.21) 7.61 (1.22)	3.08 =525/170 1.6 =44/28	1.17=33/28
1205 Eu 46	1200	NInf	IAsp	2x 6 mons	Detemir: 301 NPH: 148	7.99 (0.11) 7.93 (0.13) -0.05 (-0.21, 0.12)	7.60 (0.09) 7.65 (0.10)	3.74=714/189 1.89=60/32	1.17=31/26
1335 Aus, Eu 92	2400	NInf	HSI	1x 6 mons	Detemir: 492 NPH: 257	8.35 (1.20) 8.34 (1.21) -0.12 (-0.27, 0.04)	8.34 (1.21) 8.41 (1.31)	3.29=504/153 0.82=21/26	1.07=36/33
1447 Eu 52	2400	Supr timing	IAsp	2x 16 wks	Detemir (Dinner): 139 Detemir: 132 NPH: 129	8.23 7.67 8.13 7.65 8.16 7.73 p=0.64 -0.06 (-0.27, 0.15) -0.08 (-0.30, 0.13)		Detemir Dinner/NPH 4.7=810/171 1.2=34/29 1.1=29/26 1.1=32/29 Detemir/NPH 4.5=765/171 1.2=31/26	
1448 Aus, NZ, Eu 51	2400	Supr timing	IAsp	2x 16 wks	Detemir (12 hr) 137 Detemir: 139 NPH: 132	8.53 7.76 8.68 7.79 8.51 7.96 p=0.08 -0.10 (-0.33, 0.13) -0.09 (-0.32, 0.13)		Detemir 12 hr/NPH 4.2=876/210 0.97=28/29 1.1=37/35 Detemir/NPH 4.2=871/210 1.0=29/29 1.0=36/35	

Table 2 Summary of 3 Phase III studies – Type 2 diabetes patients

Trial # Place center #	Detemir nm/ml	Study design	Bolus insulin or oral add on	Basal x/day duration	Treatment: n randomized (n in HbA _{1c} analysis)	HbA _{1c} (%)		Insulin Molar ratio	
						Baseline	6 mons	Basal: nmole volume	
1166; Asia, Eu	1200	NInf	none	2x 6 mons	ID: 224 (187) NPH: 221 (209)	9.01 9.39 8.87 8.70 0.69 (0.46, 0.91)		4.2=1548/366 2.1=129/61	
1336; Eu	2400	NInf	IAsp	2x 6 mons	ID: 341 NPH: 165	7.87 7.63 7.77 7.47 0.16 (0.01, 0.31)		Basal: 4.13 Bolus: 1.12	
1337; US	2400	NInf	metfor min	1x 6 mons	ID: 309 NPH: 158	9.34 9.01 9.22 8.58 0.51 (0.27, 0.75) 0.56 (0.326, 0.784)		4.98 2023/2050=0.99	

2.2 STATISTICAL EVALUATION OF EVIDENCE ON EFFICACY

2.2.1 DETAILED REVIEW OF INDIVIDUAL STUDIES

2.2.1.1 Study 1181 – Type 1 diabetes

Study Design

This was a 6-month, multinational, open-label, randomized (1:1), and parallel group study in patients with type 1 diabetes. The objective of the study was to investigate whether treatment on a twice daily basal plus bolus regimen with insulin detemir + HSI was non-inferior to treatment with NPH + HSI as measured by HbA_{1c}.

Study Dose

The molar concentration of detemir insulin (1200 nmol/ml) was twice that of NPH insulin (600nmol/ml). The rationale for the dose was based on a phase 2 trial, which suggested that the mean molar dose of insulin detemir should be 2.2-2.5 times higher than the NPH insulin dose. Accordingly, patients switching from NPH insulin to insulin detemir started the trial on twice the usual dose. Patients were titrated to reach the targets of glycemic control.

Patient Selection

The trial was conducted in 55 sites in 5 countries (Australia 9, New Zealand 2, Germany 35, Switzerland 2, and Austria 7).

Patient population consisted of patients with type 1 diabetes at least 18 years in age (Austria ≥19), with a BMI ≤35 kg/m², a total daily basal insulin requirement of ≤100 IU/day, and an HbA_{1c} ≤12%.

Sample Size

Sample size was 440 with a 1:1 randomization and an assumed drop-out rate of 10%. Assuming a 1.4% standard deviation for HbA_{1c} after 6 months of treatment and a non-inferiority margin of 0.4% as a clinically relevant difference, 399 patients would achieve a power of 76% based on a 2-sided test with a 5% significant level.

Patient Disposition

Of the total 505 patients screened, 461 patients were randomized and 460 were exposed to trial product (ITT). Table 3 displays disposition of patients. Except for the reason 'other', the withdrawal patterns were similar in the two treatment groups.

Table 3 Patient Disposition – Type 1 Study 1181

	Insulin detemir	NPH insulin
Screened	505	
Randomized	237	224
ITT	236	224
Withdrawals		
Adverse event	5 (2.1%)	2 (0.9%)
Ineffective therapy	8 (3.4%)	9 (4.0%)
Non-compliance	3 (1.3%)	0 (0.0%)
Other	9 (3.8%)	2 (0.9%)
Completed	212 (89.5%)	209 (93.5%)

Demographic and Baseline Characteristics

The trial population comprised fairly well-controlled (HbA_{1c} baseline mean 7.7%) male and female type 1 diabetic patients 17-73 years of age with a mean diabetes duration of 15 years. 8.6% of patients had baseline HbA_{1c} measurement less than 6.0%. All but 5 patients were Caucasian. In both treatment groups, there were more male patients (62%) than female patients (38%).

Primary HbA_{1c} Analysis – Type 1 Study 1181

The analysis of covariance model included treatment and country as fixed effects and baseline HbA_{1c} as covariate. The treatment-by-country-interaction was statistically significant ($p=0.09<0.1$). The descriptive statistics of HbA_{1c} by country (Table 4) showed that the number of patients among countries varied greatly. In New Zealand and Switzerland with only 33 patients (7%), mean HbA_{1c} difference between treatment groups (detemir minus NPH) favored detemir treatment. Especially in Switzerland with the least number of patients the magnitude of the mean difference was the greatest, -0.8%. The 3 largest countries with a total of 400 patients (93%) had small between treatment differences favoring NPH insulin.

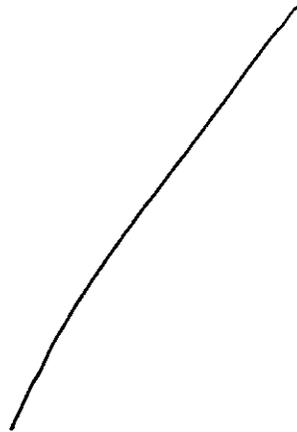
Table 4 Descriptive Statistics of HbA_{1c} (%) by Country – Type 1, Study 1181

Country	Treatment	n	HbA _{1c}			Bolus insulin	
			Baseline	Month 6	change	detemir-NPH	U detemir-NPH
Australia	Detemir	53	8.0	8.1	0.1		32
	NPH	50	8.3	8.3	0.0	0.1	28
Austria	Detemir	33	7.5	7.6	0.1		30
	NPH	34	7.9	7.7	-0.1	0.2	27
Germany	Detemir	116	7.4	7.5	0.0		33
	NPH	114	7.3	7.2	-0.1	0.1	28

		HbA _{1c}					Bolus insulin	
New Zealand	Detemir	10	8.3	8.1	-0.2		41	
	NPH	9	9.1	9.2	0.1	-0.3	21	21
Switzerland	Detemir	8	7.7	7.2	-0.6		41	
	NPH	5	7.0	7.3	0.3	-0.8	34	7
		432						

Figure 1 displays HbA_{1c} from baseline (circle) to endpoint (square) for each patient in Switzerland with the y-axis sorted by HbA_{1c} change from baseline and labeled with patient number. Patient #68008 in the NPH group had a HbA_{1c} increase from — and when excluded the treatment-by-country interaction was not significant (p=0.2). This shows the estimate from countries with only a few patients is very unstable.

Figure 1 Per Patient HbA_{1c} from Baseline to Endpoint in Switzerland



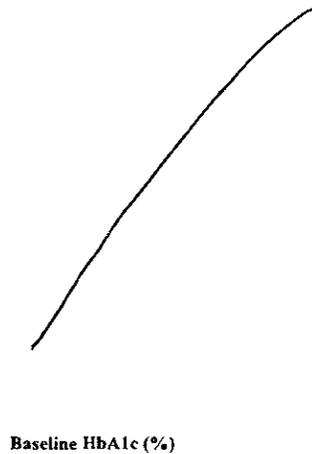
To adjust for the imbalance in the sample size among countries, this reviewer combined each of the 2 small countries by region with a larger country: New Zealand combined with Australia and Switzerland combined with Austria. With the combined countries, the treatment-by-country interaction was not statistically significant (Table 5).

Table 5 Primary efficacy analysis of HbA_{1c} - Type 1 Study 1181

	Insulin detemir n=220	NPH Insulin n=212	Detemir minus NPH
	LSMean (SE)	LSMean (SE)	LSM difference (95% CI)
Baseline	7.71 (0.08)	7.78 (0.08)	
Endpoint	7.71 (0.05)	7.61 (0.05)	0.10 (-0.03, 0.23)

Figure 2 displays the regression lines of HbA_{1c} change from baseline over baseline HbA_{1c}.

Figure 2 HbA_{1c} Change from Baseline by Baseline HbA_{1c} – Type 1 Study 1181



Insulin – Type 1 Study 1181

Table 6 displays descriptive statistics for basal insulin and bolus (HSI) insulin at the end of study. After 6 months of treatment, molar insulin was 17% higher for bolus insulin and 3.08 times higher for the basal insulin in the insulin detemir group than in the NPH insulin group.

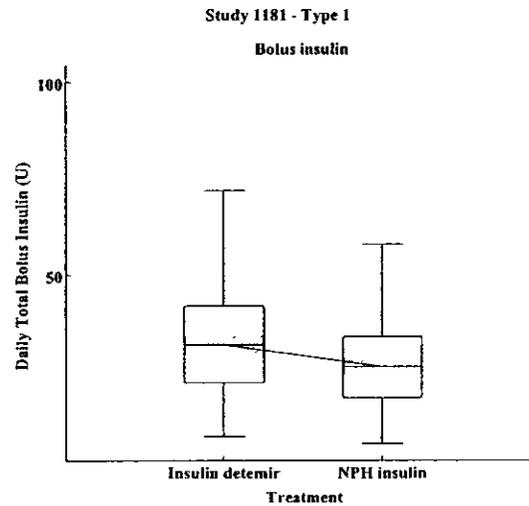
Table 6 Mean (SD) of total daily insulin dose at month 6 – Type 1, Study 1181

	Insulin detemir n=220		NPH insulin n=211		Ratio Detemir/NPH	
	nmole	U	nmole	U	Molar Ratio	Volume
Basal	525	43.8 (18.6)	170	28.4 (12.2)	3.08	1.57
Bolus	196	32.7 (14.3)	167	27.9 (12.4)	1.17	

Insulin detemir: 1(U)=12 nmol
 NPH insulin: 1(IU) =6 nmol
 HSI (bolus): 1 (U)=6 nmol

Figure 3 displays boxplot of total daily bolus insulin administered at the end of trial.

Figure 3 Boxplot for Bolus insulin (HSI) – Type 1 Study 1181



Subgroup:

The subgroups of age (≥ 65 , < 65), gender were similar in the HbA_{1c} outcome.

Conclusion – Type 1 Study 1181

Patients at baseline were well controlled in HbA_{1c}. After 6-month treatment of twice daily basal insulin and bolus insulin (HSI) for meals, HbA_{1c} changed from 7.63% to 7.69% in the detemir treatment group and from 7.69% to 7.59% in the NPH treatment group. The upper limit, 0.23% of the least square mean HbA_{1c} difference, 0.10% between insulin detemir and NPH insulin treatment groups was within the 0.4% of the non-inferiority margin. The insulin use was 17% more (196nmole/167nmol) for the bolus insulin in the detemir group and a 3.08 molar ratio (525nmol/170nmol) for insulin detemir compared to NPH insulin.

2.2.1.2 Study 1205 – Type 1 diabetes

The primary objective of this 6 month multinational multicenter, open-label, randomized study in Type 1 diabetes is to compare the effect of insulin detemir plus insulin aspart and NPH insulin plus IAsp on glycemic control, as measured by HbA_{1c}. The trial used the 1200 nmol/ml formulation for insulin detemir. The starting molar dose for insulin detemir was twice the NPH insulin dose. The rationale was based on results from a phase 2 trial in patients with type 1 diabetes (NN304-1038) which suggested a 2.2 – 2.5 times higher insulin detemir molar dose compared to NPH insulin in order to obtain similar 24-hour blood glucose profiles, when keeping bolus insulin constant.

A total of 46 centers participated in 5 European countries: 27 in France; 8 in Belgium; 1 in Luxembourg; 3 in The Netherlands; and 7 in Norway.

A total of 471 patients were screened and 448 were randomized to treatment group insulin detemir or NPH insulin in a 2 to 1 ratio. Of the 447 patients exposed to trial products, 301 were in the insulin detemir group and 146 were in the NPH insulin group.

Table 7 displays disposition of patients.

Table 7 Patient disposition – Type 1 study 1205

	Insulin detemir n=301 (100%)	NPH insulin n=147 (100%)
Reason for withdrew		
Adverse event	2 (0.7%)	0 (0.0%)
Ineffective therapy	5 (1.7%)	2 (1.4%)
Non-compliance	5 (1.7%)	0 (0.0%)
Other	5 (1.7%)	4 (2.7%)
Completed	284 (94.4%)	141 (95.9%)

The demographic and baseline characteristics are comparable between the 2 treatment groups. Patients averaged 40 years of age with a mean duration of diabetes approximately 17 years and a mean baseline HbA_{1c} of 8.16% (1.13, SD).

Primary efficacy analysis on HbA_{1c} – Type 1 study 1205

The ANCOVA model included treatment and country as fixed effect and baseline HbA_{1c} value as a covariate. The country-by-treatment interaction was not statistically significant; therefore, it was eliminated from the model. However, number of patients varied greatly among countries. A little more than half of the patients were in France (n=225) and Luxembourg had only 6 patients (1.4%). Table 8 displays the descriptive statistics of HbA_{1c}.

Table 8 Descriptive statistics of HbA_{1c} – Type 1 study 1205

	Insulin detemir n=286	NPH insulin n=144
	Mean (SD)	Mean (SD)
Baseline HbA _{1c}	8.17 (1.14)	8.12 (1.13)
Endpoint	7.62 (1.18)	7.62 (0.10)

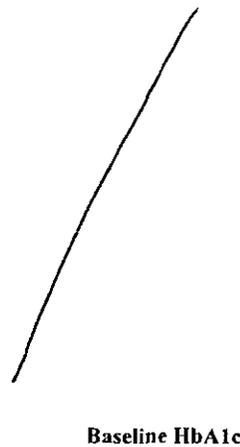
Table 9 displays the results of the ANCOVA analysis on HbA_{1c}.

Table 9 Results from the ANCOVA on HbA_{1c} (%) – Type 1 study 1205

	Insulin detemir n=286	NPH insulin n=144	detemir minus NPH
	LSM (SE)	LSM (SE)	LSM difference (95% CI)
Baseline HbA _{1c}	7.99 (0.11)	7.93 (0.13)	
Endpoint	7.60 (0.09)	7.65 (0.10)	-0.05 (-0.21, 0.12)

Figure 4 displays HbA_{1c} change from baseline by baseline HbA_{1c}. The 2 fitted regression lines were similar in slope with greater reduction of HbA_{1c} at greater baseline HbA_{1c}.

Figure 4 HbA_{1c} change from baseline (%) by baseline HbA_{1c} (%) – Type 1 study 1205



Daily insulin dose

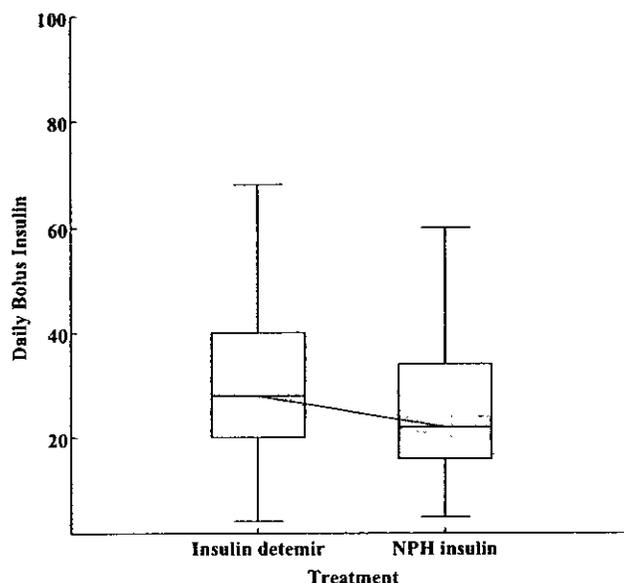
At the end of the trial, the molar dose of insulin detemir was 3.7 times higher than the molar dose of NPH insulin. The mean daily bolus insulin dose was 17% higher for patients in the insulin detemir group (Table 10). Bolus insulin dose remained similar to the pre-treatment level in the insulin detemir group, and fell slightly in the NPH insulin group. Figure 5 displays boxplots of the bolus insulins.

Table 10 Total daily basal dose after 6 months – Type 1, Study 1205

Insulin	Insulin detemir n=286		NPH insulin n=144		Ratio (Detemir/NPH)	
	Molar	Mean (SD) Volume	Molar	Mean (SD) Volume	Molar	Volume
Basal	714 (nmol)	59.5 (U) (30.56)	189 (nmol)	31.5 (U) (14.2)	3.78	1.89 (U/IU)
Bolus	185 (nmol)	30.9 (U) (15.69)	158 (nmol)	26.3 (U) (14.1)	1.17	

Insulin detemir: 1(U)=12 nmol
 NPH insulin: 1(IU) =6 nmol
 Insulin Aspart (bolus): 1 (U)=6 nmol

Figure 5 Boxplot of Daily Bolus Insulin – Type 1 Study 1205



Subgroup – Type 1 Study 1205

The subgroups of age (≥ 65 , < 65), gender were similar in the HbA_{1c} outcome.

Conclusion – Type 1 Study 1205

Patients treated with a twice-daily injection of 1200 mmoles/ml insulin detemir as basal insulin and IAsp as meal insulin and twice NPH insulin as basal insulin and the IAsp as meal insulin were similar in the outcome of HbA_{1c} after 6 months. HbA_{1c} changed from 7.99% to 7.60% in the insulin detemir group and from 7.93 to 7.65% in the NPH insulin group. The upper confidence limit, 0.12% of the least squared mean difference, -0.05% was within the non-inferiority margin of 0.4%. However, the bolus insulin injection was 17% (185 nmol/158nmol or 30.9U/26.3U) more in the insulin detemir group than in the NPH insulin group for the bolus insulin. The molar ratio of insulin detemir to NPH insulin was 3.78 (714nmol/189nmol).

2.2.1.3 Study 1335 – Type 1 diabetes

This 6- month, multicenter, open-label, 2:1 randomized study compared *once* daily insulin detemir with that of NPH insulin on the outcome variable HbA_{1c} in Type 1 diabetes on a basal-bolus regimen. Patients received the basal insulin at bedtime and human soluble insulin

(HSI) prior to meals. In Rationale for the Dose section, the sponsor stated that ‘A phase II trial (NN304-1038) including subjects with type 1 diabetes has shown that a mean increase (on a molar basis) in insulin detemir dose of 2.4 times (95% CI: 2.22, 2.48) the NPH insulin dose was required to obtain a comparable 24-hour blood glucose profile without a change in the bolus insulin requirements. In addition, preliminary results from another trial (NN304-1255) in subjects with type 2 diabetes suggested a mean increase (on a molar basis) in insulin detemir of approximately 4 times (95% CI: 3.19 – 5.11) the NPH insulin dose in order to achieve similar glycaemic control.’ The insulin detemir formulation used in this trial was 2400 nmol/ml (100U/ml). The starting dose of insulin detemir used the estimate for Type 1 diabetes which is about twice the NPH insulin dose in molar concentration (1200 nmol/600 nmol) and half the NPH insulin dose in volume for the 2400 nmol/ml preparation.

The study was designed as a non-inferiority trial based on the primary endpoint HbA_{1c} after 6 months of treatment. The sample size of 540 patients was increased to 750 (500:250, detemir:NPH); to ensure a sufficient number of patients exposed to insulin detemir.

A total of 838 patients were screened and 749 randomized. Of the 749 patients randomized, 747 patients were exposed to trial products and were therefore included in the ITT analysis set. Table 11 displays patient disposition.

Table 11 Patient Disposition – Type 1 Study 1335

	Insulin detemir	NPH insulin
Screened	838	
Randomized	492	257
Withdrawals	27	22
Adverse Event	5 (1.0%)	2 (0.8%)
Ineffective therapy	3 (0.6%)	0 (0.0%)
Non-compliance	2 (0.4%)	5 (1.9%)
Other	17 (3.5%)	15 (5.8%)
Completed	465 (94.5%)	235 (91.4%)

Patients in the treatment groups were comparable in the demographic and baseline characteristics. The trial population was comprised of 64% male and 36% female patients with a mean age of 41 years and a mean duration of diabetes of 17 years. All but 6 patients were Caucasian. The mean and median HbA_{1c} at baseline was 8.3%.

Primary Efficacy Analysis – Type 1 Study 1335

Table 12 displays descriptive statistics of HbA_{1c}. The primary analysis of HbA_{1c} (%) at endpoint is displayed in Table 13. The analysis of covariance model included treatment, country and treatment-by-country interaction as fixed factors and HbA_{1c} at baseline as a covariate. The treatment-by-country interaction was statistically significant (p=0.016).

Table 12 Descriptive statistics of HbA_{1c} -Type 1, Study 1335

	Insulin detemir n=474	NPH Insulin n=239
	Mean (SD)	Mean (SD)
Baseline	8.35 (1.20)	8.34 (1.21)
Endpoint	8.34 (1.21)	8.41 (1.31)

Table 13 Primary efficacy analysis of HbA_{1c} -Type 1, Study 1335

	Insulin detemir n=474	NPH Insulin n=239	Detemir – NPH
	LSMean (SE)	LSMean (SE)	LSM difference (95% CI)
Baseline	8.29 (0.06)	8.29 (0.09)	
Endpoint	8.26 (0.05)	8.37 (0.06)	-0.12 (-0.27, 0.04)

Descriptive statistics by center:

Ninety-two centers in 11 countries participated in the study. Table 14 displays the number of centers and the number of patients by country. Luxembourg had only 2 (0.3%) patients, one per treatment group. The sponsor pooled Luxembourg with Belgium in the analysis.

Table 14 Number of patients by country

Country	# center	n	%
Australia	8	93	13
Belgium	4	31	4
Denmark	7	94	13
Finland	5	34	5
France	13	89	12
Ireland	2	19	3
Luxembourg	1	2	0.3
Norway	9	74	10
Sweden	10	90	13
The Netherlands	7	52	7
United Kingdom	23	135	19
Total	89	713	100

The descriptive statistics by country for HbA_{1c} (%) and total daily bolus insulin dose (IU) are displayed in Table 15 according to the sample size. The smaller countries either favored detemir group (big negative difference) or favored NPH group (big positive difference) which caused a significant treatment-by-country interaction. As the sample size increased, the magnitude of difference between treatments in HbA_{1c} change decreased.

Table 15 Descriptive statistics by country – Type 1 Study 1335

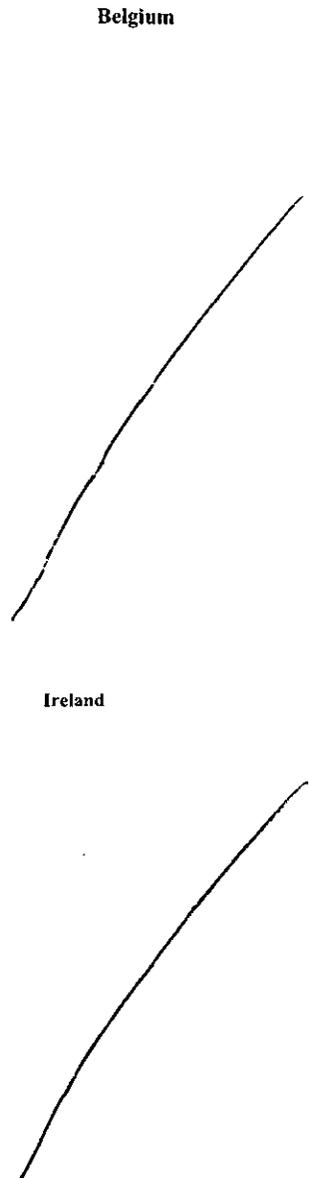
Country	Treatment	n	Baseline HbA _{1c} %	HbA _{1c} Change	Difference detemir - NPH	Bolus insulin	Difference of bolus IU
Luxembourg	Detemir	1					
Luxembourg	NPH	1	8.2	4.6	-3.9	36	-18
Ireland	Detemir	13	8.0	-0.12		31.2	
Ireland	NPH	6	8.3	-0.92	0.8	31.8	-0.7
Belgium	Detemir	20	7.9	0.13		33.9	
Belgium	NPH	11	8.6	-0.12	0.3	25.8	6.4
Finland	Detemir	24	8.1	0.04		31.8	
Finland	NPH	10	7.7	0.58	-0.5	30.5	1.3
The Netherlands	Detemir	33	8.8	-0.71		39.2	
The Netherlands	NPH	19	8.2	-0.03	-0.7	35.6	3.6
Norway	Detemir	51	8.4	-0.12		35.2	
Norway	NPH	23	8.6	0.32	-0.4	38.3	-3.1
France	Detemir	58	8.5	-0.03		35	
France	NPH	31	8.2	-0.3	0.3	30.8	4.2
Sweden	Detemir	60	8.6	-0.1		33	
Sweden	NPH	30	8.3	0.11	-0.2	30.7	2.3
Australia	Detemir	62	7.8	0.46		38.9	
Australia	NPH	31	8.4	0.63	-0.1	35	3.9
Denmark	Detemir	63	8.2	-0.15		31.1	
Denmark	NPH	31	8.2	-0.15	0	29.3	1.8
United Kingdom	Detemir	89	8.7	-0.15		39.6	
United Kingdom	NPH	46	8.6	-0.09	-0.1	37.9	1.8
Total	Detemir	474	8.4	-0.06		35.6	
Total	NPH	239	8.3	0.06	-0.1	33.5	2.1

Figure 6 displays the HbA_{1c} from baseline (circle) to 6-month (square) for the smaller countries with increasing HbA_{1c} in black, no change in blue and decreasing in red. The y-axis is sorted by the change and labeled with the bolus insulin dose (U). In the analysis patients in Luxembourg were pooled with patients in Belgium. When pooled, the difference between treatment groups in HbA_{1c} changed from favoring NPH (0.3%) to favoring detemir (-0.2%) because the — increase of the one patient in Luxembourg was in the NPH treatment group (top figure).

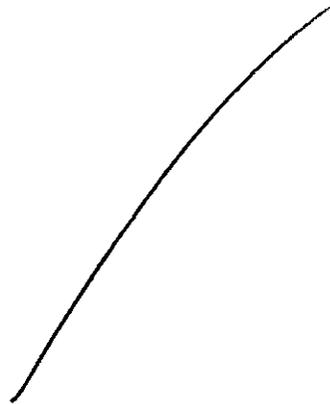
HbA_{1c} decreased in all 6 patients treated with NPH insulin in Ireland (mean -0.92%). With a change of -0.12% in the detemir group, the difference between detemir and NPH was +0.8% favoring NPH.

In Finland, the mean baseline HbA_{1c} value was lower than other countries with 7.7% in the NPH group and 8.1% in the detemir group. Mean HbA_{1c} in both groups increased from baseline with a -0.5% difference between the treatment groups. These estimates from smaller countries were unstable and caused the significant treatment-by-country interaction.

Figure 6 HbA_{1c} (%) from baseline to endpoint by patients

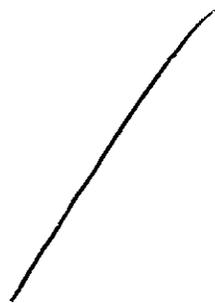


Insulin detemir **Finland** **NPH insulin**



The treatment-by-baseline HbA_{1c} interaction was also significant ($p=0.08<0.1$) (Figure 6).

Figure 7 HbA_{1c} Change from Baseline by Baseline HbA_{1c} – Type 1, Study 1335



Insulin – Study 1335, Type 1

During the first 2 weeks of the trial, the basal insulin dose increased considerably due to a lower starting dose for patients in the insulin detemir group (half pretrial dose for insulin detemir). Table 16 displays descriptive statistics for the daily insulin dose for the basal insulin and bolus insulin. Figure 8 displays boxplots for the total daily doses of bolus insulin. At the end of the trial, the mean basal insulin dose was 3.29 times higher for detemir-treated patients than for NPH –treated patients. The mean bolus insulin dose was 7% higher for detemir-treated patients.

Table 16 Total daily insulin dose after 6 months – Type 1, Study 1335

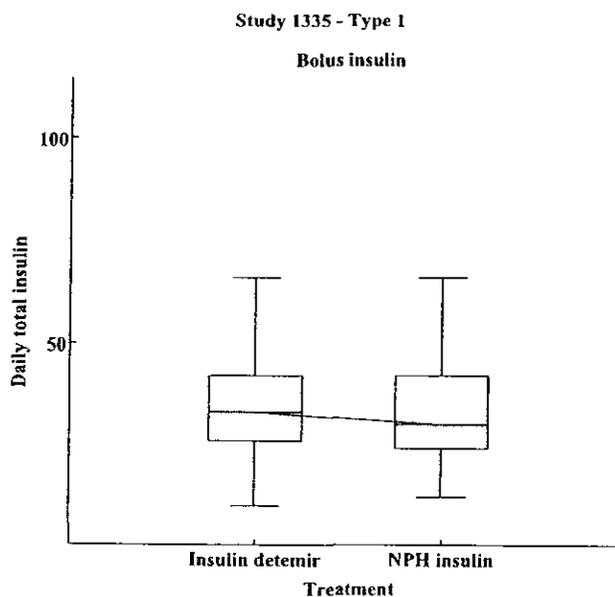
Insulin	Insulin detemir n=474		NPH insulin n=239		Ratio (Detemir/NPH)	
	Molar	Mean (SD) Volume	Molar	Mean (SD) Volume	Molar	Volume
Basal	504 (nmol)	21.0 (U) (10.40)	153 (nmol)	25.5 (U) (12.0)	3.29	0.82 (U/IU)
Bolus	214 (nmol)	35.6 (U) (13.73)	200 (nmol)	33.4 (U) (12.8)	1.07	

Insulin detemir: 1(U)=24 nmol

NPH insulin: 1(IU) =6 nmol

Human Soluble Insulin (bolus): 1 (U)=6 nmol

Figure 8 Box Plot of Total Daily Bolus Insulin –Type 1, Study 1335



The descriptive statistics for subgroup of gender and age group are displayed in Tables 17 and 18, respectively. The treatment-by-subgroup interaction was not significant.

Table 17 Mean (SD) of HbA_{1c} (%) and Daily Insulin by Gender and Treatment Group – Type 1, Study 1335

	Female		Male	
	Insulin detemir n=162	NPH insulin n=97	Insulin detemir n=312	NPH insulin n=142
Baseline HbA _{1c}	8.19 (1.24)	8.38 (1.21)	8.44 (1.17)	8.32 (1.22)
Endpoint HbA _{1c}	8.18 (1.11)	8.33 (1.40)	8.35 (1.05)	8.46 (1.25)
HbA _{1c} Change	-0.01 (0.89)	-0.05 (1.16)	-0.08 (0.93)	0.14 (0.96)
Daily Bolus Insulin (IU)	31 (11.0)	29 (10.1)	38 (14.5)	37 (13.5)

Table 18 Mean (SD) of HbA_{1c} (%) and Daily Insulin by Age & Treatment Group – Type 1, Study 1335

	≥ 65 years		<65 year	
	Insulin detemir n=21	NPH insulin n=11	Insulin detemir n=453	NPH insulin n=228
Baseline HbA _{1c}	8.08 (1.04)	8.39 (1.65)	8.37 (1.21)	8.34 (1.19)
Endpoint HbA _{1c}	7.98 (0.94)	8.18 (1.18)	8.31 (1.08)	8.42 (1.32)
HbA _{1c} Change	-0.10 (0.86)	-0.21 (1.64)	-0.06 (0.92)	0.08 (1.02)
Daily Bolus Insulin (IU)	32 (9.4)	34 (7.3)	36 (13.0)	33 (13.0)

Conclusion of Type 1 Study 1335:

For HbA_{1c} descriptive statistics pooling all patients, the change from baseline was minimal, -0.01% for the insulin detemir group and +0.06% for the NPH insulin group. The once daily basal insulin regimen seems insufficient in HbA_{1c} reduction since HbA_{1c} at endpoint remained well above 8% in both groups. The insufficient basal insulin dose and the few patients in some of the countries might cause a significant treatment-by-country interaction. Including the statistically significant treatment-by-country interaction in the ANCOVA, the least squared mean at baseline was 8.29 for both groups. The mean difference between groups in HbA_{1c} was -0.12% with an upper confidence interval of 0.04 which is less than the 0.4% non-inferiority margin. The mean daily molar dose of bolus insulin was slightly higher after 6 months in the insulin detemir treatment group than in the NPH insulin group (214 nmol vs. 200 nmol) with a ratio of 1.07. The molar dose ratio for basal insulin was 3.27 (504 nmol vs. 153 nmol) for insulin detemir:NPH. The insufficient dosing regimen for the basal insulin might have compromised assay sensitivity in this non-inferiority trial.

2.2.1.4 Study 1447 – Type 1 diabetes

This was a 16-week study comparing administration of insulin detemir given morning and pre-dinner, insulin detemir given morning and bedtime, and NPH insulin given morning and bedtime in patients with type 1 diabetes. All patients received bolus insulin aspart (IAsp).

The purpose of the study was to address the question of optimal dosing time. The rationale was based on the later onset of action of insulin detemir than NPH insulin which may allow a pre dinner administration of insulin detemir that is earlier than the usual bedtime administration of NPH insulin. The profile of insulin detemir may promise a reduced risk of hypoglycemia and a long enough effect to cover the early morning insulin requirements.

Based on the 2 previous phase 3 studies (1181, 1205), the molar dose for detemir was changed from a factor of approximately 2 to approximately 4 compared to NPH insulin. The insulin detemir formulation used was 2400 nmol/ml (100 U/ml). The starting dose of insulin detemir was 2.8 times the NPH insulin dose as measured in molar concentration and 70% the NPH insulin dose as measured in volume. Patients randomized to NPH insulin also started on 70% of the NPH insulin dose that they were taking previously. In order to ensure sufficient glycemic control for both treatment groups, patients were titrated up rapidly.

The primary efficacy variable is HbA_{1c} measurements after 16 weeks of treatment. The analysis of covariance model with baseline HbA_{1c} as a covariate was used to test the null hypothesis that all treatments have the same effect against the alternative hypothesis that at least one of the treatments has a different effect from one of the others. To account for multiple comparisons, the protected Fisher's LSD (least significant difference) method was used per protocol. It first tests the null hypothesis that all the population means are equal. After (and only after) the rejection of the null hypothesis that all the population means are equal, the LSD can be applied to all pairwise comparisons using t-tests at the 5% level of significance.

Patient Disposition – Type 1 Study 1447

A total of 426 patients were screened and 400 patients were randomized to treatment. Approximately 95% of the randomized patients completed the trial. The per protocol analysis set included approximately 80% of the patients. Table 19 displays the patient disposition.

Table 19 Patient Disposition – Type 1 study 1447

	Insulin detemir morning + pre- dinner	NPH insulin morning + bedtime	Insulin detemir morning + bedtime	Total
Randomized	139	129	132	400
Withdrawals				
Total	7 (5%)	4 (3%)	10 (8%)	21
Adverse event	2	0	4	6
Ineffective therapy	2	4	1	7
Non-compliance	2	0	2	4
Other	1	0	3	4
Completers	132 (95%)	125 (97%)	122 (92%)	379
PP analysis	112 (81%)	105 (81%)	105 (80%)	322

All of the 4 patients (3%) who withdrew from NPH insulin group did so due to ineffective therapy. The 2 insulin detemir groups had more withdrawals than the NPH insulin group (5%, 8%).

Demographic and Baseline Characteristics – Type 1 Study 1447

The study population consisted of all Caucasians. Overall approximately 60% of the patients were males and 40% were females. The detemir morning and bedtime group, however, had approximately 70% males and 30% females. Patients were around 50 years of age with a mean duration of diabetes around 15 years. The mean HbA_{1c} at baseline was 8.07% and the mean fasting plasma glucose (FPG) was 10.4mmol/L.

Primary Efficacy Analysis – Type 1 Study 1447

The primary efficacy endpoint was HbA_{1c} at week 16. Table 20 displays the descriptive statistics of HbA_{1c}.

Table 20 Mean (SD) of HbA_{1c} – Type 1 Study 1447

	Detemir morning, dinner n=136	Detemir morning, bedtime n=124	NPH morning, bedtime n=125
Baseline HbA _{1c}	8.02 (1.25)	8.13 (1.38)	8.09 (1.14)
Endpoint	7.59 (1.12)	7.64 (1.11)	7.70 (0.98)

The overall treatment difference was not statistically significant (p=0.64). Therefore, according to the planned protected Fisher’s LSD, the sponsor did not perform pairwise comparisons.

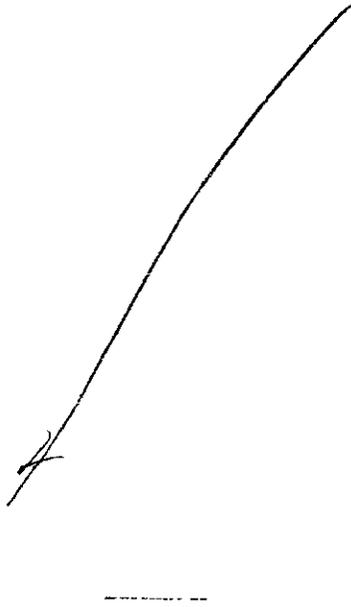
This reviewer presented the Bonferroni adjusted pairwise confidence intervals of difference between treatment groups in Table 21.

Table 21 ANCOVA of HbA_{1c} (%) after 16 Weeks of Treatment – ITT (LOCF) Type 1 Study 1447

Treatment Group	n	Baselin HbA _{1c} (SE)	HbA _{1c} (SE)	Treatment difference (95% adjusted C.I.)
Detemir morning, dinner	136	8.23 (0.11)	7.67 (0.06)	Detemir morning, dinner – NPH morning, bedtime -0.06 (-0.27, 0.15)
Detemir morning, bedtime	125	8.13 (0.11)	7.65 (0.07)	Detemir morning, bedtime – NPH morning, bedtime -0.08 (-0.30, 0.13)
NPH morning, bedtime	124	8.16 (0.11)	7.73 (0.07)	Detemir morning, dinner – Detemir morning, bedtime 0.02 (-0.19, 0.23)
			p=0.64	

Figure 10 displays change from baseline HbA_{1c} by baseline HbA_{1c}. The 3 similar negative slopes indicated that as the baseline increases the reduction of HbA_{1c} from baseline also increases.

Figure 10 HbA_{1c} change from baseline by baseline HbA_{1c} - Type 1, Study 1447



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Insulin Dose

The mean basal and bolus insulin dose (units) at week 16 (visit 7) for each dose time and their daily total are displayed in Table 22.

Table 22 Total daily insulin dose at week 16 – Type 1, Study 1447

n	Detemir Morning, Dinner		Detemir Morning, Bedtime		NPH Morning, Bedtime		Ratio (Detemir/NPH)	
	U/IU	nmol	U/IU	nmol	U/IU	nmol	molar	Volume
	34 (19.4)	810	32 (13.6)	765	29 (12.0)	171	4.7, 4.5	1.17, 1.10
	28.5 (15.9)		30.6 (15.8)		25.6 (10.3)		1.11, 1.19	

Insulin detemir: 1 unit (U) = 24 nmol

NPH insulin: 1 unit (IU) = 6 nmol

Insulin Aspart: 1 unit (U) = 6 nmol

The molar dose ratio in this trial for insulin detemir was higher compared to previous phase 3 trials. The molar ratio for basal insulin dose was 4.7, and 4.5 for the insulin detemir groups to the NPH insulin group. For insulin Aspart (bolus insulin), 11% and 19% more insulin was used in the detemir groups than the NPH insulin group. Figure 11 displays the boxplots for daily total basal insulin and daily total bolus insulin.

Figure 11 Boxplots for Daily Total Basal and Bolus Insulin (units) – Type 1 Study 1447

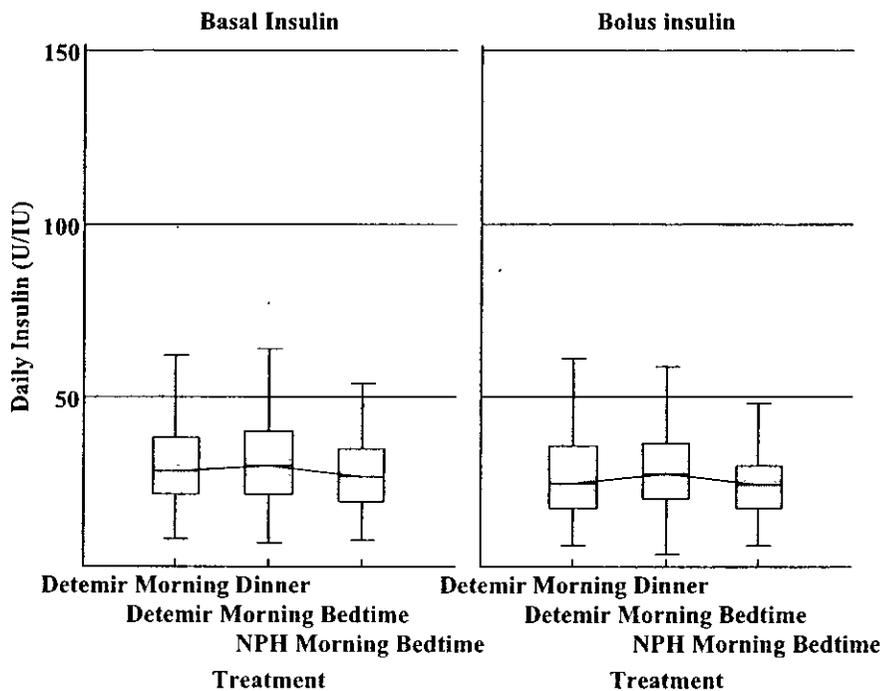


Figure 12 displays HbA_{1c} from baseline to endpoint for patients using at least 62 units daily basal insulin (y-axis sorted by insulin unit).

Figure 12 Patients with Daily Basal Insulin ≥ 62 U

Treatment
Detemir Morning, Dinner Detemir Morning, Bedtime NPH Morning, Bedtime

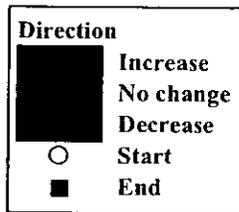
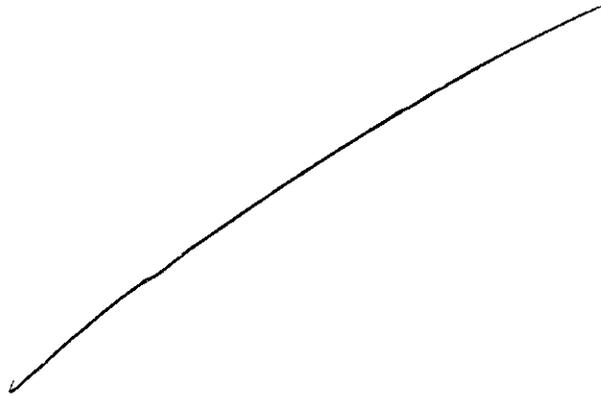
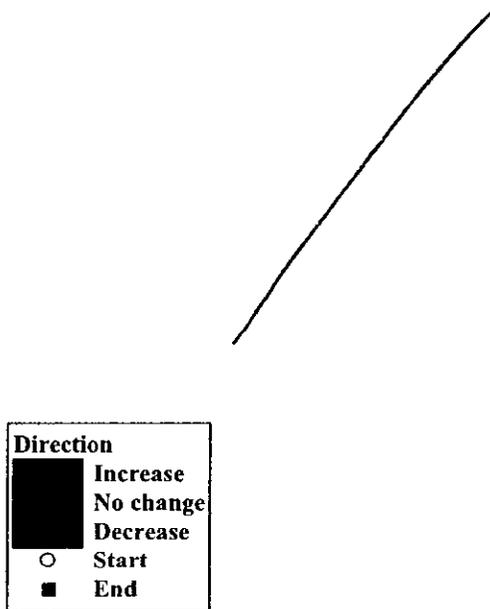


Figure 13 displays HbA_{1c} from baseline to endpoint for patients using at least 52 units daily bolus insulin (y-axis sorted by insulin unit).

Figure 13 HbA_{1c} of Patients with Daily Bolus Insulin (LAspart) ≥ 52 U
Treatment
Detemir Morning, Dinner Detemir Morning, Bedtime NPH Morning, Bedtime



Subgroup – Type 1 Study 1447

For both gender and year group, the HbA_{1c} reductions from baseline in all 3 treatment groups were comparable.

Conclusion – Type 1 Study 1447

The study was designed to show superiority of at least one treatment group in HbA_{1c} after 16 weeks of treatment. The HbA_{1c} was not statistically significantly different (p=0.6) among the 3 treatment groups which administered nighttime basal insulin at dinnertime or bedtime. HbA_{1c} reduction was approximately 0.4% (8.1% to 7.7%). The insulin molar ratio of insulin detemir to NPH insulin was 4.9 for the detemir dinnertime group and 4.5 for the detemir bedtime group. The mean daily bolus insulin was 11% higher in the detemir morning/dinner time group and 19% higher in the detemir morning/bedtime group than in the NPH morning/bedtime group.

2.2.1.5 Study 1448 – Type 1 diabetes

This was a 16-week, multi-center, multi-national, open, randomized 3-group parallel study comparing administration of insulin detemir at 12 hour intervals, insulin detemir at morning and bedtime, and NPH insulin at morning and bedtime in patients with type 1 diabetes. The primary objective of the trial was to compare the twice-daily basal insulins as measured by HbA_{1c} on a basal-bolus regimen. Patients received insulin aspart (IAsp) at meals.

The rationale for administering insulin detemir at fixed time intervals instead of the traditional insulin regimen of morning and bedtime was that the even interval might provide more stable daily basal insulin profiles and could potentially improve metabolic control and/or reduce the risk of hypoglycemia.

The primary efficacy variable is HbA_{1c} measurements after 16 weeks of treatment. The analysis of covariance model with treatment and country as fix effects and baseline HbA_{1c} as a covariate was used to test the null hypothesis that all treatments have the same effect against the alternative hypothesis that at least one of the treatments has a different effect from one of the others. If this overall F test is significant then all 3 pairwise comparisons can be tested at a 0.05 alpha level.

Patient Disposition – Type 1 Study 1448

A total of 52 trial sites in 7 countries participated in the study. A total of 441 patients were screened and 409 patients were randomized to treatment and 408 were exposed to trial products. Approximately 96% of the randomized patients completed the trial. Table 23 displays the patient disposition.

Table 23 Patient Disposition – Type 1 Study 1448

	Detemir _{12hr}	NPH _{Morn&Bed}	Detemir _{Morn&Bed}	Total
Randomized	137	133	139	409
Withdrawals				
Total	5 (3.6%)	8 (6.0%)	4 (2.9%)	17
Adverse event	1 (0.7%)	1 (0.8%)	0 (0.0%)	1
Ineffective therapy	3 (2.2%)	1 (0.8%)	0 (0.0%)	4
Non-compliance	1 (0.7%)	5 (3.8%)	2 (1.4%)	8
Other	0 (0.0%)	1 (0.8%)	2 (1.4%)	3
Completers	132 (96.4%)	124 (93.2%)	135 (97.1%)	391
PP analysis	112 (81.8%)	117 (88.0%)	126 (90.6%)	355

Demographic and Baseline Characteristics

The study population consisted of 99% Caucasians with more male patients (54%) than female patients (46%). The average age was 40 years and the mean weight was 75 kg. The mean HbA_{1c} at baseline was 8.6%.

Primary Efficacy Analysis

The primary efficacy endpoint was HbA_{1c} at week 16. Table 23 displays the descriptive statistics of HbA_{1c} at endpoint.

Table 24 Descriptive statistics of HbA_{1c} (%) – Study 1448, type 1

HbA _{1c}	Detemir 12h Interval	Detemir Morning Bedtime	NPH Morning Bedtime
Baseline Mean (SD)	8.56 (1.20)	8.72 (1.19)	8.53 (1.17)
Week 16 Mean (SD)	7.76 (1.01)	7.88 (0.93)	7.94 (1.12)
Change (SD)	-0.80 (0.89)	-0.84 (1.06)	-0.59 (0.87)

For the primary efficacy analysis on HbA_{1c} at week 16, treatment-by-country interaction in the ANCOVA model was not statistically significant and was deleted from the model. The overall p-value and the Bonferroni adjusted pairwise confidence intervals for differences between treatments are displayed in Tables 25 and 26 for the ITT population and PP population, respectively. P-value from the overall F-test was not significant (p=0.075), therefore, no further pairwise comparison was performed by the sponsor.

Table 25 ANCOVA Results of HbA_{1c} (%) after 16 Weeks of Treatment – ITT (LOCF), Type 1 #1448

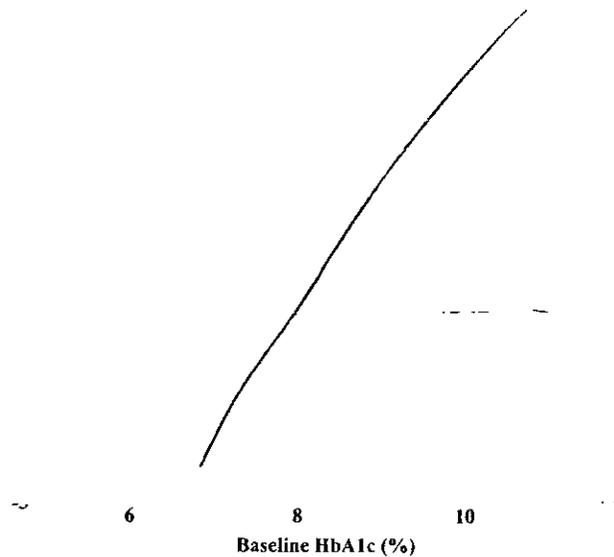
Treatment Group	n	Baseline LSM (SE)	Endpoint LSM (SE)	Treatment difference (2-sided, 95% adjusted C.I.)
Detemir 12 hr interval	135	8.53 (0.10)	7.76 (0.07)	Detemir 12 hr interval – NPH Morning, Bed -0.19 (-0.42, 0.03)
Detemir Morning, Bed	136	8.68 (0.10)	7.79 (0.07)	Detemir Morning, Bed – NPH Morning, Bed -0.17 (-0.39, 0.05)
NPH Morning, Bed	127	8.51 (0.11)	7.96 (0.07)	Detemir 12 hr interval – Detemir Morning, Bed -0.03 (-0.24, 0.19)
F-test			p=0.075	

Table 26 ANCOVA Results of HbA_{1c} (%) after 16 Weeks of Treatment – PP, Type 1 Study 1448

Treatment Group	n	Baseline LSM (SE)	Week 16 LSM (SE)	Treatment difference (95% adjusted C.I.)
Detemir 12h interval	112	8.59 (0.11)	7.79 (0.07)	Detemir 12 hr interval – NPH Morning, Bed -0.10 (-0.33, 0.13)
Detemir Morning, Bed	126	8.71 (0.11)	7.80 (0.07)	Detemir Morning, Bed – NPH Morning, Bed -0.09 (-0.32, 0.13)
NPH Morning, Bed	117	8.49 (0.11)	7.89 (0.07)	Detemir 12 hr interval – Detemir Morning, Bed 0.01 (-0.24, 0.22)
F-test			p=0.50	

Figure 14 displays HbA_{1c} change from baseline by baseline HbA_{1c} for the 3 treatment groups. The fitted regression lines indicated that patients with greater baseline HbA_{1c} value experience a greater reduction in HbA_{1c} than patients with smaller baseline HbA_{1c} value. The treatment-by-baseline HbA_{1c} interaction was significant (p=0.003).

Figure 14 HbA_{1c} change from baseline by baseline HbA_{1c} – Type 1, Study 1448



Insulin Dose – Study 1448, type 1

The mean basal and bolus insulin dose (molar, units) at week 16 (visit 7) for each dose time and their daily total are displayed in Table 27 .

Table 27 Total daily insulin dose at week 16 – Type 1, Study 1448

	Detemir 12 hr		Detemir morn, bed		NPH morn,bed		Ratio (Detemir/NPH)	
	Molar	U/IU	Molar	U/IU	Molar	U/IU	Molar	Volume
Basal	876	36.5 (16.3)	871	36.3 (16.5)	210	34.9 (13.5)	4.17, 4.15	1.06 1.03
Bolus	165	27.5 (15.0)	176	29.4 (12.1)	176	29.4 (12.4)	0.97	1.00

Figure 15 displays the boxplot for basal and bolus insulin.

Figure 15 Boxplot for Insulin – Type 1 Study 1448

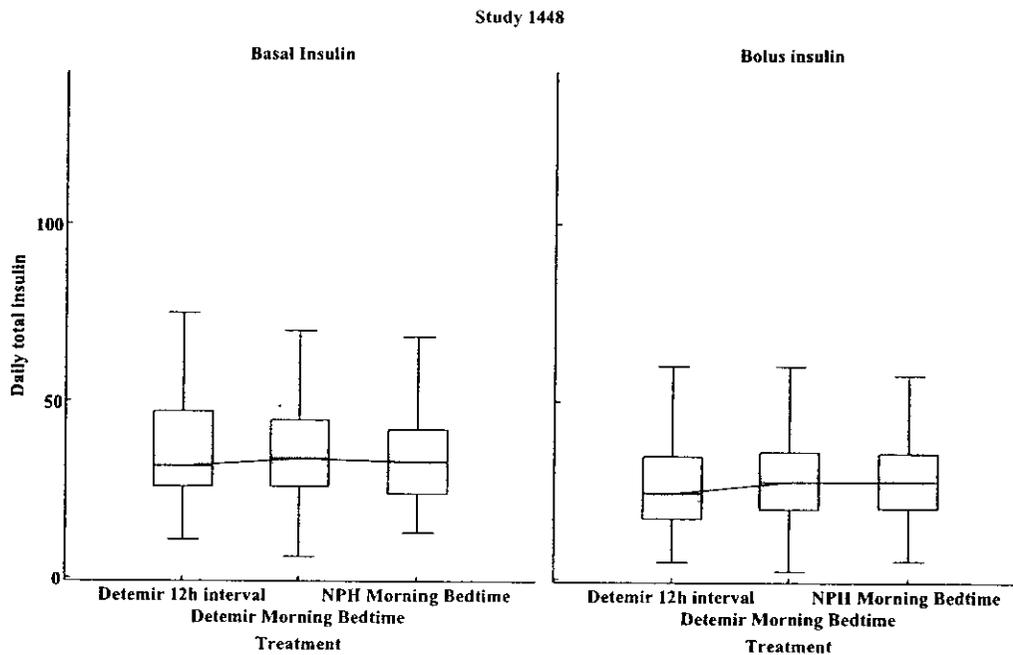


Figure 16 displays HbA_{1c} from baseline to endpoint by patient whose daily basal insulin was at least 62U (y-axis).

Figure 16 HbA_{1c} from baseline to endpoint by patient with basal insulin ≥ 62 U

Treatment

Detemir 12h interval Detemir Morning Bedtime NPH Morning Bedtime

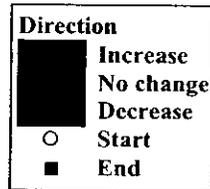
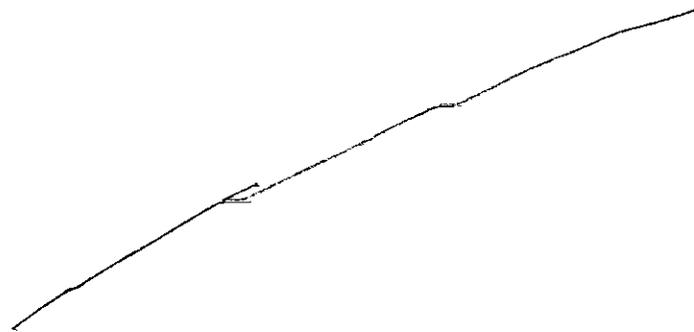
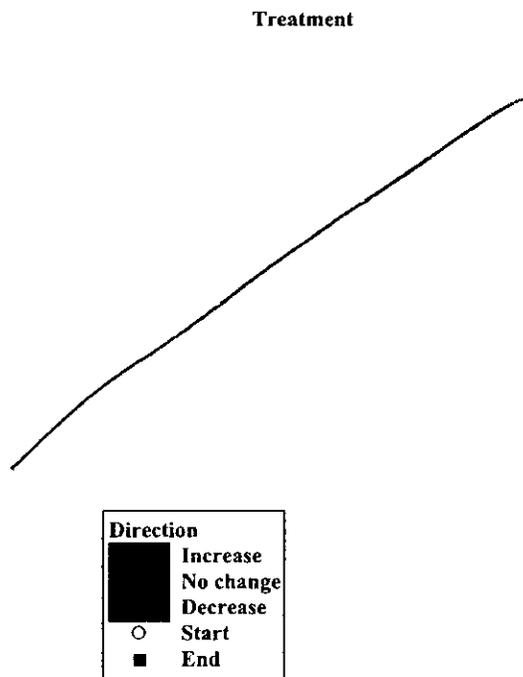


Figure 17 displays patients whose daily bolus insulin was at least 52 U.

Figure 17 HbA_{1c} from baseline to endpoint by patient with bolus insulin ≥ 52 U



Conclusion – Type 1 Study 1448

After 16 weeks of treatment with insulin detemir 12h interval, insulin detemir morning+bedtime and NPH insulin morning+bedtime in combination with insulin aspart, HbA_{1c} was not statistically significant different between the 3 treatment groups. HbA_{1c} changes from baseline were -0.8%, -0.9% and -0.6% from baselines of 8.5%, 8.7% and 8.5% for the 3 treatment groups of detemir 12 h interval, detemir morning and bedtime, and NPH morning and bedtime, respectively. The molar ratios of insulin detemir to NPH insulin were approximately 4.2 for basal insulin and approximately 1 for bolus insulin Aspart.

Study 1166 – Type 2 diabetes

This 6-month trial in Type 2 diabetes was conducted in Asia and Europe. The primary objective of the study was to compare the effect of insulin detemir with NPH insulin on glycemic control, as measured by HbA_{1c}, in patients with type 2 diabetes after six months of treatment on a twice-daily regimen.

The trial recruited patients age ≥ 35 years who were treated with intermediate/long-acting insulin ≤ 120 IU in total daily dose or patients unsatisfactorily controlled with oral hypoglycemic agent (HbA_{1c} $> 8.0\%$).

The formulation for insulin detemir was 100 U=1200 nmole and for NPH insulin it was 100 IU=600 nmol. According to the 2.2 to 2.5 times molar dose estimate of insulin detemir to the NPH insulin dose from a phase 2 trial in type 1 diabetes (NN304-1038), the initial dose of detemir was 2 times patient's usual molar dose of NPH insulin. The initial detemir were adjusted every second day in order to optimize dosing with insulin detemir.

Sample size was based on a non-inferiority trial with 1:1 randomization, a 2-sided t-test at 5% significant level, assuming a 1.4% standard deviation for HbA_{1c} and a non inferiority margin of 0.4% HbA_{1c} as a clinically relevant difference. A total of 440 patients were considered sufficient with a 10% drop out rate and a power of 81%.

Patient disposition

The 43 trial sites (9 in Asia and 34 in Europe) screened a total of 553 patients. Of the 553 patients, 445 patients were randomized, 224 to the insulin detemir group and 221 to the NPH insulin group. The completion rate was 80% for the insulin detemir group and 93% for the NPH insulin group. Approximately 11% (24) patients in the insulin detemir group and 1% (2) patients in the NPH insulin group withdrew for ineffective therapy. Table 28 displays disposition of patients.

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Table 28 Patient disposition – Type 2 study 1166

	Insulin detemir n=224 (100%)	NPH insulin n=221 (100%)
Reason for withdrawal		
Adverse event	8 (3.6%)	2 (0.9%)
Ineffective therapy	24 (10.7%)	2 (0.9%)
Non-compliance	2 (0.9%)	4 (1.8%)
Other	10 (4.5%)	7 (3.2%)
Completed	180 (80.4%)	206 (93.2%)

The 2 treatment groups were comparable in the demographic and baseline characteristics. A larger percentage of male patients (60%) were in the insulin detemir group than in the NPH insulin group (51%). The race distribution was 1/3 Asian and 2/3 Caucasian. Average age was 59 years. The mean baseline HbA_{1c} was 8.87%.

Of the 445 patients randomized, 439 were exposed to trial products and were included in the ITT population. Of the 439 patients (221, detemir and 218 NPH), 396 patients (187, detemir and 209 NPH) had both a baseline and at least one follow up measurement of HbA_{1c} and were included in the primary efficacy analysis on HbA_{1c}.

Primary efficacy analysis on HbA_{1c} – type 2 study 1166

Table 29 displays descriptive statistics of HbA_{1c}.

Table 29 Mean (SD) of HbA_{1c} (%) – Type 2 Study 1166

HbA _{1c} (%)	Insulin detemir n=187	NPH insulin n=209
Baseline	8.92 (1.37)	8.78 (1.40)
Month 6	9.29 (1.62)	8.55 (1.42)
Change from baseline	+0.37 (1.56)	-0.24 (1.35)

The ANCOVA model included treatment and country as fixed effects and baseline HbA_{1c} value as a covariate. The country-by-treatment interaction was not statistically significant; therefore, it was eliminated from the model. In addition, the race-by-treatment was not statistically significant. Table 30 displays the results of the ANCOVA analysis on HbA_{1c}.

Table 30 Results from the ANCOVA on HbA_{1c} (%) – Type 2 Study 1166

	Insulin detemir n=187	NPH insulin n=209	detemir minus NPH
	LSM (SE)	LSM (SE)	LSM difference (95% CI)
Baseline HbA _{1c}	9.01 (0.12)	8.87 (0.11)	
Endpoint	9.39 (0.10)	8.70 (0.10)	0.69 (0.46, 0.91)

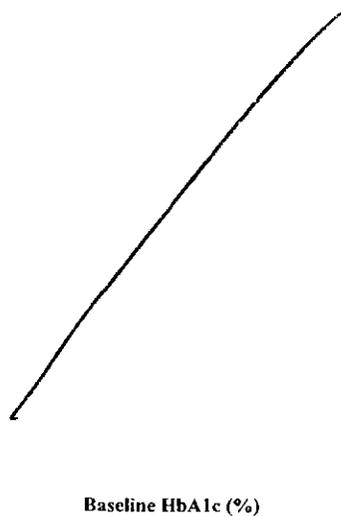
The insulin detemir was inferior to the NPH insulin in glycemic control measured by HbA_{1c}. Both the confidence limits were greater than 0 which indicated that the NPH insulin was

statistically significantly better than insulin detemir. The mean difference between the treatments (0.69%) as well as both the upper and lower bound of the 95% confidence interval exceeded the 0.4% margin for noninferiority where the criteria is that the upper bound should be within the margin.

Figure 18 displays the change from baseline HbA_{1c} by baseline HbA_{1c} of the 2 treatment groups.

The regression lines were parallel which indicated a consistent mean difference over the HbA_{1c} baseline range. Mean HbA_{1c} change from baseline went from positive (HbA_{1c} increases) to negative (HbA_{1c} decreases) as baseline HbA_{1c} increases.

Figure 18 Change from baseline HbA_{1c} by Baseline HbA_{1c} – Type 2 Study 1166



Insulin – Study 1166, type 2

Table 31 displays the total daily basal dose after 6 months.

Table 31 Total daily basal dose after 6 months – Type 2 1166

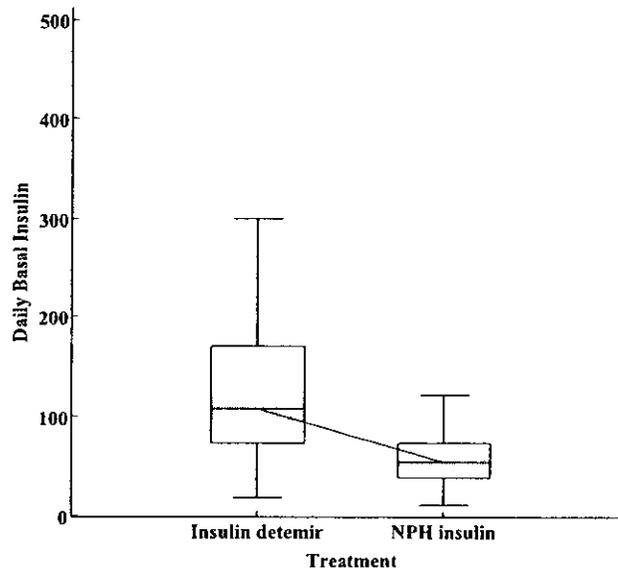
Insulin detemir n=187		NPH insulin n=209		Ratio (Detemir/NPH)	
Mean U (SD)	nmol	Mean IU (SD)	nmol	Volume	Molar
129 (79)	1548	61 (34)	366	2.1	4.2

Insulin detemir: 1 U=12 nmol

NPH insulin: 1 IU=6 nmol

Figure 19 displays HbA_{1c} change from baseline by daily total basal insulin (U) for the two treatment groups.

Figure 19 Boxplot of Total Daily Basal Insulin by Treatment Group – Type 2, Study 1166



Subgroup – Study 1166, type 2

Gender

Table 32 displays descriptive statistics on HbA_{1c} and daily insulin by gender. HbA_{1c} changes from baseline were similar in both male patients and female patients with increases in insulin detemir treated patients and decreases in NPH treated patients. The insulin daily dose in

female patients and male patients were also similar for both insulin detemir and NPH insulin.

Table 32 Mean (SD) of HbA_{1c} (%) and Daily Insulin by Gender and Treatment Group – Type 2, Study 1166

	Female		Male	
	Insulin detemir n=77	NPH insulin n=103	Insulin detemir n=110	NPH insulin n=106
Baseline HbA _{1c}	9.00 (1.49)	8.95 (1.34)	8.87 (1.28)	8.62 (1.45)
Endpoint HbA _{1c}	9.42 (1.80)	8.62 (1.34)	9.20 (1.48)	8.48 (1.50)
HbA _{1c} Change	0.43 (1.67)	-0.33 (1.38)	0.33 (1.48)	-0.14 (1.32)
Daily insulin (U or IU)	130 (80.2)	61 (31.3)	128 (79.0)	61 (34.1)

Race

The treatment-by-race interaction was not significant (p=0.13). Table 33 displays descriptive statistics on HbA_{1c} (%) and daily insulin by race. For Asian patients, HbA_{1c} increased 0.9% in insulin detemir treated patients and increased slightly, 0.09% in NPH treated patients. For Caucasian patients, HbA_{1c} increased slightly (0.05%) in insulin detemir treated patients and decreased 0.4% in NPH treated patients.

Table 33 Mean (SD) of HbA_{1c} (%) and Daily Insulin by Race and Treatment Group – Type 2, Study 1166

	Asian		Caucasian	
	Insulin detemir n=71	NPH insulin n=77	Insulin detemir n=116	NPH insulin n=132
Baseline HbA _{1c}	9.04 (1.53)	8.96 (1.55)	8.85 (1.26)	8.68 (1.30)
Endpoint HbA _{1c}	9.94 (1.82)	9.06 (1.75)	8.90 (1.34)	8.25 (1.10)
HbA _{1c} Change	0.90 (1.78)	0.09 (1.44)	0.05 (1.30)	-0.43 (1.26)
Daily insulin	114 (69.8)	61 (33.0)	138 (83.6)	61 (35.1)

Age

Table 34 displays descriptive statistics in HbA_{1c} and daily insulin dose for patients ≥ 65 or <65 years in age. In both age groups, HbA_{1c} increased in insulin detemir treated patients and decreased in NPH insulin treated patients.

Table 34 Mean (SD) of HbA_{1c} (%) and Daily Insulin by Age and Treatment Group – Type 2, Study 1166

	≥65 years		<65 years	
	Insulin detemir n=49	NPH insulin n=63	Insulin detemir n=138	NPH insulin n=146
Baseline HbA _{1c}	8.80 (1.14)	8.65 (1.38)	8.97 (1.44)	8.84 (1.42)
Endpoint HbA _{1c}	9.50 (1.60)	8.34 (1.38)	9.22 (1.62)	8.64 (1.51)
HbA _{1c} Change	0.70 (1.61)	-0.31 (1.09)	0.25 (1.53)	-0.20 (1.45)
Daily insulin (U or IU)	116 (73.7)	52 (27.1)	134 (80.9)	65 (36.3)

Conclusion - Study 1166 (Type 2)

The analysis of covariance showed that after 6 months treatment with either insulin detemir or NPH insulin, HbA_{1c} was statistically significant higher in insulin detemir group compared with the NPH insulin. The criterion for non-inferiority was not met. The baseline adjusted least means was 9.39% and 8.70% for insulin detemir and NPH, respectively. The LSM difference was 0.69% with 95% confidence interval of 0.46% and 0.91%.

2.2.1.6 Study 1336 - Type 2 diabetes

This was a 6-month, multi-center (63), multinational (5), randomized (2:1, detemir:NPH) study in type 2 diabetes patients on a basal (once to twice daily) and bolus (IAsp) insulin regimen.

A total of 506 patients were randomized and 505 were exposed to trial drugs. Approximately 99% of patients were White and 1% were Asian. Approximately 93% of patients completed the study (Table 35).

Table 35 Patient Disposition – Study 1336, type 2

	detemir	NPH	all
Screen			545
Randomized	341	165	506
Withdrawals	26 (7.6%)	9 (5.5%)	35 (6.9%)
Adverse Event	8 (2.3%)	2 (1.2%)	10 (2.0%)
Ineffective therapy	8 (2.3%)	2 (1.2%)	5 (1.0%)
Other	9 (2.6%)	2 (1.2%)	11 (2.2%)
Completers	315 (92.4%)	156 (94.5%)	471 (93.1%)

Patients were enrolled in 63 sites in 5 countries: 43 sites in Germany, 8 sites in Austria, 7 sites in Italy, 4 sites in Switzerland and 1 site in Slovenia. The percentages of total patients in the 5 countries were 71%, 11%, 9%, 6% and 3%, respectively (Fig 20). Baseline HbA_{1c} level is low in Germany compared to Slovenia (Table 36). The gross imbalance in the number of patients in each makes it inappropriate to include country as a factor in the statistical model.

Figure 20 Frequency over HbA_{1c} by country

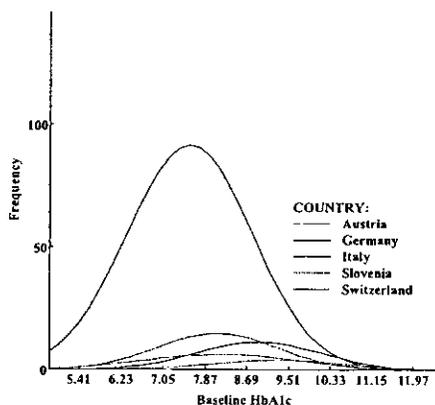


Table 36 displays the difference between the arithmetic mean and the least squared mean for baseline HbA_{1c} with country as a factor.

Table 36 Baseline HbA_{1c} (%)

	detemir	NPH
Mean	7.9	7.8
Least Squared Mean	8.5	8.4

The difference between the arithmetic mean and least squared mean resulted from the fact that the mean baseline HbA_{1c} in Germany (71% of patients) was low and the mean baseline HbA_{1c} in Italy and Slovenia was high (Table 37). Table 38 displays daily total bolus insulin by country.

Table 37 Descriptive statistics of HbA_{1c} by country

Country	Germany		Austria		Switzerland		Italy		Slovenia	
	detemir	NPH	detemir	NPH	detemir	NPH	detemir	NPH	detemir	NPH
n	231	109	36	17	19	10	27	15	11	5
baseline	7.6	7.5	8.2	7.8	8.2	8.1	8.9	9.0	9.6	8.8
change	-0.1	-0.3	-0.2	-0.3	-0.2	-0.3	-0.8	-0.9	-1.4	-0.9

Table 38 Descriptive Statistics of Daily Total Bolus Insulin (unit) by country

Country	Germany		Austria		Switzerland		Italy		Slovenia	
	detemir	NPH	detemir	NPH	detemir	NPH	detemir	NPH	detemir	NPH
n	231	109	36	17	19	10	27	15	11	5
Bolus	43.47	41.52	36.39	31.94	32.58	25.60	31.96	31.53	61.45	27.60
SD	27.23	23.10	22.98	19.63	13.91	11.84	13.19	12.57	49.80	16.76
Basal	35.08	36.85	40.97	35.82	33.47	35.8	24.59	25.67	88.72	42.40

The magnitude of HbA_{1c} change from baseline is dependent on baseline HbA_{1c}. Patients in Italy and Slovenia had a greater baseline and a greater reduction in HbA_{1c} compared with the other 3 countries. Patients in general administered more bolus insulin in the insulin detemir group than patients in the NPH group, especially in Slovenia (61.45 vs. 27.60).

The imbalances in the number of patients, the baseline HbA_{1c} in different countries and the differential dosage of insulin injection between treatment groups and the low baseline HbA_{1c} combine to make assay sensitivity a questionable premise in this trial.

The descriptive statistics for mean baseline HbA_{1c}, mean endpoint HbA_{1c} and change from baseline HbA_{1c} are displayed in Table 39.

Table 39 Descriptive statistics of HbA_{1c} (%) – Study 1136, type 2

	detemir n=325		NPH n=157	
	Mean (SD)	Min, Max	Mean (SD)	Min, Max
Baseline HbA _{1c}	7.87 (1.33)	(5.10, 12.30)	7.77 (1.34)	(5.00, 11.60)
Endpoint HbA _{1c}	7.62 (1.10)	(5.30, 12.00)	7.41 (0.95)	(5.10, 10.60)
Change from baseline	-0.25 (1.04)	(-4.40, 2.50)	-0.36 (1.04)	(-3.60, 1.90)

The results from the analysis of covariance with treatment, country as fixed factors and baseline HbA_{1c} as covariate are displayed in Table 40.

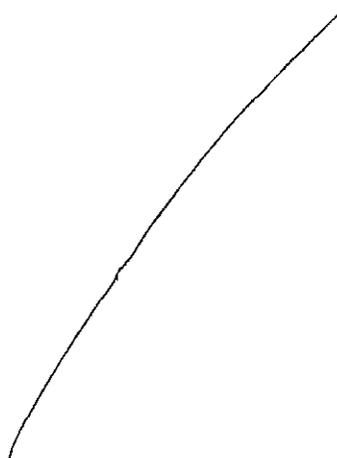
Table 40 ANCOVA results in HbA_{1c} (%) – Study 1136, type 2

	detemir n=325	NPH n=157	detemir – NPH 2-sided 95% CI
Mean (SE)	7.87 (0.07)	7.77 (0.11)	
LSM (SE)	7.63 (0.07)	7.47 (0.08)	0.16 (0.01, 0.31)

The upper confidence limit 0.3% was within the 0.4 noninferior margin. The lower limit is greater than 0 which means NPH is statistically superior to detemir (p=0.04).

Figure 21 displays HbA_{1c} change from baseline by baseline HbA_{1c}. The 2 regression lines are not parallel over the range of the baseline HbA_{1c} values. As the baseline HbA_{1c} value increases, the regression lines start to separate.

Figure 21 HbA_{1c} by baseline HbA_{1c} – Study 1136, type 2



Insulin

The insulin molar ratio of detemir/NPH was 4.1 for the basal insulin and 1.12 for the bolus insulin (Table 41).

Table 41 Mean (SD) daily insulin dose for basal insulin and bolus insulin.

	Insulin detemir n=325 324		NPH insulin n=157		Ratio	
	Molar	U	Molar	IU/U	Molar	Volume
Basal Insulin	878	36.6 (25.0)	215	35.8 (21.6)	4.1	1.02
Bolus insulin	244	40.7 (26.9)	218	36.3 (21.1)	1.12	

Figure 22 displays boxplots for basal and bolus insulins. Figure 23 displays HbA_{1c} of individual patients with daily bolus insulin greater or equal to 80 U.

Figure 22 Boxplot of Bolus Insulin and Basal Insulin -- Type 2 Study 1336

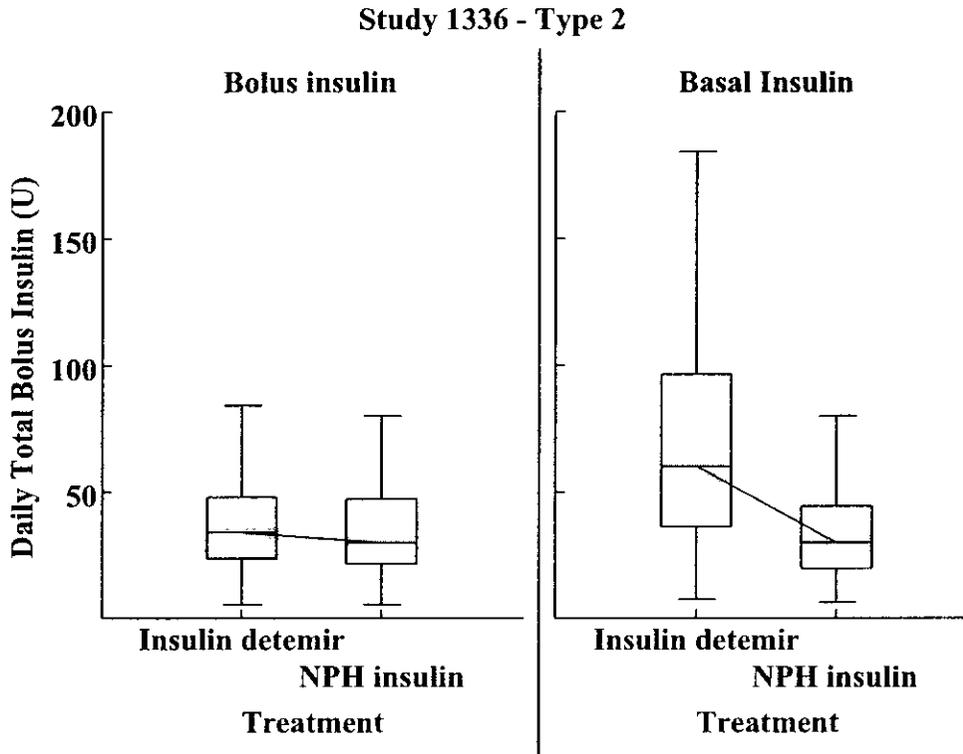
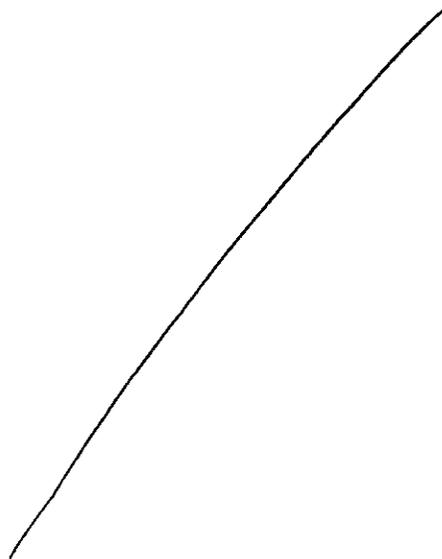


Figure 23 HbA_{1c} of patients with bolus insulin dose ≥ 80 U

Insulin detemir Treatment NPH insulin



Conclusion – Type 2 Study 1336

The cell sizes by country were extremely imbalance with 70% patients in Germany and only 3% in Slovenia. The mean baseline HbA_{1c} was 7.8%, which is low compared to other studies. The 0.16% treatment difference with a confidence interval of 0.01 to 0.31 is within the margin of 0.4%, however, the lower limit excludes 0 which means statistically NPH is superior to detemir. The molar ratio of basal insulin detemir to NPH insulin was 4.1 (876/210) and the ratio for the bolus insulin of the two treatment groups was 1.12.

2.2.1.7 Study 1337 - Type 2 diabetes

This is a study of once daily evening dosing of insulin detemir or human insulin NPH added to a maximally tolerated dose of metformin in patients with type 2 diabetes previously inadequately controlled with monotherapy or oral combination therapy with metformin.

The formulation of insulin detemir used in this study was 2400 nmol/ml, which was 4 times the molar concentration of NPH insulin. The rationale for the equal volume dosing was based on the results of a phase 2 study in type 2 diabetic patients (NN304-1255). In the phase 2 study a similar metabolic effect to insulin NPH was achieved with a 4.1-fold higher molar dose of insulin detemir. In both treatment groups the insulin dose started at 0.1 units/kg in patients whose fasting blood glucose was ≤ 180 mg/dl or 0.2 units/kg for patients whose fasting blood glucose was >180 mg/dl with subsequent insulin dose titration.

The study was conducted at 72 trial sites in the United States and Puerto Rico for 24 weeks. Randomization of patients was in a 2 to 1 ratio of insulin detemir and insulin NPH.

A total of 467 patients were randomized, 309 to the detemir group and 158 to the NPH group. Fourteen percent of detemir patients (43) and 11% of the NPH patients (18) discontinued from the study. All 8 patients who withdrew due to a reason of ineffective therapy were in the detemir treatment group. Table 42 displays patient disposition.

Table 42 Patient Disposition – Type 2, Study 1337

	Detemir	NPH	Total
Screened			517
Randomized	309	158	467
Completed	266 (86%)	139 (88%)	405 (87%)
Discontinued	43 (14%)	18 (11%)	61 (13%)
Adverse Events	9 (2.9)	4 (2.5%)	13 (2.8%)
Non-compliance	18 (5.8%)	8 (5.1%)	26 (5.5%)
Ineffective therapy	8 (2.6%)	0 (0%)	8 (1.7%)
Other	8 (2.6%)	6 (3.8%)	14 (3.0%)

The 2 treatment groups were comparable with respect to demographics, baseline characteristics and diabetic history. The mean age was 55.8 years. More males than females were in the NPH group (59% vs. 41%). There were 60% of Caucasians, 30% of Hispanic and 6% of Black. Mean year with diabetes was 9.2. Baseline HbA_{1c} was 9.4%.

Primary Efficacy Analysis

The protocol specified analysis of variance but the sponsor performed analysis of covariance for the primary analysis on HbA_{1c} at endpoint. The ANCOVA model included treatment, center, and previous treatment as fixed effects and baseline HbA_{1c} as covariate. The sponsor's endpoint analysis (EOS) on the 'modified ITT population' had 290 insulin detemir patients and 144 NPH insulin patients. However, this reviewer's ANCOVA analysis had 280 insulin detemir patients and 142 NPH insulin patients (Table 44) from the efficacy data submitted by the sponsor. Table 43 displays the descriptive statistics of HbA_{1c}.

Table 43 Mean (SD) of HbA_{1c} – Study 1337, type 2

	Detemir (n=280)	NPH (n=142)
Baseline HbA _{1c} %	9.45 (1.20)	9.39 (1.12)
HbA _{1c} at week 24	8.48 (1.28)	7.93 (1.18)
Change from baseline	-0.97 (1.26)	-1.45 (1.32)

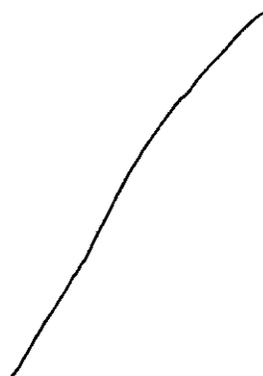
Table 44 LSM (SE) of ANCOVA analysis in HbA_{1c} – Study 1337, type 2

	Detemir (n=280)	NPH (n=142)	Detemir minus NPH Difference (2-sided, 95% CI)
Baseline HbA _{1c} %	9.41 (0.09)	9.38 (0.11)	
HbA _{1c} at week 24	8.46 (0.08)	8.01 (0.11)	0.45 (0.21, 0.69)

The upper bound of the confidence interval, 0.69% for treatment mean difference is greater than the 0.4% noninferiority margin, hence; the noninferiority criteria was not met for insulin detemir in comparison to NPH insulin. The sponsor's treatment difference was 0.56% with a confidence interval of 0.326 to 0.784

Treatment-by-baseline interaction was significant (p=0.07). Figure 24 displays the regression of HbA_{1c} change from baseline by baseline HbA_{1c}. The difference between treatment groups increased as the baseline increased.

Figure 24 HbA_{1c} change from baseline by baseline HbA_{1c} (%) – Study 1337, type 2



Insulin

Table 45 Basal insulin dose – Study 1337, type 2

	Detemir (n=280)		NPH (n=142)		Ratio (Detemir/NPH)	
	U	nmol/ml	U	nmol/ml	Volume	Molar
Basal insulin	53.6 (38.0)	1286	42.6 (27.7)	255	1.26	5.0

The sponsor reported a mean (SD) 0.57 unit/kg (0.36) for the 292 insulin detemir patients and 0.46 unit/kg (0.26) for the 149 NPH insulin patients. The molar ratio of insulin detemir to NPH insulin was 4.98 which is similar to the 5.0 molar ratio in Table 45.

Subgroup

Race

Treatment-by-race interaction was significant when included in the ANCOVA model ($p=0.06$). Figure 25 displays the HbA_{1c} change from baseline by baseline HbA_{1c} by race. Tables 46 & 47 display descriptive statistics for the subgroup race for HbA_{1c} and daily basal insulin dose, respectively. The least square mean difference between the insulin detemir group and the NPH group was 0.70% favoring NPH insulin in Caucasian patients and 0.1% in Hispanic patients.

The daily insulin dose was greater in Caucasian patients than in Hispanic patients. Figures 26 and 27 display HbA_{1c} from baseline to endpoint by median of the basal insulin dose in Caucasian and Hispanic patients, respectively. The figures showed that a higher proportion of Caucasian patients in the insulin detemir group who took an above the median insulin dose had an increase of HbA_{1c} from baseline.

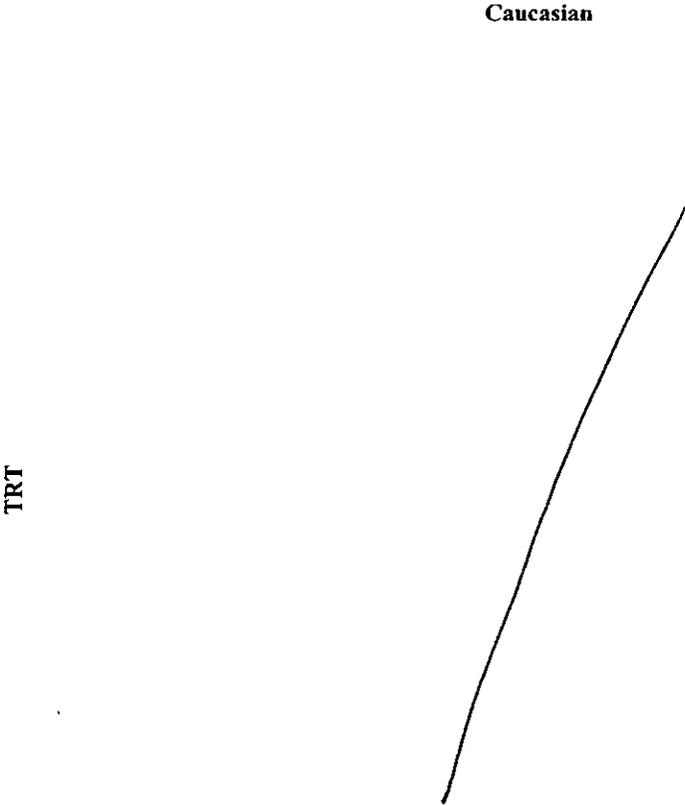
Table 46 HbA_{1c} (%) descriptive statistics by race – Study 1337, type 2

	Detemir				NPH				Difference
	n	baseline	week 24	change	n	baseline	week 24	change	
Caucasian	181	9.3	8.4	-0.9	89	9.4	7.8	-1.6	0.7
Hispanic	70	9.8	8.6	-1.2	40	9.5	8.1	-1.3	0.1
Black	17	9.8	8.3	-1.4	8	9.5	8.2	-1.4	0.0
Other	6	9.2	8.1	-1.1	3	8.6	7.7	-0.9	-0.2
Asia	6	9.0	8.8	-0.2	2	9.1	8.9	-0.3	0.1

Table 47 Descriptive statistics by race for daily basal insulin dose

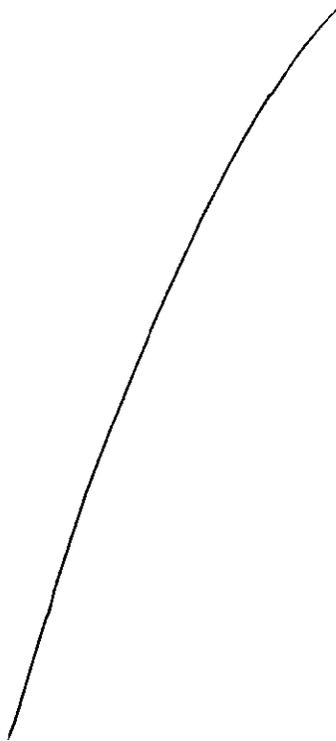
	Detemir		NPH		Difference
	n	U	n	U	
Caucasian	181	61	89	49	12
Hispanic	70	37	40	31	6
Black	17	45	8	38	7
Other	6	64	3	45	19
Asia	6	51	2	23	28

Figure 26 HbA_{1c} from baseline to endpoint in Caucasian patients
with insulin dose ≤ 50 U or > 50 U



*Figure 27 HbA_{1c} from baseline to endpoint in Hispanic patients
with insulin dose ≤ 28 U or > 28 U*

Hispanic



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Gender

Table 48 displays descriptive statistics on HbA_{1c} and daily insulin by gender. HbA_{1c} change from baseline was similar in both male patients and female patients. The daily insulin dose was also similar with respect to genders for both insulin detemir and NPH insulin.

Table 48 Mean (SD) of HbA_{1c} (%) and Daily Insulin by Gender and Treatment Group – Type 2, Study 1337

	Female		Male	
	Insulin detemir n=151	NPH insulin n=64	Insulin detemir n=155	NPH insulin n=91
Baseline HbA _{1c}	9.60 (1.23)	9.35 (1.09)	9.38 (1.16)	9.51 (1.23)
Endpoint HbA _{1c}	8.67 (1.36)	8.03 (1.13)	8.53 (1.29)	8.18 (1.43)
HbA _{1c} Change	-0.93 (1.27)	-1.32 (1.30)	-0.84 (1.20)	-1.34 (1.36)
Daily insulin (U or IU)	50 (35.8)	43 (31.8)	54 (42.4)	42 (28.3)

Age

Table 49 displays descriptive statistics in HbA_{1c} and daily insulin dose for the 2 age groups.

Table 49 Mean (SD) of HbA_{1c} (%) and Daily Insulin by Age and Treatment Group – Type 2, Study 1337

	≥65 years		<65 years	
	Insulin detemir n=53	NPH insulin n=24	Insulin detemir n=227	NPH insulin n=118
Baseline HbA _{1c}	9.31 (1.20)	8.95 (0.90)	9.48 (1.20)	9.47 (1.14)
Endpoint HbA _{1c}	8.41 (1.16)	7.87 (0.86)	8.49 (1.31)	7.95 (1.23)
HbA _{1c} Change	-0.90 (1.27)	-1.08 (0.86)	-0.99 (1.26)	-1.53 (1.39)
Daily basal insulin (U or IU)	32 (22.6)	37 (21.2)	59 (39.1)	44 (28.8)

Conclusion – Type 2 Study 1337

Insulin detemir in combination with metformin was not as efficacious in HbA_{1c} reduction as NPH insulin in combination with metformin. The treatment-by-race interaction was significant; however, the interaction was quantitative with all subgroups having a mean reduction of HbA_{1c} from baseline.

2.3 STATISTICAL AND TECHNICAL ISSUES

Basal Insulin Dose

The noninferiority trial requires a more rigorous design than a superiority trial because there is no direct evidence of assay sensitivity without a placebo group. Although 3 of the noninferiority trials in type 1 diabetes achieved the noninferiority criteria, 2 might not have assay sensitivity because of an insufficient basal insulin dose (1200 nmol/ml). The 3 noninferiority trials in type 1 diabetic patients started patients in the insulin detemir group on a 2 times molar dose of NPH insulin and the 2 superiority trials started with a 4 times ratio.

The titrated dose of the only study with a once daily basal insulin regimen (#1335) was the least among the 3 trials (500nmol/150nmole) and HbA_{1c} was unchanged from baseline for both treatment groups. In Study 1181, HbA_{1c} was unchanged from baseline for the insulin detemir group and the change was -0.17% for NPH insulin group with a molar ratio of 3 (525nmol/170nmol). The insufficient dosing might have compromised assay sensitivity in both trials. In contrast, Study 1205 with a greater molar dose (714nmol/189nmol) and a greater molar ratio (3.8) had a mean change in HbA_{1c} from baseline of -0.5%.

The molar ratio of the 2 superiority trials in type 1 diabetes was changed from 2 times to 4 times higher for insulin detemir than NPH insulin. The final titrated dose ratio for both studies was greater than 4. Study 1448 with the greatest molar dose for both treatment groups in the type 1 studies (>870/210) also had the greatest change in HbA_{1c} from baseline (-0.8%, insulin detemir, and -0.6%, NPH insulin). Both studies did not demonstrate superiority; however, the upper limit of the confidence interval for the difference between treatment groups was within the noninferiority margin of 0.4%.

Study in Type 2 Diabetes

All 3 trials in type 2 diabetes were noninferiority trials. Two of the trials had a >9% baseline HbA_{1c} and failed the criteria for noninferiority. The low baseline HbA_{1c} (<8%) of the third trial (#1336) might have compromised assay sensitivity. The upper limit of the confidence interval for the treatment difference in HbA_{1c} was within the 0.4% noninferiority margin; however, the lower limit was greater than 0 which means NPH insulin was statistically better than insulin detemir. The molar ratio of 4 for insulin detemir to NPH insulin was not sufficient for type 2 diabetic patients. Study 1166 with a twice basal insulin dose regimen started with a 2 times molar ratio and ended with a 4.16 times titrated molar ratio which was not sufficient (1548nmol/366nmol) for HbA_{1c} reduction. Mean HbA_{1c} increased 0.4% from baseline in insulin detemir treated patients and decreased 0.17% in NPH treated patients. The molar ratio of 5 times (1286nmol/255nmol) in the US study of insulin detemir added to a maximum tolerated dose of metformin was not high enough for insulin detemir to demonstrate noninferiority to NPH insulin. The mean HbA_{1c} change was -1% for the insulin detemir group but was inferior to the -1.5% mean change for the NPH insulin group.

Open Label Study

The open label design with no blinding of the treatment with titration for both basal and bolus insulin might potentially bias the result toward no difference in HbA_{1c} outcome. The basal insulin and the bolus insulin were consistently higher in the insulin detemir group.

2.4 CONCLUSIONS AND RECOMMENDATIONS

Insulin detemir in type 2 diabetic patients was inferior to NPH insulin in HbA_{1c} reduction using a 4 times molar ratio of insulin detemir to NPH insulin. Two studies in type 1 diabetic patients with a 4-time higher insulin detemir than NPH insulin in molar dose demonstrated noninferiority of the insulin detemir to NPH insulin with a greater use of bolus insulin. One

superiority trial with the greatest dosage of basal insulin failed superiority but demonstrated noninferiority with an equal amount of bolus insulin use.

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