CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-536

MEDICAL REVIEW(S)

MEDICAL OFFICER REVIEW

Division of Metabolic and Endocrine Drug Products (HFD-510)

APPLICATION #:	**NDA 21536**	**APPLICATION TYPE:**	**New NDA.....**
SPONSOR:	**Novo Nordisk**	**PROPRIETARY NAME:**	**LEVEMIR.....**
CATEGORY OF DRUG:	**Antidiabetic**	**USAN / Established Name:**	**Insulin Detemir.....**
MEDICAL REVIEWER:	**Robert I Misbin..**	**REVIEW DATE:**	**May 13, 2005, revised.. ...June 9, 2005..**

SUBMISSIONS REVIEWED IN THIS DOCUMENT

Document Date:	CDER Stamp Date:	Submission Type:	Comments:
Dec 5, 2002	Dec 9, 2002	Original NDA	
Dec 20, 2004		Response to AE letter	
January 5, 2005		Safety update	
May 11, 2005		Response to questions	

The efficacy and safety of Insulin Detemir has been established for patients with type 1 and type 2 diabetes. Pending changes in the label, Insulin Detemir can be approved

Insulin Detemir binds to plasma albumin and is cleared more slowly than regular insulin. Detemir is less potent than human insulin and has been formulated to have a four fold the molar concentration of other insulin products. At least for patients with type 2 diabetes, there appears to be less hypoglycemia with Detemir than with NPH insulin at the same level of HbA1c. An additional advantage of Detemir is that it causes less weight gain than NPH insulin.

Executive Summary:

1. Recommendations:

Insulin Detemir is an analog of human insulin in which a c14 fatty acid (myristic acid) is covalently bound to B29 Lys and position B30 is omitted. The fatty acid associates with albumin in plasma and tissues. Approximately 98-99% of Insulin Detemir is bound to albumin and its protracted course of action is due to slow release from the albumin molecule. The advantage of Detemir over NPH is that the action of Detemir probably has less intra-patient variability. At least for patients with type 2 diabetes, there appears to be less hypoglycemia with Detemir than with NPH insulin at the same level of HbA1c. An additional advantage of Detemir is that it causes less weight than NPH.

The efficacy and safety of Insulin Detemir has been established for patients with type 1 and type 2 diabetes. Pending changes to the label, Insulin Detemir can be approved.

2. Summary of Clinical Findings

Novo Nordisk first submitted this NDA in December 2002. In my review of Sept 5, 2003, I noted that the safety and efficacy of Detemir had been established for type 1 diabetes but not for type 2 diabetes. I also noted an ethnicity-based difference in responsiveness to Detemir in one study, and recommended that approval be delayed until additional studies had been performed. The resubmission contains results of studies that address these issues adequately. This review deals with the full application (original submission and resubmission)

The full application contains data from twelve phase 3 controlled clinical trials. There were seven trials in patients with type 1 diabetes and five trials in patients with type 2 diabetes.

The studies were mostly randomized open-label comparisons of Insulin Detemir to NPH insulin. Patients with type 1 diabetes received Detemir or NPH as basal insulin in addition to boluses of rapid acting insulin (regular human insulin or insulin aspart) before meals. Similar basal/bolus regimens were used in two of the trials of patients with type 2 diabetes. The other trials in type 2 diabetes were comparison of Detemir to NPH without bolus insulin.

The demonstration of efficacy was based on a non-inferiority comparison to NPH insulin with respect to HbA1c. But the concomitant use of bolus insulin complicated interpretation of the efficacy results in many of the studies. Although not so designated by the Sponsor, I consider trial 1448 (type 1 diabetes) and trial 1530 (type 2 diabetes) to be pivotal in establishing the efficacy of Detemir.

Type 1 Diabetes:

Of the phase 3 studies that directly compared Detemir to NPH, only trial 1448 is clearly positive. I consider this to be the pivotal trial and describe it in detail below. Being only supportive, the other trials are summarized here only briefly.

Trials 1181 and 1243 were done with a formulation of Detemir that has half the concentration as the to-be-marketed formulation. Trial 1181 was a six month randomized comparison of Detemir and NPH. Trial 1243 was a 24-week extension of trial 1181 Although the non-inferiority test was nominally met, additional regular insulin was used in the Detemir group. Therefore this should not be used as a pivotal study to establish that Detemir is non-inferior to NPH for treatment of type 1 diabetes. The claim of durability appears to be valid.

Trial 1205 was a 24-week randomized comparison of Detemir and NPH. Trial 1316 was a 24-week extension of trial 1205. Trials 1205 and 1316 were done with a formulation of Detemir that has half the concentration of the to-be-marketed formulation. Although the non-inferiority test was nominally met, additional bolus insulin (insulin aspart) was used in the Detemir group. Therefore this should not be used as a pivotal study to establish to that Detemir is non-inferior to NPH for type 1 diabetes. However, the efficacy of Detemir does appear to last 12 months. An additional finding is that Detemir appeared more effective than NPH with respect to lowering FPG. This is consistent with the longer duration of action of Detemir, brought out in this study because the bolus insulin was the rapid acting insulin aspart (as opposed to trials 1181/1243 in which regular insulin was used)

Trial 1447 was a 16 week randomized comparison of Detemir with NPH. Patients used insulin aspart as bolus insulin before meals. Although insulin Detemir nominally met the test of non-inferiority to NPH insulin, patients on Detemir received somewhat more insulin than patients on NPH. Trial 1447 did not clearly establish the non-inferiority of Detemir relative to NPH.

Trial 1335 was a six month comparison of Detemir 2400 nmol/mL and NPH each given once daily at bedtime in patients with Type 1 diabetes who use boluses of regular insulin before meals. Detemir given once a day was approximately as effective as NPH once a day, but neither was effective in achieving good control. The glycemic goals were not met. The decrease in the dose of basal insulin given as Detemir was compensated for by an increase in the dose of regular. Therefore, the non-inferiority of Detemir relative to NPH was not clearly established. The results indicate that both Detemir and NPH need to be given more than once daily in order to achieve good glycemic control.

Trial 1448

This was a 16 week trial comparing NPH insulin to two regimens of insulin Detemir (2400 nmol/mL), and NPH insulin (600 nmol/mL). The NPH was given in the morning and at bedtime. In one arm, Detemir was given in the morning and at bedtime. In a second arm, Detemir was given every 12 hours. For the sake of simplicity, these arms are referred to as NPH am/hs, Detemir am/hs and Detemir q 12hr. All patients received boluses of insulin aspart before meals. This was designed to be a superiority trial. The primary measure of efficacy was HbA1c at 16 weeks using the ITT population. The trial was conducted at 40 Centers in Europe, Australia, and New Zealand.

The trial population consisted of patients with type 1 diabetes, BMI < 35, HBA1c< 12%, basal insulin dose at least 30% of total insulin dose and total basal insulin requirement of 100 units or less.

Patients who were previously receiving once daily basal insulin were transferred to twice daily regimen with 25-30% in the morning and 70-75% pre-dinner/bedtime. The starting dose of Detemir (on a molar basis) was recommended to be 2.8 times the previous dose of basal insulin. The starting dose of NPH was recommended to be 70% the previous dose of basal insulin. There was an expectation that the doses of both basal insulins would be increased during the titration period and that the final dose of Detemir (on a molar basis) would be increased to approximately 4x the dose of NPH. This means that the expected final volume of NPH and Detemir would be approximately the same.

The insulin dose was titrated with the goal of premeal and night time (2:00-4:00 am) to be 72-126 mg/dl and 90 min post-prandial glucose to be < 180 mg/dl. During the first 4 weeks, it was recommended that the dose of basal insulin be adjusted while the dose of bolus insulin remained constant. The weeks following initial titration were used to finely adjust the doses of both bolus and basal insulin.

The ITT population was 53% male, 99% white (one black patient on Detemir and one on NPH), mean age about 40 years with 16 years of diabetes, mean BMI 25. At baseline mean HbA1c was about 8.6% and mean FPG was about 11.7 mM. The mean dose of basal insulin was bout 0.37 U/kg and the mean dose of bolus insulin was about 0.40 U/kg. 3/137 patients withdrew from the Detemir q 12 hour arm because of 'ineffective therapy", 1/133 from the NPH am/hs arm and zero from the Detemir am/hs arm.

HbA1c for ITT (from table 4.4)

HbA1c	Detemir q12	NPH am/hs	Detemir am/hs
<-3 weeks	8.56 (n=133)	8.51 (n=125)	8.71 (n=134)
16 weeks	7.76	7.91	7.87

Accounting for the slight differences in baseline, the change in HbA1c was -0.8 for Detemir 12 hr, -0.6 for NPH am/hs and -0.84 for Detemir am/hs. Nonoe of these were statistically different from each other.

Pre-study Dose of insulin for ITT

	Detemir q 12hr	NPH am/hs	Detemir am/hs
Basal U or IU	26.4	29.5	28.1
Bolus	30.9	30.5	29.4

Dose of insulin at end of 16 weeks: ITT

	Detemir q 12hr	NPH am/hs	Detemir am/hs
Basal U or IU	36.7	34.8	36.3
Bolus	27.9	29.4	29.4

Comparisons of Daily Dose of Insulin at 16 weeks

	Detemir q 12hr	NPH am/hs	Detemir am/hs
Basal U or IU	36.7	34.8	36.3
Ratio (Detmr/NPH)	1.06	1.00	1.04
	Detemir q 12hr	NPH am/hs	Detemir am/hs
Bolus U or IU	27.9	29.4	29.4
Ratio (Detmr/NPH)	0.95	1.00	1.00

Insulin Detemir U = 24 nmol
NPH insulin IU= 6 nmol
Insulin aspart IU = 6 nmol

Summary: In trial 1448, Insulin Detemir met the test of non-inferiority to NPH insulin without additional amounts of bolus insulin. This is the pivotal study to support approval for type 1 diabetes. As is noted in other studies, Detemir is more effective than NPH at lowering FPG. This finding is consistent with Detemir's longer duration of action.

Trial 1374 was an 18 week comparison of two basal/bolus regimens. The two regimens were Detemir (as basal insulin) plus mealtime boluses of insulin aspart vs NPH (as basal insulin) plus mealtime boluses of human soluble insulin. The Detemir/Aspart regimen was better than NPH/HSI with respect to the primary endpoint which was HbA1c. On average patients on Detemir/aspart lost weight or gained less weight than patients on NPH /HSI.

Trial 1372 was a 26 week comparison of Detemir to Insulin Glargine. Detemir was given twice daily and Glargine was given once daily. Insulin aspart was used as the bolus insulin in both arms. HbA1c at endpoint was the same in both groups.

Type 2 diabetes:

Of the three phase 3 studies in the original NDA, none clearly establish the efficacy of Insulin Detemir. However, the resubmission contains Trial 1530. This trial was a head to head comparison of Detemir to NPH in insulin naïve patients. Good glycemic control was achieved with both drugs. I consider this to be the pivotal trial in for type 2 diabetes and describe it below in detail. Trial 1337 is the only trial done in the United States and is summarized here in detail also. The two earlier trials are summarized only briefly.

Trial 1166 was a six-month comparison of Detemir and NPH as the only form of therapy in patients with type 2 diabetes. Detemir was found to be inferior to NPH insulin. But Detemir was administered at 1200 nmole/ml, one half the concentration of the to-be-marketed formulation. The Sponsor has argued that patients were reluctant to administer the large volumes of Detemir that would have been needed to demonstrate non-inferiority to NPH.

Trial 1336 was a six-month comparison of Detemir to NPH in patients with type 2 diabetes who had previously been on an insulin regimen. Insulin aspart was given before meals. Although Insulin Detemir nominally met the test of non-inferiority, patients on Detemir received additional amounts of bolus insulin (insulin aspart). Therefore, this should not be considered a pivotal trial to establish efficacy.

Trial 1337 was a randomized six month comparison of Detemir (2400 nM) vs NPH) in combination with metformin. The trial was performed at 72 sites in the USA and Puerto Rico.

The trial population was patients with type 2 diabetes who had been on metformin, either alone or in combination with other oral antidiabetic agents. There was a two-week washout of other oral agents during which time the dose of metformin was "optimized" to 2000-2550 mg/d or maximum tolerated dose. Patients who failed to reach FPG of 7 mM (126 mg/dl) were randomized to Detemir or NPH as a single evening dose. This regimen of metformin plus Detemir/NPH was maintained for six months.

The trial was designed to test non-inferiority of Detemir vs NPH. HbA1c at six months in the ITT population was the primary endpoint with a margin of 0.4% units.

467 patients were randomized (309 to Detemir and 158 to NPH), and 405 (266 and 139) completed the study. There were 12% withdrawals of Detemir and 11% on NPH. This difference in withdrawals was accounted for by "ineffective therapy" in 2.6% of patients on Detemir and none on NPH.

Insulin Detemir (1U=24 nmol) or NPH (U=6 nmol) were initiated at 0.1U/kg for FBG<180 mg/dl or 0.2 U/kg for FBG>180mg/dl. The dose was then increased every three days to achieve a goal of FBG of 7 mmol/L. The mean initial dose of insulin was 0.17 U/kg for Detemir and 0.16 U/kg for NPH, about 15 units in both groups. At endpoint the mean dose of Detemir was 0.57 U/kg (about 51 units), compared to 0.45 U/kg (about

41 units) for NPH. The molar ratio Detemir/NPH was 4.19 at baseline, 4.8 at 2 months, and 4.98 at endpoint.

As shown in the table below, HbA1c values fell significantly in both arms. But the HbA1c value at EOS was lower in the NPH group than in the Detemir group. Because the upper limit of the 95% CI is 0.78 (>0. 4% units), the predefined criterion for non-inferiority was not fulfilled.

HbA1c values in Modified ITT population

	Detemir	NPH	Diff (95% CI)
Baseline	9.5	9.4	0.01
EOS	8.5	8.0	0.56 (0.33- 0.78)
Change from baseline	-0.9	-1.5	
P value	<0.0001	<0.0001	

Trial 1530

The trial was conducted at 58 centers throughout Europe.

This was a 24 week randomized open label trial comparing Insulin Detemir to NPH insulin in insulin-naïve patients with type 2 diabetes.. The 24-week comparison was preceded by a two-week run-in in patients with type 2 diabetes who had been inadequately controlled on one or two oral antidiabetic drugs (OAD), excluding thiazolidinediones. The starting dose of both insulin products was 10 units in the morning and 10 units in the evening. The dose was titrated with a goal of plasma glucose concentration <6 mM before breakfast and dinner. The previous OAD regimen was continued.

The primary efficacy variable was HbA1c at end of treatment for ITT population. Data are also presented for the per protocol population. The per protocol population excludes non-completers and patients with protocol violations, primarily change in oral antidiabetic agents during the trial. Other efficacy variables were FPG at endpoint and proportion of patients with HbA1c < 7% without symptomatic hypoglycemia confirmed by glucose< 4 mM and no single glucose < 3.1 mM. Other variables were self-measured glucose, and change in body weight.

475 patients were randomized and received treatment. This constitutes the ITT population. The completion rate was 96 %.for Detemir and 94% for NPH. The patients were 99% white, 53% male, mean age 61 years, mean body weight 84.4 kg, BMI 28.9 and mean duration of diabetes 9.7 years. Combination therapy was used by 65% and metformin monotherapy by 28%. The two treatment arms were well matched. The ITT population was 237 for Detemir and 239 for NPH insulin

The primary variable, HbA1c at EOS for the ITT population showed no difference between the two treatments. This was 6.58 (n=230) for Detemir and 6.46 (n=232 for NPH. The 95% CI for the difference Detemir – NPH was -0.002 to 0.254.

Mean FPG decreased from 11.1 mmol/l to 6.9 with Detemir and from 10.8 to 6.6 mmol/L with NPH. Mean weight gain on Detemir was 1.2 kg compared to 2.8 kg on NPH ($p<0.001$).

The proportion of "responders", reaching HbA1c of 7% without hypoglycemia was 26% for Detemir and 16% for NPH ($p=0.008$)

Integrated Review of Safety (all phase 3 trials):

There was little difference in reporting of hypoglycemic episodes between patients Detemir and patients in patients with type 1 diabetes. For patients with type 2 diabetes, there appears to be less hypoglycemia with Detemir than with NPH at the same level of HbA1c. An additional advantage of Detemir is that it causes less weight than NPH. If sustained over the life of a patient, this weight-sparing effect of Detemir would be a major advantage over NPH.

Findings at the site of injection were more frequently reported with Insulin Detemir than with other basal insulins. Insulin Detemir appears somewhat more antigenic than NPH, but there was little evidence of clinically significant consequences.

Adverse events unrelated to control of diabetes were the same with Detemir as with NPH insulin.

Clinical Review

I Introduction and Background

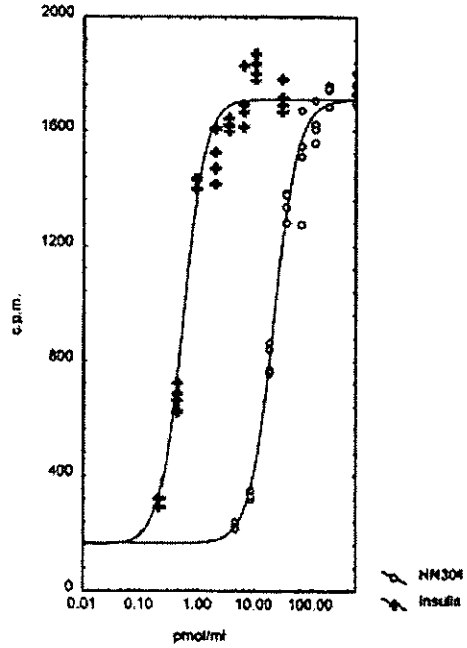
Insulin Detemir is an analog of human insulin in which a c14 fatty acid (myristic acid) is covalently bound to B29 Lys and position B30 is omitted. The fatty acid associates with albumin in plasma and tissues. Approximately 98-99% of Insulin Detemir is bound to albumin and its protracted course of action is due to slow release from the albumin molecule. Delayed absorption from subcutaneous injection and slower clearance may also contribute to its protracted course.

Insulin Detemir is much less potent than regular insulin in standard in vitro bioassays. This point is illustrated by the two figures that appear on the following pages. The first figure shows a comparison of Detemir to insulin on glucose incorporation into lipids in isolated fat cells. The Sponsor estimated that Detemir had about 2.7% the potency of insulin. Correcting for binding of Detemir to albumin, the potency estimate rises to 43%. The second figure shows competition of Detemir and insulin for binding of labeled insulin to immobilized insulin receptors. Even in this albumin-free system, Detemir only has about 20% the potency of insulin. But despite its lower potency, Detemir is a full insulin agonist, ie the **maximal** effect of Detemir is the same as that of insulin. These results would lead to the prediction that Detemir's effect in patients with diabetes would be the same as that of insulin, but the amount of Detemir required to achieve this effect would be very much greater.

Detemir was initially formulated to have twice the molar concentration of other insulin products. This formulation appeared inadequate to demonstrate equivalence between Detemir and NPH insulin. In later studies, a 4:1 ratio was used. The to be marketed formulation of Detemir has four times the molar concentration of NPH insulin.

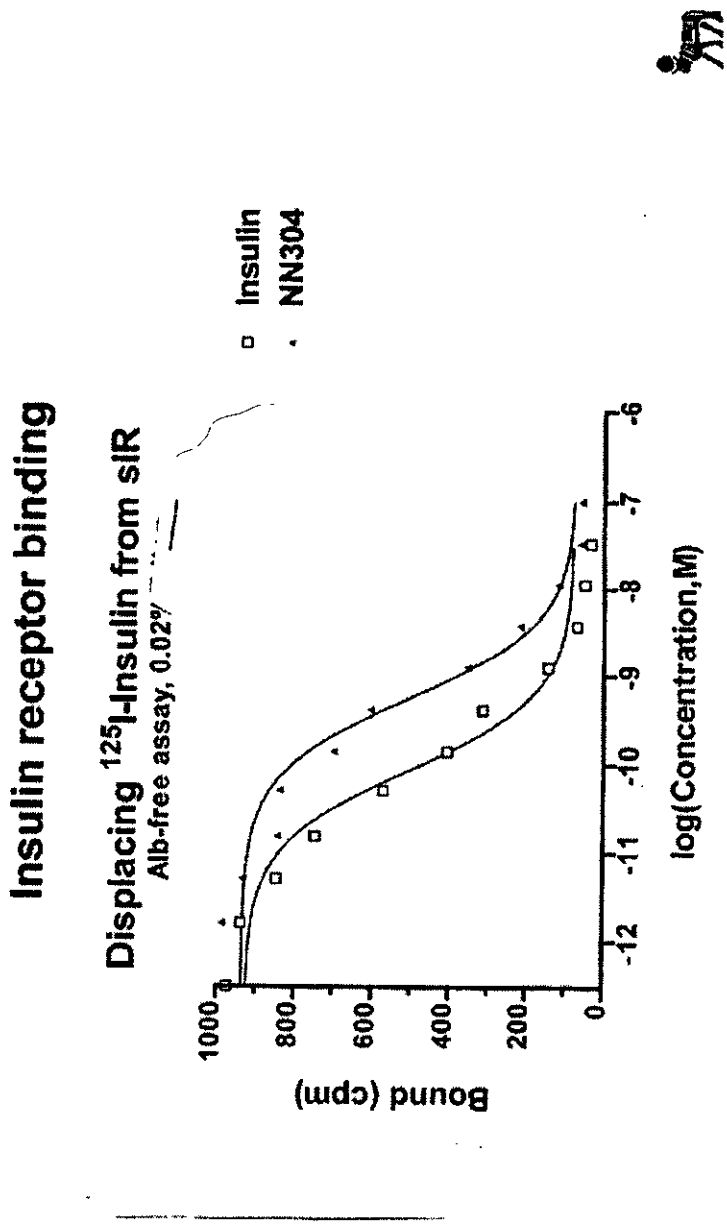
In the original NDA, the Sponsor demonstrated that glycemic control achieved with Detemir in patients with type 1 diabetes was similar to that achieved with NPH insulin provided that four times the molar dose was used. However, in patients with type 2 diabetes, non-inferiority of Detemir to NPH had not been demonstrated. The current resubmission contains a clinical trial in patients with type 2 diabetes (trial 1530) in which the dose of Detemir was increased adequately in order to achieve equivalent results to NPH insulin. The dose of Detemir required to achieve equivalent control was about six fold greater than NPH insulin on a molar basis. The current resubmission also contains a PK/PD trial that shows pharmacodynamic equivalence between Detemir and NPH provided that the molar dose of Detemir was about six fold greater than NPH.

Metabolic potency *in vitro* (free fat cell assay, 1% HSA)



- Measured: 2.7% (95% CI: 2.1 -3.8%)
- Corrected for albumin binding: ca 43 %

This figure shows the dose-response relationships for insulin and Detemir on glucose incorporation into lipid in isolated fat cells.



This figure shows competition curves for insulin and Detemir for binding of 125I insulin to immobilized insulin receptors obtained from hamster kidney. The affinity constant for insulin was approximately 0.10 nM. The affinity constant for Detemir was approximately 0.5nM. In other words, it took five times the molar concentration of Detemir to displace labeled insulin is it took for insulin itself.

Defining a unit of potency for Detemir that will be useful clinically presents a challenge. To dose patients based on nanomoles or milligrams would cause confusion. On the other hand, DMEDP should be reluctant to allow the Sponsor to define a "unit" of insulin that would apply solely to Detemir. In consultation with DMEDP, NovoNordisk attempted to adjust the molar concentration of Detemir so that patients taking NPH insulin could be switched to an equal **volume** of Detemir. Based on preliminary data, the initial concentration of Detemir was 1200 nmol/ml (2x other insulin products). The concentration was later increased to 2400 nmol/ml (4x other insulin products). This is the concentration of the to-be-marketed formulation. The hope was that a patient who ordinarily takes 50 units (300 nmoles) or **0.5 ml** of NPH insulin would get the same result if treated with **0.5 ml** (1200 nmoles) of Detemir. In general, this turned out to be the case for patients with type 1 diabetes but not for patients with type 2 diabetes.

II Chemistry and Pharmacology:

Chemistry – No comments

Pharmacology

Insulin Detemir is an analog of human insulin in which a c14 fatty acid (myristic acid) is covalently bound to B29 Lys and position B30 is omitted. The fatty acid associates with albumin in plasma and tissues. Approximately 98-99% of Insulin Detemir is bound to albumin and its protracted course is due to slow release from the albumin molecule. Delayed absorption from subcutaneous injection and delayed clearance may also contribute to its protracted course. The Detemir-albumin complex does not bind to the insulin receptor. Binding to albumin is not affected by 0.4-mM palmitic acid or myristic acid fatty acids.

FDA expressed the concern that binding of Detemir to albumin (and hence the ability of Detemir to bind with insulin receptors) might be affected by the lipid content of plasma. As stated by the Sponsor, these studies were done to address the possibility that in some patients with hyperlipidemia, there could displacement of insulin Detemir from the albumin binding site, with possible partitioning in the hydrophilic and lipophilic interphase, potential loss of biological activity, or unpredictable release of insulin Detemir.

The Sponsor performed a study of the binding of Detemir to plasma samples obtained from subjects with hyperlipidemia. An additional study was performed on the effect of a high fat meal on the binding of Detemir to plasma. The results of these studies (taken from the 6/4/02 briefing document) are shown below:

Group	Mean Chol, mg/dl	Mean Trigly, mg/dl	% binding, Mean(SD)
Hyperchol n=3	466	359	99.55(0.10)
Hypertrigly n=7	301	2001	99.61(0.10)
Normal n=3	167	77	99.3(0.31)
Normal n=3, after fatty mean	162	129	99.6(0.09)

As shown in the table above, binding was higher in the hyperlipidemic patients than in the normal controls and binding went up 0.3 (SD=0.23) in the normal controls following a fatty meal. This increase in binding in the three normals was associated with a rise in triglycerides. But the hypertriglyceridemia achieved is very much less than the fasting levels in the 7 hypertriglyceridema subjects, even though the % binding was the same. Thus, there was no correlation between binding and triglyceride levels. This latter finding was confirmed in a pooled study of 31 subjects. There was no correlation between fasting

triglycerides and Detemir binding (Spearman Correlation Coef = 0.16, p=0.38). However, there was a correlation with fasting cholesterol (Spearman =0.38, p=0.08). Two/nine normal subjects had large increases in binding following a fatty meal (99.0 to 99.5).

In considering the possible significance of these results, it must be borne in mind that the **unbound** Detemir is what is physiologically active. A change in binding from 99.0% to 99.5% would seem more important if expressed as a decrease in **unbound** Detemir from 1.0% to 0.5%. I am also concerned about the technological limitations of these experiments (counting radioactive samples to detect small differences, intactness of the ligand , etc).

III Biopharmacy

Defining Potency:

Insulin products are currently formulated as U100 (100 units per ml). Although a unit of insulin was originally derived from animal bioassays, a modern definition applicable to pure insulin is that 1 unit=6nmoles=0.036mg. This relationship holds for the human insulin and synthetic insulin analogs that are currently in use as well as the beef and pork insulins that had been widely used in the past. But these relationship will break down if applied to insulin Detemir. As shown in the table below, there exists a wide range of potencies for Detemir among various mammalian species. Defining a unit of potency that would be useful clinically presented an even greater challenge. To dose patients based on nanomoles or milligrams would cause great confusion. On the other hand, FDA was reluctant to allow the Sponsor to define a "unit" of insulin that would apply solely to Detemir. In consultation with FDA, NovoNordisk attempted to adjust the molar concentration of Detemir so that patients taking NPH insulin could be switched to an equal volume of Detemir. Based on preliminary data, the initial concentration of Detemir was 1200 nmol/ml (x2 other insulin products). The concentration was later increased to 2400 nmol/ml. The hope was that a patient who ordinarily takes 50 units (300 nmoles) or 0.5 cc of NPH insulin would get the same result if treated with 0.5 cc (1200 nmoles) of Detemir.

Overview of Potency of Detemir relative to human insulin in mammals*

Mouse	6%	Detemir compared to soluble human insulin by SC injection
Rabbit	<5%	Detemir compared to NPH insulin by SC injection
Rat	15%	Detemir compared to soluble human insulin by IV injection
Dog	approx 100%	Detemir compared to soluble human insulin by IV injection
Pig	approx 100%	Detemir compared to NPH insulin by SC injection
Human	25%	Detemir compared to NPH insulin by SC injection

*from submission of Feb 13, 2002

Based on early studies, the Sponsor believed that approximately twice the molar dose of Detemir would be required to achieve the same glucodynamic effect as NPH. This higher dose reflects the lower affinity (46%) of Detemir for the human insulin receptor. As noted above, the estimate was later revised to 4:1. The concentration of Detemir used in the phase 3 program was 1200 or 2400 nmole/ml. But the to-be-marketed formulation will be 2400 nmole/ml.

Drug Metabolism:

It is generally recognized that the rate-limiting step in insulin degradation is binding of insulin to its receptor. The bound insulin is metabolized by protease(s) associated with the cell surface and the internalized insulin and insulin fragment(s) are metabolized by lysosomes.

The Sponsor has incubated Detemir and insulin with liver and kidney cytosol. Results were submitted in the original NDA, and led to the conclusion that Detemir and insulin shared the same degradation pathways, and that the first step in degradation was cleavage of the disulfide bonds. Although this conclusion may be correct with respect to degradation in unpurified cellular extracts in vitro, no evidence was provided that these results have anything to do with the physiological relevant pathway(s) of insulin degradation. The concentration at which these experiments were performed was over a thousand-fold higher than one might expect in vivo. No controls were included to see if the reaction was specific for insulin or if any S-S containing peptide would be similarly degraded.

Novo Nordisk has attempted to address these shortcomings in the resubmission. As suggested by FDA, they attempted to study degradation of Detemir and insulin in liver cells. They reported that the extent of degradation in this system was too low to get reliable data. The resubmission does have new data showing that degradation of Detemir and of insulin by Cathepsin D occurs at the same site, specifically a cleavage at the B24-B25 phenylalanine residues. This is a perhaps more likely to be physiologically meaningful because, there is strong evidence that receptor-bound insulin is inactivated by a proteolytic cleavage near the carboxy- terminus of the B chain. There is also evidence that insulin and/insulin fragments are degraded by lysosomal enzymes, of which Cathepsin D is an example.

Study 1221: PK/PD study in patients with Type 1 and Type 2 Diabetes

Information about the relative potency of Detemir comes from a PK/PD study 1221 performed in Austria during 2000 and submitted with the original NDA. This utilized a euglycemic clamp. Regular insulin and two doses of Detemir were infused. The FPG level was brought down from a mean baseline of about 11mM and "clamped" at about 5 mM by infusion of glucose for 600 minutes. In this model, the effectiveness of the insulin preparation can be judged from the amount of glucose necessary to maintain euglycemia. The steady state insulin concentration of about 60 uU/ml is in the range of what is observed in normal subjects after eating. Although not actually measured, this insulin level would be expected to shut off hepatic glucose output, therefore what is being measured is insulin-stimulated glucose uptake by muscle and fat.

The authors had to reject data from a few "outliers" among the patients with type 2 diabetes. The explanation given was interference with endogenous antibodies, although antibodies levels were not actually presented. For this reason I am skeptical about the validity of some of the measurements and the parameters derived from them.* However, comparison of the glucose infusion rates and drug doses still lead to some interesting results. The insulin infusion rate (6 pmol/kg/min, 6 pmol=0.001Unit) appears to have been chosen to give an insulin level that would be sub-maximal with respect to response. The doses of Detemir (18 and 30 pmol/kg/min) appear to have been chosen to bracket the insulin response, assuming that it would take about 4 times as much Detemir (24 pmol/kg/min of Detemir) to give the same response as insulin (6 pmol/kg/min). As shown in the following tables, the effectiveness of Detemir fell short of expectations. Even 30 pmol/kg/min of Detemir did not have the same effect as 6 pmol/kg/min of insulin. The Sponsor estimated that the potency of Detemir to insulin was 1:10 in type 1 diabetes. In type 2 diabetes, they estimated that the potency of Detemir to insulin was 1:12, but commented on the large confidence interval and that this estimate might still be too low.

Glucose infusion rate to maintain FPG=5mM during infusion of Insulin or Detemir

Glucose infusion rate, mg/kg.min	Human insulin, 6 pmol/kg/min	Detemir 18 pmol/kg/min	Detemir 30 pmol/kg/min
Type 1 diabetes	6.36	3.46	4.79
Type 2 diabetes	4.32	2.38	3.12

From PK section of NDA vol 35

It should be noted that the glucodynamic activity of both insulin and Detemir was greater in type 1 diabetes than in type 2 diabetes. This is an expected finding and reflects the insulin resistance that is usually present in type 2 diabetes.

Study 1439: PK/PD study in three ethnic groups

This was a randomized, double-blind, six-period, cross-over trial investigating the dose-response relationship of insulin Detemir and NPH insulin in Blacks, Hispanics, and Whites with type 2 diabetes. The study was done at one cite in Chula Vista, California. The iso-glycemic clamp level was maintained at 7.2 +-1 mmol/L (129.6+-18 mg/dL) using glucose infusion. Each patient received three doses of Insulin Detemir (0.3, 0.6, and 1.2 U/kg) and three doses of NPH insulin (0.3, 0.6, and 1.2 IU/kg). There were 4 to 14 days between each clamp visit. Trial products were administered sc in the thigh. The clamp was stopped after 16 hours, the period from 16 to 24 hours after dosing has been shown to be influenced by endogenous insulin secretion, particularly for the low doses.

Patients had type 2 diabetes and had been on insulin (< 1.2 units/kg) for at least nine weeks at the time of screening. Oral hypoglycemic agents were withdrawn for at least one week before the initial clamp. The insulin regimen was adjusted to achieve fasting blood glucose levels < 10 mM. Patients with a fasting blood glucose > 13 mM or with a hypoglycemic episode within 24 hours were not studied. Between clamps, patients were instructed to return to their usual insulin regimens.

Two hours prior to administration of the test products, the glucose level was "clamped" at about 7.2 mM (130 mg/dl) by infusion of human insulin. The infusion of human insulin at a rate of 0.2 mU/kg/min was established one hour before administration of test drug and was maintained throughout the study. Glucose was infused to maintain the glucose clamp after administration of test drug. The amount of glucose that was infused to maintain the clamp glucose level is the glucodynamic measure.

Fifty patients (17 Blacks, 16 Hispanic, and 17 Whites) were randomized into this trial. The patients comprised 16 women and 34 men. The ratio between men and women was approximately the same for the three ethnic groups. Subjects were between 24 and 73 years and had a BMI between 22.2 and 36.5 kg/m2. Mean age (50 years) and BMI (29.3) did not differ markedly between the three ethnic groups. Duration of diabetes varied from 1 to 30 years and was approximately the same for the three ethnic groups. Individual HbA1c varied between 4.6% and 10.2% with a mean HbA1c of 8.0% (7.5% for Blacks, 8.3% for Hispanic and 8.1% for Whites). Fasting C-peptide was between 0.17 and 2.42 nmole/L. Forty-three patients completed the study, 14 Blacks, 15 Hispanics, and 14 Whites.

The primary endpoint, AUCgir,0-16h, was derived from the individual GIR (glucose infusion rate) curves for each of the three ethnic groups and the six different treatments. Results are summarized in Table (AUCgir,0-16h, descriptive statistics) and the mean GIR curves are presented in Figures 1 (Detemir) and Figure 2 (NPH insulin)

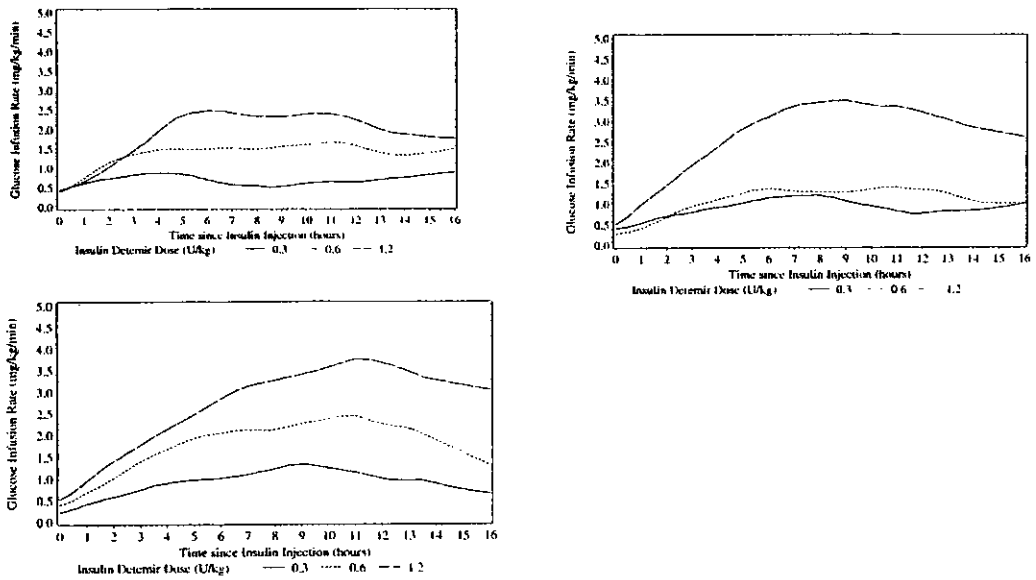


Figure 1. Mean GIR curves for **Insulin Detemir** in Blacks (Upper panel, left), Hispanics (Upper panel, right) and Whites (lower panel).

Appears This Way
On Original

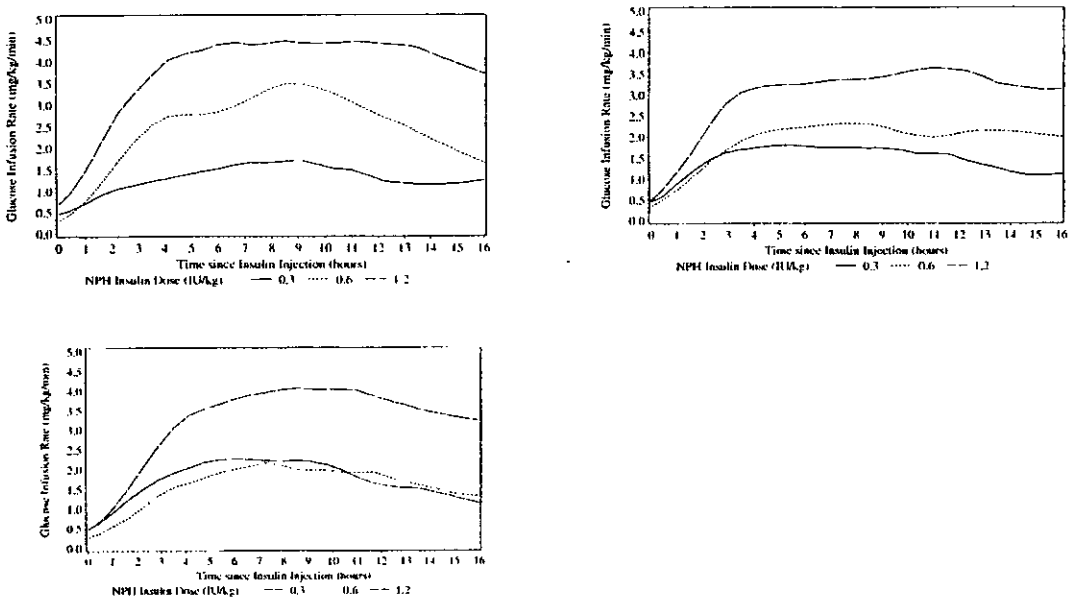


Figure 2. Mean GIR curves for **NPH insulin** in Blacks (Top, left), Hispanics (Top, right), and Whites (Bottom, left)

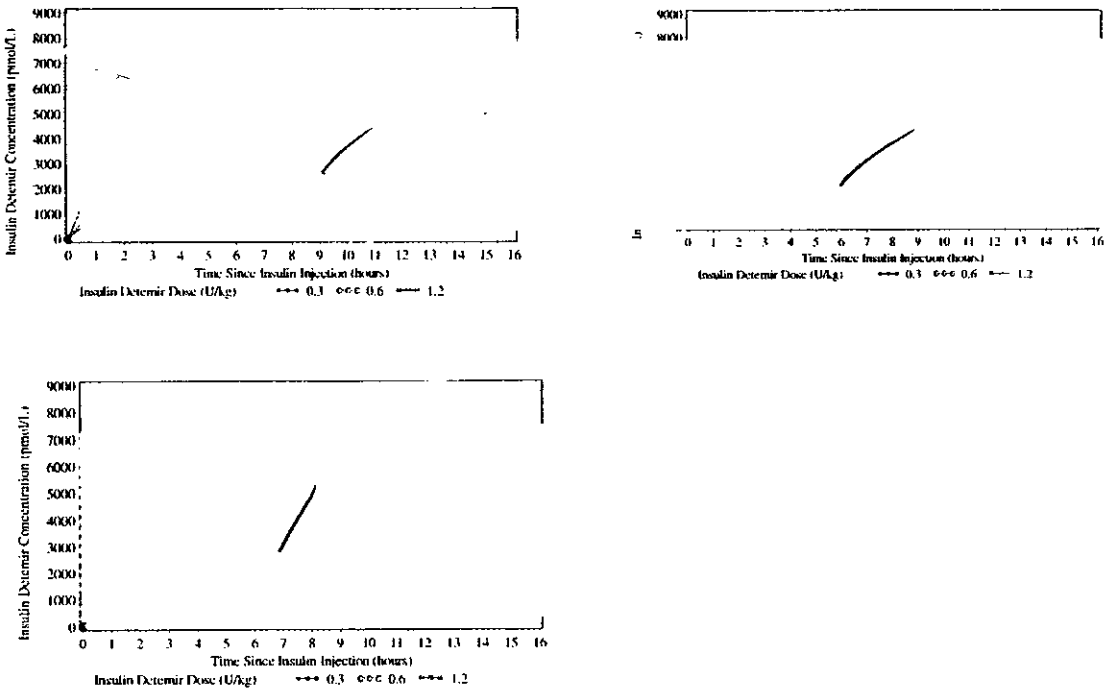
Appears This Way
On Original

Table 1. AUCgir,0-16h - Descriptive Statistics

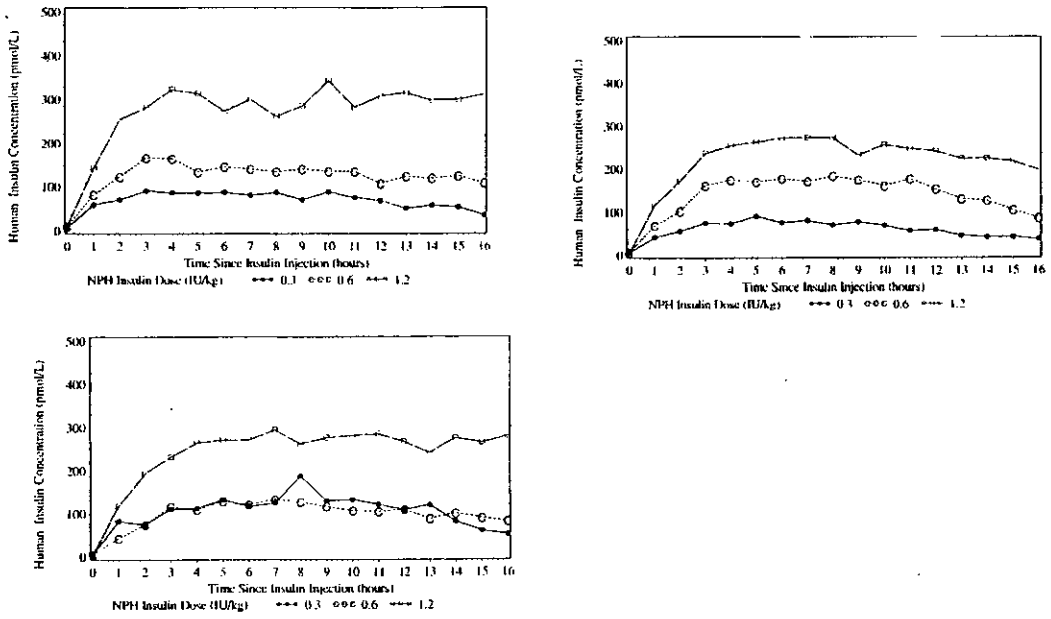
Treatment		AUC(GIR,0-16h) (mg/kg) Black Subjects	Hispanic Subjects	White Subjects
IDet 0.3 U/kg	N	15	14	14
	Mean	645	851	867
	Geometric Mean	207	538	283
	STD	826	649	1008
	Minimum			
	Maximum			
IDet 0.6 U/kg	N	15	15	15
	Mean	1311	1055	1712
	Geometric Mean	1202	824	1126
	STD	778	778	1422
	Minimum			
	Maximum			
IDet 1.2 U/kg	N	15	14	14
	Mean	1832	2574	2628
	Geometric Mean	1497	1987	2254
	STD	1258	1171	1462
	Minimum			
	Maximum			
NPH 0.3 IU/kg	N	14	14	14
	Mean	1408	1238	1653
	Geometric Mean	733	1091	930
	STD	1573	1034	1765
	Minimum			
	Maximum			
NPH 0.6 IU/kg	N	15	14	15
	Mean	1840	2367	1524
	Geometric Mean	1418	1976	1070
	STD	1241	1314	1264
	Minimum			
	Maximum			
NPH 1.2 IU/kg	N	15	14	15
	Mean	2887	3673	3130
	Geometric Mean	2411	3296	2442
	STD	1649	1784	1886
	Minimum			
	Maximum			

The dose-response relationship for the three ethnic groups was same for insulin Detemir and NPH insulin. The Sponsor has estimated that the dose ratio for equal potency of Detemir to NPH insulin is 1.57 U/IU (CI95% [1.12; 2.33]). Since the molar concentration of the insulin Detemir formulation is four times higher than the molar concentration of the NPH insulin formulation (2400 versus 600 nmole/mL), the dose ratio between insulin Detemir and NPH insulin on a molar scale was 6.28 (CI95% [4.48;9.32]).

Concentration-time curves for Detemir and NPH are shown in the figures below:



Mean **insulin Detemir** curves in Blacks (Upper Left), Hispanics (upper right) and Whites (Lower left)



Mean **NPH Insulin** curves in Blacks (upper left), Hispanics (upper right) and Whites (lower left)

Statistical analysis showed no difference among the three ethnic groups for insulin Detemir or NPH insulin with regard to AUC0-16h and Cmax.

It should be noted that the distinction between the two lowest doses (particularly for NPH in white patients) is not clear. This is probably because of endogenous insulin secretion, particularly toward the end of the clamp. Although not shown here, C peptide levels were not completely suppressed. For this reason, I believe the most reliable comparison are among the glucose infusion rates at the highest doses of Detemir and NPH insulin. Looking at these data alone, it is clear that NPH is more potent than Detemir in all three ethnic groups. These data are reproduced below for the sake of illustration.

Glucose infusion, mg/kg

Treatment	Black subject	Hispanic subject	White subjects
Detemir, 1.2 U/kg	1832	2574	2628
NPH insulin 1.2 IU/kg	2887	3673	3130

The difference between Detemir and NPH in white patients, (2628 vs 3130) appears somewhat less than the difference between Detemir and NPH in black patients (1832 vs 2887). This is exactly the opposite of the finding in trial 1337.

Leaving the ethnic issue aside, it is important to note that the peak concentration of Detemir (approximately 7000 pmol/L) is very much higher than the peak concentration of NPH insulin (approx 300 pmol/L). Despite this difference, the pharmacodynamic activity of NPH is greater. Using the Sponsor's estimate that the highest dose of NPH has 57% more PD activity than the highest dose of Detemir, one can estimate that the molar potency of Detemir at the cellular level is approximately 2.5% that of human insulin. (300/7000 x 57%)

IV Description of Clinical data and Sources

The application contains data from twelve phase 3 controlled clinical trials. There were seven trials (plus two extension trials) in patients with type 1 diabetes and five trials in type 2 diabetes.

The studies were mostly randomized comparisons of Insulin Detemir to NPH insulin. Detemir is a clear solution and NPH is a suspension. Because patients taking NPH must be sure that the suspension is homogeneous, blinding of NPH and Detemir was not feasible. For this reason the trials were open label.

Patients with type 1 diabetes received Detemir or NPH as basal insulin in addition to boluses of rapid acting insulin (regular human insulin or insulin aspart) before meals. A trial was also performed that compared Detemir to Glargine in type 1 diabetes. A basal/bolus regimen was used in one of the trials of patients with type 2 diabetes.

The demonstration of efficacy was based on a non-inferiority comparison to NPH insulin with respect to HbA1c. As will be discussed later, the concomitant use of regular insulin complicates interpretation of the efficacy results.

Protocols submitted on January 31, 2005:

Trial 1632: 20 week comparison of Detemir in the evening, Detemir in the morning and NPH insulin in the evening in insulin-naïve patients with type 2 diabetes. A total of 500 patients will be randomized. The trial will be conducted in the United States and Western Europe.

Trial 2175: 26 week comparison of Detemir to insulin Glargine when used in combination with mealtime insulin aspart in patients with type 2 diabetes. The trial is being conducted in the United States and Canada and will consist of 300 patients (200 on Detemir and 100 on Glargine) 'of ethnic groups characteristic of the population of type 2 diabetes in the United States.' To be randomized, patients will be inadequately controlled on oral hypoglycemic agents, or will be receiving insulin therapy but would benefit from intensified insulin treatment.

V Clinical Review Methods:

The review was conducted of the hard copy of the NDA. Routine inspections of sites involved in the pivotal trials were performed, one site from trial 1448 and two sites from trial 1530. In a report by the Division of Scientific Investigations, dated June 6, 2005, the data submitted were found to be acceptable to support the NDA. Although the consent document was not reviewed, the trials appear to have been conducted in accordance with acceptable ethical standards. The financial disclosure documentation appears adequate.

Documents submitted:

NDA 21-536, submitted December 11, 2002

Response to request for information (fax from FDA March 26, 2003) submitted by Sponsor on April 2, 2003

Complete response dated December 20, 2004 to FDA"s "approvable letter".

Regulatory statements regarding submission of documents;

The Sponsor, Novo Nordisk submitted debarment and financial disclosure documents December 5, 2002 and updated the submission in December 2004. I have examined these documents and found them to be acceptable. The debarment statement indicated that Novo Nordisk had not and will not use the services of any person debarred under section 306 of the Federal Food, Drug and Cosmetic Act.

The following financial disclosure information has been submitted:

1 Form OMB No. 0910-0396. The applicant certifies that Novo Nordisk has not entered into any financial arrangement with the clinical investigators named in the lists included in the NDA whereby the value of compensation to the investigator could be affected by the outcome of the study. It was signed 6/12/04.

2 The applicant further certifies that none of the listed clinical investigators disclosed a proprietary interest in the product or an equity interest in Novo Nordisk.

3 The applicant certifies that no listed investigator was the recipient of other payments such as honoraria, consultation fees, research grants, or compensation in the form of equipment from Novo Nordisk .

4 Analyses of efficacy data in this NDA did not reveal any significant effect of center on outcomes. Furthermore, the data on both safety and effectiveness were consistent across the multiple trials submitted to the NDA. Thus a potential conflict of interest from any investigator does not call into question the overall integrity of the data submitted.

V1 – Review of Efficacy

Unlike other insulin products, Insulin Detemir shows a marked variation in potency in different species. FDA has never previously had to face the situation of an insulin product that was substantially less potent that other insulin products. A brief digression seems appropriate at this point in the review to explain our thinking about the development of Detemir and how trials were designed and data evaluated.

Although Detemir is less potent than human insulin on a molar basis, data from studies with isolated cells suggested that the same effect could be achieved with Detemir as with human insulin provided that enough Detemir was given. In the parlance of enzymology, one would say that Detemir had a higher Km (lower affinity) than insulin but that the Vmax of insulin and Detemir were the same. The clinical correlate of this result is that the same degree of glycemic control could be achieved with Detemir as with insulin but that a larger dose of Detemir would be required.

There is no fixed dose for insulin. The correct dose of insulin in any given patient is determined by titration. Given that the dose of insulin in the pivotal trials was titrated to optimize effect on glycemia, it seemed reasonable to set a standard for approval of Detemir based on glycemic control alone without regard for dose.*

Patients with type 1 diabetes (and some with type 2 diabetes) are generally treated with two insulin products. A basal insulin (NPH, Lente or Glargine) is given once or twice a day and boluses of regular insulin or one of the fast acting analogs, Lispro or Aspart, are given before meals.

Phase 3 trials were designed to compare Insulin Detemir to NPH respect with respect to HbA1c. It was recognized that the dose of Detemir (on a molar basis) would be greater than the dose of NPH insulin. Initially, the phase three trials were done with a Detemir preparation that contained 1200 nmoles/ml. The concentration was later increased to 2400 nmoles/ml. Because of this change in concentration, the definition of a "unit" of Detemir also changed. The concentration of other insulin products is 600 nmoles/ml. What remains constant in all insulins used in these trials is the number of units per volume of product. This is true for Detemir, NPH insulin, regular insulin, and insulin aspart. They are all 100 units per ml.

Unlike the situation with previously approved insulin products, the dose of test product required to achieve glycemic control was not considered an important variable in these trials. However the dose of bolus insulin (regular or Aspart) took on special significance. A small amount additional bolus insulin in Detemir-treated patients could potentially give the impression that Detemir was more effective than it really was. **Thus the finding of non-inferiority of Detemir to NPH insulin could not be made if Detemir treated-patients received more bolus insulin than NPH-treated patients.**

*This is not unlike the situation with sulfonylureas. Glyburide, Glipizide, Chlorpropamide and other sulfonylureas have the nearly the same efficacy, but the mg doses required to achieve the same amount of glucose lowering are different. A larger tablet does not of itself constitute a disadvantage.

Type 1 Diabetes:

Trial 1181

Six month trial of Detemir + regular insulin vs NPH + regular insulin in patients with type 1 diabetes This trial was conducted in 55 sites in Australia, New Zealand, Germany, Switzerland and Austria.

The trial population was adults with type 1 diabetes BMI< 35, total insulin requirement no greater than 100 units/d and HbA1c no greater than 12%. Patients had to have been on a regimen of basal insulin (twice daily) plus pre-meal boluses for at least 2 months. This was designed as a non-inferiority trial with a margin of 0.4% units using the ITT population. The dose of insulin Detemir was initiated at twice the patient's previous dose of NPH, so that the volume of basal insulin was the same in both groups at the start of the trial. Basal insulin was administered twice daily in the morning and at bedtime.

The ITT population was defined as all randomized patients who received at least one dose of trial product. The per protocol population was defined as subjects who completed the trial, did not have protocol violations that could potentially affect the efficacy results.

Treatments: Insulin Detemir, 1200 nmol/mL 1 unit=12 nmol
NPH insulin, 600nmol/mL 1 unit= 6 nmol
Human soluble insulin, 600nmol/mL – all given in 3 ml pens
Glycemic goals: FBG 4-7 mM (72-126 mg/dl)
90 min Postprandial blood glucose < 10 mm (180 mg/dl)
BG 2:00-4:00 am 4-7 mM (72-126 mg/dl)

Safety Assessment:

Major hypoglycemia – severe CNS symptoms consistent with hypoglycemia in which patients requires assistance, with BG<2.8 mM (50 mg/dl) or reversal by food or glucagon

Minor hypoglycemia- episode with BG< 2.8 handled by patient or asymptomatic

237 patients were randomized to Detemir and 224 to NPH. The withdrawal rate was 10.5% for Detemir and 6.7% for NPH. Withdrawal due to "ineffective therapy" was 3.4% for Detemir and 4% for NPH. Non-compliance, unwillingness to continue and "other" reasons accounted for 5.1% for Detemir and 1.8% for NPH. The ITT population was 62% male, 99% white, mean age 39 years (15 years of diabetes), BMI 25.3, HbA1c 7.7%, Mean basal insulin dose was 26.5 units for Detemir patients and 26.3 units for NPH patients. Mean bolus insulin dose was 29 units for Detemir patients and 26.4 units for NPH patients. Thus, Detemir patients were using approximately 10% more bolus insulin than NPH patients at baseline.

Efficacy results are shown in the next few tables. With respect to HbA1c, the two groups were well matched at baseline. There was a very small rise in the mean HbA1c in the Detemir group and a very small fall in the NPH group. At 26 weeks, HbA1c were not statistically different either in the ITT or per protocol populations. With respect to plasma glucose, there was a dip in the NPH group at 13 weeks. However, by 26 weeks there was no difference between Detemir and NPH.

HbA1c at Baseline and 26 weeks for ITT population

	Detemir n=210	NPH n=206
<-3 weeks	7.63	7.68
26 weeks	7.66	7.61

HbA1c at Baseline and 26 weeks for per protocol population

	Detemir n=136	NPH n=146
<-3 weeks	7.73	7.63
26 weeks	7.74	7.59

FPG for ITT population

	Detemir n=209	NPH n=204
<-3 weeks	10.7	10.6
13 weeks	10.2	9.81
26 weeks	10.5	10.6

FPG for PP population

	Detemir n=135	NPH n=143
<-3 weeks	11.0	10.5
13 weeks	10.2	9.69
26 weeks	10.5	10.2

Although Detemir and NPH gave similar efficacy results, the patients on Detemir required more insulin. This result is seen in the following tables.

Insulin Dose at 26 weeks

	Detemir	NPH
Basal U or IU	44.1	28.5
Ratio (Detmr/NPH)	1.54	1.00

	Detemir	NPH
Bolus U or IU	33.0	27.9
Ratio (Detmr/NPH)	1.18	1.00

Insulin Detemir U = 12nmol
NPH insulin IU= 6 nmol
Insulin aspart IU = 6 nmol

The volume ratio of Detemir to NPH at EOS was 1.54 while the molar ratio of Detemir to NPH at EOS was 3.09. Detemir patients used 18% more regular insulin than NPH patients. But some of this difference had been present at baseline.

Trial 1243

This was a 6 month extension trial of Detemir vs NPH for patients who completed trial 1181. The purpose of the trial was to examine the 12-month safety of Detemir and to determine if efficacy could be maintained long-term.

HbA1c at 6 and 12 months for ITT population

	Detemir n=139	NPH n=124
6 months	7.63	7.57
12 months	7.73	7.67

HbA1c at 6 and 12 months for per protocol population

	Detemir n=86	NPH n=81
6 months	7.70	7.54
12 months	7.80	7.62

The doses of basal and bolus insulins are given in the following tables:

Basal Insulin, Detemir (U) or NPH (IU), ITT population

	Detemir	NPH
6 months	44.9	29.4
12 months	46.7	29.8

Bolus Regular Insulin (IU)

	Detemir	NPH
6 months	33.1	27.7
12 months	33.4	29.2

Insulin Detemir U = 12nmol
NPH insulin IU= 6 nmol
Regular insulin IU = 6 nmol

Basal Insulin, Detemir (U) or NPH (IU), pp population

	Detemir	NPH
6 months	46.0	29.5
12 months	48.2	30.5

Bolus Regular Insulin (IU)

	Detemir	NPH
6 months	34.0	28.0
12 months	33.8	30.1

Conclusion:

Trials 1181 and 1243 were done with a formulation of Detemir that has half the concentration as the to-be-marketed formulation. Although the non-inferiority test was nominally met, additional regular insulin was used in the Detemir group. Therefore this cannot be used as a pivotal study to establish to that Detemir and NPH are equally effective. However, the glucose–lowering effect of Detemir appears to be last 12 months.

Trial 1205

Six month trial of Detemir + insulin aspart vs NPH+ insulin aspirate in patients with type 1 diabetes. This trial was conducted in 45 sites in France, Belgium, Luxembourg, Netherlands, and Norway

The trial population was adults with type 1 diabetes BMI< 35, total insulin requirement no greater than 100 units/d and HbA1c no greater than 12%. Patients had to have been on a regimen of basal insulin (once or twice daily) plus pre-meal boluses for at least 2 months. This was designed as a non-inferiority trial with a margin of 0.4% units using the ITT population. The dose of insulin Detemir was initiated at twice the patient's previous dose of NPH, so that the volume of basal insulin was the same in both groups at the start of the trial. Basal insulin was administered twice daily in the morning and at bedtime.

The ITT population was defined as all randomized patients who received at least one dose of trial product. The per protocol population was defined as subjects who completed the trial, did not have protocol violations that could potentially affect the efficacy results.

Treatments: Insulin Detemir, 1200 nmol/mL 1 unit=12 nmol
NPH insulin, 600 nmol/mL 1 unit= 6 nmol
Human soluble insulin, 600nmol/mL – all given in 3 ml pens
Glycemic goals: FBG 4-7 mM(72-126 mg/dl)
90 min Postprandial blood glucose < 10 mM(180 mg/dl)
BG 2:00-4:00 am 4-7 mM (72-126 mg/dl)
Safety Assessment:
Major hypoglycemia – severe CNS symptoms consistent with hypoglycemia in which patients requires assistance, with BG<2.8 mM (50 mg/dl) or reversal by food or glucagon

Minor hypoglycemia- episode with BG< 2.8 handled by patient, or asymptomatic

301 patients were randomized to Detemir and 147 to NPH. The withdrawal rate was 5.6% for Detemir and 4.1% for NPH. Withdrawal due to "ineffective therapy" was 1.7% for Detemir and 1.4% for NPH. Non-compliance unwillingness to continue and "other" reasons accounted for 3.4% for Detemir and 2.7% for NPH. The ITT population was 53% male, 99.5% white, mean age 40 years (17 years of diabetes), BMI 24.6, HbA1c 8.27%, Mean basal insulin dose was 27.4 units for Detemir patients and 25.2 units for NPH patients. Mean bolus insulin dose was 30.9 units for Detemir patients and 29.6 units for NPH patients.

Efficacy results are shown in the next few tables. With respect to HbA1c, the two groups were well matched at baseline. There was a fall in the mean HbA1c both groups which probably reflects intensification of the insulin regimen during the trial (twice daily basal with aspart instead of regular insulin). At 26 weeks, there were no statistically significant differences between Detemir and NPH either in the ITT or per protocol populations. With

respect to plasma glucose, there was a trend for lower glucose with Detemir in the ITT population. In the per protocol population, the difference between Detemir and NPH at 26 weeks (-1.82 by ANOVA) was statistically significant (p=0.012)

HbA1c at Baseline and 26 weeks for ITT population

	Detemir n=280	NPH n=139
<-3 weeks	8.18	8.11
26 weeks	7.62	7.61

HbA1c at Baseline and 26 weeks for Per protocol population

	Detemir n=123	NPH n=55
<-3 weeks	8.09	8.31
26 weeks	7.38	7.59

FPG for ITT population

	Detemir n=274	NPH n=138
<-3 weeks	11.7	11.6
13 weeks	10.8	11.0
26 weeks	9.60	10.3

FPG for PP population

	Detemir n=120	NPH n=54
<-3 weeks	11.6	13.3
13 weeks	10.6	10.2
26 weeks	9.33	11.1

Although Detemir and NPH gave similar efficacy results, the patients on Detemir required more bolus insulin. This result is seen in the following tables.

Pre-study Insulin Dose for ITT

	Detemir	NPH
Basal U or IU	27.4	25.2
Bolus	30.9	29.6

Insulin Dose at 26 weeks for ITT

	Detemir	NPH
Basal U or IU	59.2	31.7
Ratio (Detmr/NPH)	3.74	1.00

	Detemir	NPH
Bolus U or IU	30.7	26.0
Ratio (Detmr/NPH)	1.18	1.00

Insulin Detemir U = 12 nmol
NPH insulin IU= 6 nmol
Insulin aspart IU = 6 nmol

The volume ratio of Detemir to NPH at EOS was 1.87 while the molar ratio of Detemir to NPH at EOS was 3.74. Detemir patients used 18% more insulin aspart than NPH patients.

Trial 1316

This was a 6-month extension trial of Detemir vs NPH for patients who completed trial 1205. The purpose of the trial was to examine the 12-month safety of Detemir and to determine if efficacy could be maintained long-term. Patients continued to be treated with twice daily basal insulin and insulin aspart before meals. As shown below, there was little of no change in HbA1c or insulin dose between 6 and 12 months.

HbA1c at 6 and 12 months for ITT population

	Detemir n=210	NPH n=96
6 months	7.50	7.46
12 months	7.51	7.47

HbA1c at 6 and 12 months for per protocol population

	Detemir n=87	NPH n=33
6 months	7.27	7.41
12 months	7.30	7.52

Basal Insulin, Detemir (U) or NPH (IU), ITT population

	Detemir	NPH
6 months	58.3	32.6
12 months	60.8	33.6

Bolus Regular Insulin (IU)

	Detemir	NPH
6 months	30.2	27.1
12 months	31.7	27.3

Insulin Detemir U = 12 nmol
NPH insulin IU= 6 nmol
Regular insulin IU = 6 nmol

Conclusion:

Trials 1205 and 1316 were done with a formulation of Detemir that has half the concentration as the to-be-marketed formulation. Although the non-inferiority test was nominally met, additional bolus insulin (insulin aspart) was used in the Detemir group. Therefore this cannot be used as a pivotal study to establish to that Detemir and NPH are equally effective. The claim of durability is supported by the data. An additional finding is that Detemir appeared more effective than NPH with respect to lowering FPG. This is consistent with the slower action of Detemir, brought out in this study because the bolus insulin was the rapid acting insulin aspart (as opposed to trials 1181/1243 in which regular insulin was used)

Trial 1335

Six month comparison of Detemir 2400 nmol/mL and NPH each given once daily at bedtime in patients with Type 1 diabetes who use boluses of regular insulin before meals The trial was conducted in Europe and Australia

The trial population was adults with type 1 diabetes, for at least 1 year, with HbA1c of no more than 12% taking no more than 100 units of basal insulin once daily in the evening.

Patients randomized to NPH were started on their previous dose of NPH, but patients on Detemir started at ½ the previous dose of NPH. The dose of NPH or Detemir was then increased as needed to achieve the glucose targets described for previous studies. The bolus insulin dose was kept constant for the first two weeks to allow the basal insulin to be titrated.

The trial was designed to test non-inferiority in the ITT population using HbA1c at endpoint with a non-inferiority margin or 0.4%.

Withdrawals were 5.5% in the Detemir arm and 8.6% in the NPH arm. 3/492 patients on Detemir withdrew for "lack of efficacy" and none on NPH. "Other" reasons for withdrawal constituted 3.5% for Detemir and 5.8% for NPH.

Of the ITT population about 63% were male, all but six patients were white. The mean age was 40 years, 17 years of diabetes, mean BMI about 25.2.

HbA1c at baseline and 26 weeks are shown in the tables below for the ITT and per protocol populations. There was little change in HbA1c over the course of the study and no statistically significant differences between Detemir and NPH.

HbA1c at Baseline and 26 weeks for ITT population

	Detemir n=464	NPH n=236
<-3 weeks	8.35	8.35
26 weeks	8.30	8.41

HbA1c at Baseline and 26 weeks for Per protocol population

	Detemir n=447	NPH n=227
<-3 weeks	8.34	8.34
26 weeks	8.29	8.40

With respect to FPG, there was a dip in the Detemir group at 13 weeks, which was partially maintained at 26 weeks. The difference in FPG (Detemir-NPH) of –1.16 mM was significant (p=0.001). But both groups fell far short of the glycemic goal which was FBG 4-7 mM.

FPG for ITT population

	Detemir n=453	NPH n=230
<-3 weeks	11.9	11.6
13 weeks	9.8	11.3
26 weeks	10.3	11.4

As shown in the table below, both groups were well matched with respect to insulin dose before initiation of treatment.

Insulin Dose at <-3 weeks

	Detemir n=478	NPH n=250
Basal	23.5	24.1
Bolus	33.7	33.7

Insulin Dose at 26 weeks

	Detemir	NPH
Basal	20.9	25.6
Ratio Detemir/NPH	0.82	1.00
Bolus	35.6	33.5
Ratio Detemir/NPH	1.06	1.00

Insulin Detemir U = 24 nmol
NPH insulin IU= 6 nmol
Regular insulin IU=6 nmol

According to the protocol, patients on NPH started on their previous dose of NPH, but patients on Detemir started at ½ the previous dose of NPH. The dose of NPH or Detemir was then increased as needed. By endpoint, there was a small net rise in the NPH dose (24.1 to 25.6); however, the Detemir patients never caught up, so their mean dose of Detemir at 26 weeks (20.9) was still less than their pre-study dose of NPH (23.5). At EOS, the ratio of basal insulins by volume, Detemir/NPH, was 0.82 and the molar ratio was 3.27. The dose of regular insulin changed little in the NPH group, but the dose of regular insulin in the Detemir group rose from 33.7 to 35.6. Thus, the relative decrease in dose of basal insulin in the Detemir group was compensated for by a small increase in the dose of regular.

Conclusion: Detemir given **once a day** was approximately as effective as NPH once a day, **but neither was effective in achieving good control**. The glycemic goals were not met. The decrease in the dose of basal insulin given as Detemir was compensated for by an increase in the dose of regular. Therefore, the non-inferiority of Detemir relative to NPH was not clearly established

Trial 1447

This was a 16 week trial comparing NPH insulin (600 nmol/mL) to two regimens of insulin Detemir (2400 nmol/mL). NPH was given in the morning and at bedtime. Detemir was given in the morning with a second injection either at bedtime or before dinner. For the sake of simplicity, these arms are referred to as NPH bedtime, Detemir bedtime and Detemir dinner. All patients received boluses of insulin aspart before meals. This was designed to be a superiority trial. The primary measure of efficacy was HbA1c at 16 weeks using the ITT population. The trial was conducted at 52 Centers in Europe.

The trial population consisted of patients with type 1 diabetes, BMI < 35, HBA1c< 12%, basal insulin dose at least 30% of total insulin dose and total basal insulin requirement of 100 units or less. Patients with known hypoglycemia unawareness were excluded, as were patients with creatinine over 1.7 mg/dl, ALT greater than 2x ULN or NYHA class 111 or 1V heart failure. Use of corticosteroids or beta blockers were also prohibited.

Patients who were previously receiving once daily basal insulin were transferred to twice daily regimen with 25-30% in the morning and 70-75% pre-dinner/bedtime. The starting dose of Detemir (on a molar basis) was recommended to be 2.8 times the previous dose of basal insulin. The starting dose of NPH was recommended to be 70% the previous dose of basal insulin. There was an expectation that the doses of both basal insulins would be increased during the titration period and that the final dose of Detemir (on a molar basis) would be increased to approximately 4x the dose of NPH. This means that the expected final volume of NPH and Detemir would be approximately the same.

The insulin dose was titrated with the goal of premeal and night time(2:00-4:00 am) to be 72-126 mg/dl and 90 min post-prandial glucose to be < 180 mg/dl. During the first 4 weeks, it was recommended that the dose of basal insulin be adjusted while the dose of bolus insulin remained constant. The weeks following initial titration were used to finely adjust the doses of both bolus and basal insulin. The injection site area was to remain constant but the exact site within the area was rotated to prevent lipohypertrophy. All insulin injections were given with 3 ml Penfill.

The ITT population was about 60% male, 100% white, mean age 40 years (15 years of diabetes), BMI 25.2, HbA1c 8.07, FPG 10.4 mM. 62% had been taking 2 or more injections of basal insulin per day. The mean pre-study daily doses of insulin were and bolus insulin was 0.34 U/kg and 0.39 U/kg respectively.

Results:

As shown in the table below, the primary measure of efficacy, HbA1c at endpoint for the ITT population, was not statistically different among the three groups

HbA1c for ITT

HbA1c	Detemir dinner	NPH bedtime	Detemir bedtime
Baseline	8.01 (n=133)	8.09 (n=125)	8.13 (n=123)
16 weeks	7.58 (n=133)	7.70 (n=125)	7.64 (n=123)

Accounting for the slight differences in baseline, the change in HbA1c was -0.53 for Detemir dinner, -0.39 for NPH bedtime and -0.49 for Detemir bedtime. The results with the per protocol population (shown below) is essentially the same as for the ITT population.

HbA1c for per protocol

HbA1c	Detemir dinner	NPH bedtime	Detemir bedtime
Baseline	8.09 (n=112)	8.08 (n=105)	8.11 (n=105)
16 weeks	7.57 (n=112)	7.69 (n=105)	7.62 (n=105)

Within subject variation by self-testing of fasting glucose and 10 point glucose profiles were lower in the two Detemir arms than in the NPH arm.

Insulin doses before the study and at endpoint are shown in the tables below. Mean basal insulin and total insulin rose in all three groups. The dose of bolus insulin was essentially unchanged in the Detemir bedtime group but fell in the other two groups. In comparisons to the NPH patients, Detemir patients took on average about 5-10% more insulin at baseline and about 10-20% more insulin endpoint.

Pre-study Dose of insulin for ITT

	Detemir dinner	NPH bedtime	Detemir bedtime
Basal U or IU	26.3	24.1	26.7
Bolus	29.1	27.9	30.5
Total	55.4	52	57.2

Dose of insulin at end of 16 weeks: ITT

	Detemir dinner	NPH bedtime	Detemir bedtime
Basal U or IU	34	28.6	31.7
Bolus	28.7	25.6	30.6
Total	62.7	54.2	62.3

Comparisons of Daily Dose of Insulin at 16 weeks

	Detemir dinner	NPH bedtime	Detemir bedtime
Basal U or IU	34	28.6	31.7
Ratio (Detmr/NPH)	1.19	1.00	1.11

	Detemir dinner	NPH bedtime	Detemir bedtime
Bolus U or IU	28.7	25.6	30.6
Ratio (Detmr/NPH)	1.12	1.00	1.20

Insulin Detemir U = 24 nmol
NPH insulin IU= 6 nmol
Insulin aspart IU = 6 nmol

Conclusion:

Trial 1447 did not clearly establish the non-inferiority of Detemir relative to NPH. Although insulin Detemir nominally met the test of non-inferiority to NPH insulin, patients on Detemir received somewhat more insulin than patients on NPH.

Trial 1448

This was a 16 week trial comparing NPH insulin to two regimens of insulin Detemir (2400 nmol/mL), and NPH insulin (600 nmol/mL). The NPH was given in the morning and at bedtime. In one arm, Detemir was given in the morning and at bedtime. In a second arm, Detemir was given every 12 hours. For the sake of simplicity, these arms are referred to as NPH am/hs, Detemir am/hs and Detemir q 12hr. All patients received boluses of insulin aspart before meals. This was designed to be a superiority trial. The primary measure of efficacy was HbA1c at 16 weeks using the ITT population. The trial was conducted at 40 Centers in Europe, Australia, and New Zealand.

The inclusion/exclusion criteria dose selection, titration and conduct of the trial are the same as in trial 1447. For France a local amendment, dated 30 August 2001, was made to the final protocol:

Glucose metabolism and especially insulin sensitivity varies upon patients ethnic origins. Health Authorities request that subjects in a phase III programme with a new insulin reflect the principal ethnic groups of a patient's population. Patients will have to approve recording of his/her ethnic origin.

The ITT population was 53% male, 99% white (one black patient on Detemir and one on NPH), mean age about 40 years with 16 years of diabetes, mean BMI 25. At baseline mean HbA1c was about 8.6% and mean FPG was about 11.7 mM. The mean dose of basal insulin was bout 0.37 U/kg and the mean dose of bolus insulin was about 0.40 U/kg. 3/137 patients withdrew from the Detemir q 12 hour arm because of 'ineffective therapy", 1/133 from the NPH am/hs arm and zero from the Detemir am/hs arm.

Average timing of Dose of insulin for ITT

	Detemir q 12hr	NPH am/hs	Detemir am/hs
Basal	7:55/19:56	7.56/22:30	7:42/22:36
Bolus	7:38/12:32/18:42	7:54/12:35/18:48	7:49/12;42/1842

HbA1c for ITT (from table 4.4)

HbA1c	Detemir q12	NPH am/hs	Detemir am/hs
<-3 weeks	8.56 (n=133)	8.51 (n=125)	8.71 (n=134)
16 weeks	7.76	7.91	7.87

Accounting for the slight differences in baseline, the change in HbA1c was -0.8 for Detemir 12 hr, -0.6 for NPH am/hs and -0.84 for Detemir am/hs. The results with the per protocol population (shown below) is essentially the same as for the ITT population.

HbA1c for per protocol (from table 4.5)

HbA1c	Detemir q 12	NPH am/hs	Detemir am/hs
<-3weeks	8.62 (n=111)	8.51 (n=117)	8.73 (n=124)
16 weeks	7.82	7.84	7.88

The change in HbA1c was -0.8 for Detemir 12 hr, -0.67 for NPH am/hs and -0.85 for Detemir am/hs. A combined ANOVA analysis of final HbA1c pooling the two Detemir arms (from table 9.3) is shown below:

Insulin Detemir Mean (SE)	NPH insulin Mean (SE)	Detemir-NPH Mean (95% CI)	p value
7.76	7.94	-0.18 (-0.34, -0.02)	0.0269

Mean FPG was higher ($p<0.0001$ for the comparison of NPH vs Detemir in the NPH am/hs arm (11.24 mM) than in the Detemir q12 hr arm (9.75mM) and in the Detemir am/hs arm (8.94 mM). Within subject day to day variation for FBG (home) was reported to be significantly lower with Detemir. These results are shown below:

	Mean FPG	SD	CV,%
Detemir 12 hr	8.23	2.95	35.9
Detemir morning/bedtime	8.20	2.91	35.5
NPH morning/bedtime	8.96	3.49	39.0

Pre-study Dose of insulin for ITT

	Detemir q 12hr	NPH am/hs	Detemir am/hs
Basal U or IU	26.4	29.5	28.1
Bolus	30.9	30.5	29.4

Dose of insulin at end of 16 weeks: ITT

	Detemir q 12hr	NPH am/hs	Detemir am/hs
Basal U or IU	36.7	34.8	36.3
Bolus	27.9	29.4	29.4

Comparisons of Daily Dose of Insulin at 16 weeks

	Detemir q 12hr	NPH am/hs	Detemir am/hs
Basal U or IU	36.7	34.8	36.3
Ratio (Detmr/NPH)	1.06	1.00	1.04
	Detemir q 12hr	NPH am/hs	Detemir am/hs
Bolus U or IU	27.9	29.4	29.4
Ratio (Detmr/NPH)	0.95	1.00	1.00

Insulin Detemir U = 24 nmol
NPH insulin IU= 6 nmol
Insulin aspart IU = 6 nmol

Conclusion:

In trial 1448, insulin Detemir meets the test of non-inferiority to NPH insulin without additional amounts of bolus insulin. This is the pivotal study to support approval for type 1 diabetes. As is noted in other studies, Detemir is more effective than NPH at lowering FPG. This finding is consistent with Detemir's slower action.

Study 1374

This non-pivotal study was conducted in patients with type 1 diabetes and compared Insulin Detemir plus Insulin aspart to NPH insulin plus regular insulin. The study was conducted at various sites in Europe. The randomized controlled portion lasted 18 weeks and was preceded by a two week run-in. Following randomization, there was 6 week titration phase followed by 12 weeks of maintenance. Patients were randomized to receive twice daily insulin Detemir plus mealtime insulin aspart or twice daily NPH insulin plus mealtime human soluble insulin (HSI). During the titration phase the doses of insulin were adjusted with the glucose targets of 5.7-7.3 mM (102-134 mg/dl) pre-breakfast and pre-dinner.

The ITT population consisted of 595 patients, 63% male, 99.8% white, mean age 39 years, mean BMI 24.9. The two treatment arms were well matched. 80% of patients enrolled had been using a basal-bolus insulin regimen with 1 or 2 injections of basal insulin and 2-4 injections of mealtime insulin boluses. The mean doses of basal insulin was about 24 units and 28 units of bolus insulin in both treatment arms. The insulin doses at endpoint were largely unchanged except for the doses of basal insulin in the Detemir group that rose to 32.1Units. The ratio of final dose of Detemir to NPH was 1.14. The ratio of final dose of aspart to regular was 1.01.

The primary endpoint measure was HbA1c. Values for HbA1c over the course of the trial are shown in the below for the ITT population:

	Detemir +Aspart	NPH + HSI
Screening	8.61 n=285	8.41 n=283
Randomization	8.48 n=280	8.30 n=280
Week 18	7.95 n=285	8.04 n=283

Mean HbA1c at endpoint was lower by 0.221 ($p=0.004$) in the Detemir + Aspart arm. Despite the greater efficacy of Detemir plus aspart, patients lost a mean of 0.8 kg over 18 weeks compared to a mean gain of 0.1 kg ($p< 0.001$) with NPH + HSI.

Conclusion: This trial shows that better glycemic control can be achieved with a regimen of Detemir plus aspart than with a regimen of NPH plus HSI. Patients on Detemir plus aspart showed weight loss compared to patients on NPH plus regular. Despite these favorable results, this trial can not be used as a pivotal trial to support the approval of Detemir because the effects of Detemir (in comparison to NPH) cannot be isolated from the effects of aspart (in comparison to HSI).

Trial 1372

This was a 26 week randomized open label comparison of Insulin Detemir given twice daily to insulin Glargine given once daily in patients with type 1 diabetes. The bolus insulin was insulin aspart in both treatment arms. The primary variable was HbA1c at endpoint. This 26 week trial was divided into a 6 week titration phase followed by a 20 week maintenance phase. During the titration phase, there was frequent contact with patients to adjust the insulin doses with the goals of pre-meal glucose < 7.3 mM and 90 min postprandial < 10.1 mM.

The ITT population was 51% male. The mean age was 40 years, mean BMI 25.2, mean duration of diabetes was 16.7 years. Mean HbA1c was 8.84%. The mean dose of pre-study basal insulin was 27 units. The mean dose of pre-study bolus insulin was 28 units. The two treatment arms were well matched at baseline

161 patients were randomized to each group. Three Detemir patients and one Glargine patients withdrew because of adverse events. Zero Detemir patients and five Glargine patrients withdrew because of "ineffective therapy".

Final insulin doses:

The mean dose of basal insulin at endpoint was 36.8 U (0.47 U/kg) for Detemir and 26.8 IU (0.35 IU/kg) for Insulin glargine. The mean dose of bolus insulin at endpoint was 28.5 IU (0.36 IU/kg) for Detemir patients and 29.3IU (0.39 IU/kg) for Glargine patients. Thus, total insulin requirement was approximately 30% greater for Detemir patients, most of which was due to a difference in basal insulin.

Efficacy:

HbA1c at screening, randomization and 26-week endpoint are shown in the following table for the ITT and PP populations:

	Detemir	Glargine
ITT patients	161	159
HbA1c at screening, mean	8.86	8.81
HbA1c at randomization, mean	8.78	8.70
HbA1c at 24 week endpoint	8.12	8.11
Per protocol patients	128	124
HbA1c at screening, mean	8.86	8.81
HbA1c at randomization, mean	8.78	8.68
HbA1c at 24 week endpoint	8.05	8.05

Mean self measured fasting glucose at endpoint was higher with Detemir than with Glargine, 7.71mM vs 7.01 mM ($p<0.001$). But the glucose value after dinner was lower with Detemir than with Glargine, 8.28 mM vs 8.96 mM

Type 2 diabetes

Trial 1166

This trial was conducted in five countries in Asia and four in Scandanavia.
This was an open label 6 month trial comparing Detemir to NPH insulin each given twice daily. Inclusion characteristics were type 2 diabetes on a regimen or insulin and./or oral hypoglycemia agent for at least 12 months, aged 35 or greater, BMI< 35, HBA1c between 8-12%. Patients with total daily insulin dose > 120 units were excluded.

Study drug was Detemir 1200 nmol/ml or NPH 600 nMol/ml. Patients discontinued their usual antidiabetic medications at screening which was < 3 weeks from randomization. Insulin-treated patients randomized to Detemir were started on twice (molar basis) their previous dose NPH. This meant that the starting volume of study drug was the same for both Detemir and NPH The insulin dose was titrated with the goal of premeal and nigh time(2:00-4:00 am) to be 72-126 mg/dl and 90 min post-prandial glucose to be < 180 mg/dl. Insulin was given with breakfast and bedtime. The dose was made at the investigators discretion based results of home blood glucose monitoring. Fundoscopy was done at screening and endpoint.

The trial was to test non-inferiority based on the primary endpoint, HbA1c after 6 months for the ITT population, with a margin of 0.4% units.

Results:

There were 24/224 (11%) patients who dropped out of the Detemir arm because of "ineffective therapy" compared to 2/221(1%) with NPH. Patients in the ITT population were about 55% male, 65% white, 35% Asian, mean age about 59 years, mean duration of diabetes about 11 years, mean BMI about 27.6, HbA1c 8.8 and FPG 10.4 mM. Approximately 74% where taking a combination of insulin plus oral hypoglycemic agent, 45% insulin only and 25% oral agent only. Among the insulin users, the mean dose at screening was about 40 units.

Results for HbA1c at endpoint show that Detemir was inferior to NPH by 0.66 (95% cf 0.44, 0.89). There was a small decrease (-0.25) in HbA1c in patients on NPH and a small rise (0.34) in patients on Detemir. The noninferiority test was not met. Exploratory ANOVA by country, age, sex and BMI did not yield any interesting results.

HbA1c - ITT (all exposed patients)

	ITT n=221	n= 218
	Detemir n=178	NPH n=203
<-3 weeks	8.93	8.78
26 weeks	9.26	8.53

The mean FPG at endpoint for the ITT population was 9.79 for Detemir compared to 8.50 for NPH.

HbA1c - Per protocol

	n= 155	n=169
	Detemir n=153	NPH n=166
<-3 weeks	8.91	8.74
26 weeks	9.35	8.56

The mean insulin dose at 6 months for NPH was 59.8 IU (359 nmol) compared to 124 U (1493 nmoles). The molar ratio of Detemir to NPH was 4.2

Conclusion:

Trial 1166 demonstrated that Detemir at 1200 nmole/ml is inferior to NPH insulin.

Trial 1336

This was a 6-month open label trial conducted in five countries in Europe to compare Insulin Detemir to NPH insulin when used as the basal insulin in a basal/ bolus regimen. The preparation of insulin Detemir is this trial was 2400 nmol/ml. The preparation of NPH insulin is 600 nmol/ml.

Patients where age 35 years or more and were using a basal insulin dose of at last 30% of their total insulin dose and had HbA1 no greater than 12% on a total insulin dose of no more than 100 units. Patients taking oral agents within two months were excluded. After a three-week run-in patients were randomized to Insulin Detemir (2:1 randomization) or NPH. The initial dose of Detemir was taken to be half the volume of the previous dose of NPH (half the volume but twice the molar dose). Patients randomized to NPH started the same dose that they were taking previously. Insulin aspart was given as pre-meal bolus. The glycemic goals were the same as previous in studies. Patients/investigators were given discretion about insulin regimen. The initial dose of basal insulin was given at bedtime. A second dose of basal insulin could be added if glycemic goal could not be safely achieved with a single dose.

The primary variable was HbA1c at six months. This was designed as a non-inferiority trial with a margin of 0.4% units.

The ITT population was 506 patients. They were 51% male, 99% white, had a mean age of 60.4 years, 13 years of diabetes, mean BMI 30.4. Withdrawals due to ineffective therapy were 2.3% for Detemir compared to 1.2% for NPH. Withdrawals due to adverse event were 2.3% for Detemir compared to 0.6% for NPH.

HbA1c - ITT (all exposed patients)

	ITT n=341	n= 164
	Detemir n=315	NPH n=155
<-3 weeks	7.87	7.76
26 weeks	7.61	7.40

The mean change from baseline was -0.26 % units for Detemir compared to -0.36 % units for NPH.

The primary analysis ANOVA of HbA1c for Detemir –NPH at 26 weeks was 0.16 with a 95% confidence interval of 0.003-0.312. Thus the test of non-inferiority, based on a margin of 0.4 was met.

Exploratory analysis showed little difference between patients on once daily or twice daily basal insulin in HbA1c at six months as shown below:

	Detemir n=315	NPH n=155
Once daily	7.64 (n=155)	7.56(n=72)
Twice daily	7.61 (n=160)	7 41(n=83)

The mean FPG at endpoint for the ITT population was 9.73 mM for Detemir compared to 9.61 for NPH.

HbA1c - Per protocol

	n= 297	n=148
	Detemir n=297	NPH n=147
<-3 weeks	7.87	7.79
26 weeks	7.61	7.43

The mean change from baseline was -0.26 % units for Detemir compared to -0.36 % units for NPH.

The mean pretrial dose of basal insulin was 27.8U in the Detemir group and 28.0 units in the NPH arm. The mean pretrial dose of bolus insulin was 33.6U in the Detemir group and 34.8 units in the NPH arm. For the ITT population, the mean dose of basal insulin at 26 weeks was 36.4U in the Detemir group and 35.3 units in the NPH arm. The mean dose of bolus insulin at 26 weeks was 40.2U in the Detemir group and 35.8 units in the NPH arm. The ratio of insulin dose at 26 weeks, Detemir/NPH was 1.03 for basal insulin and 1.12 for bolus insulin. These results are essentially the same for the Per protocol population.

Conclusion:

Trial 1336 should not be considered a pivotal trial to establish efficacy.
Although Insulin Detemir nominally met the test of non-inferiority, patients on Detemir received additional amounts of bolus insulin (insulin aspart).

Trial 1337

This was a randomized six month trial of Detemir (2400 nM) vs NPH (2:1) in combination with metformin. The trial was performed at 72 sites in the USA and Puerto Rico.

The trial population was patients with type 2 diabetes who had been on metformin, either alone or in combination with other oral antidiabetic agents. There was a two-week washout of other oral agents during which time the dose of metformin was "optimized" to 2000-2550 mg/d or maximum tolerated dose. Patients who failed to reach FPG of 7 mM (126 mg/dl) were randomized to Detemir or NPH as a single evening dose. This regimen of metformin plus Detemir/NPH was maintained for 24 weeks.

The trial was designed to test non-inferiority of Detemir vs NPH. HbA1c at 24weeks in the ITT population was the primary endpoint with a margin of 0.4% units.

467 patients were randomized (309 to Detemir and 158 to NPH), and 405 (266 and 139) completed the study. There were 12% withdrawals of NPH and 11% on NPH. This difference in withdrawals was accounted for by "ineffective therapy" in 2.6% of patients on Detemir and none on NPH. Of the 8 patients who withdraw because "ineffective therapy", 5/8 had been on Met+TZD, 2/8 on Met w/o TZD, and 1/8 on Met alone. Randomized patients had a mean age of 56 years, 6 years of diabetes 60% Caucasian, 6% white, 30% Hispanic, mean body weight 90 kg, BMI 31.5. The Detemir group was 51% male. The NPH group was 59% male. Previous antidiabetic therapy was metformin alone, 19%, Met + TZD 37%, Met combo w/o TZD 44%. The mean dose of metformin was about 2200 mg.

Insulin titration:

Insulin Detemir (1U=24 nmol) or NPH (U= 6 nmol) were initiated at 0.1U/kg for FBG <180 mg/dl or 0.2 U/kg for FBG >180mg/dl. The dose was then increased to every three days to achieve a goal of FBG of 7 mmol/L. The mean initial dose of insulin was 0.17 U/kg for Detemir and 0.16 U/kg for NPH, about 15 units in both groups. At endpoint the mean dose of Detemir was 0.57 U/kg (about 51 units), compared to 0.45 U/kg (about 41 units) for NPH. The molar ratio Detemir/NPH was 4.19 at baseline, 4.8 at 2 months, and 4.98 at endpoint.

As shown in the table below, HbA1c values fell significantly in both arms. But the HbA1c value at EOS was lower in the NPH group than in the Detemir group. Because the upper limit of the 95% CI is 0.78 (>0. 4% units), the predefined criterion for non-inferiority was not fulfilled.

HbA1c values in Modified ITT population

	Detemir	NPH	Diff (95% CI)
Baseline	9.5	9.4	0.01
EOS	8.5	8.0	0.56 (0.33- 0.78)
Change from baseline	-0.9	-1.5	
P value	<0.0001	<0.0001	

FPG was the same in both groups at baseline (246 mg/dl) and endpoint (154mg/dl).

HbA1c response based on subgroups

The Sponsor performed the following sub-set analysis based on pretrial antidiabetic medication (metformin only, metformin plus TZD, metformin combo w/o TZD).

Metformin Only

	Detemir	NPH	Diff (95% CI)
Baseline	9.4	9.6	
EOS	7.8	7.7	-0.307,0.853
Change from baseline	-1.5	-2.0	
P value	<0.0001	<0.0001	
Metformin Dose	2065(1000-2550)	2112(1500-2550)	

Metformin Combo with TZD

	Detemir	NPH	Diff (95% CI)
Baseline	9.4	9.4	
EOS	8.7	8.0	0.23,1.15
Change from baseline	-0.6	-1.4	
P value	<0.0001	<0.0001	
Metformin Dose	2173(1000-2550)	2201(1000-2550)	

Metformin Combo without TZD

	Detemir	NPH	Diff (95% CI)
Baseline	9.6	9.4	
EOS	8.6	8.1	0.076, 0.81
Change from baseline	-0.9	-1.4	
P value	<0.0001	<0.0001	
Metformin Dose	2201(1500-2550)	2252(1000-2550)	

Based on this subset analysis, the Sponsor contends that Detemir met the test of non-inferiority to NPH in the metformin-only subset. However, this contention upon further analysis, seems poorly founded:

At the request of DMEDP, the Sponsor provided the doses of metformin at screening, baseline, and endpoint as well as the HbA1c ant screening and baseline. As shown in the tables below, there was an increase in the dose of metformin from screening to baseline in all groups. This is referred to as "optimization of metformin therapy" in the protocol. In the metformin-only subset, this change represented intensification of therapy and is manifested by fall in HbA1c and FPG **before** randomization. Thus some of the efficacy attributed to Detemir and NPH was probably a delayed effect of the increased dose of metformin. The claim of non-inferiority of Detemir to NPH is not valid because the contribution to total efficacy of the increased dose of metformin cannot be quantitated. By contrast, discontinuation of the other oral hypoglycemic agents in the metformin combo subsets led to exacerbation of hyperglycemia. Under these circumstances, Detemir was clearly inferior to NPH.

Mean doses of Metformin, mg

	INSULIN DETEMIR					NPH INSULIN			
	Met	w/oTZD	TZD	total		Met	w/oTZD	TZD	total
Screening	1768	1962	1889	1896		1743	2002	1907	1921
Baseline	2044	2201	2179	2163		2112	2245	2203	2206
EOS	2198	2235	2176	2205		2241	2243	2220	2234

Mean FPG mM

	INSULIN DETEMIR					NPH INSULIN			
	Met	w/oTZD	TZD	total		Met	w/oTZD	TZD	total
Screening	12.8	12.0	12.0	12.1		13.0	12.1	11.6	12.1
Baseline	12.0	14.1	13.9	13.6		12.3	13.8	13.7	13.5

HbA1c

	INSULIN DETEMIR					NPH INSULIN			
	Met	w/oTZD	TZD	total		Met	w/oTZD	TZD	total
Screening	9.8	9.6	9.3	9.5		9.8	9.5	9.5	9.5
Baseline	9.5	9.6	9.4	9.5		9.6	9.4	9.5	9.5

Effect of Hypertriglyceridemia

The Sponsor submitted a subset analysis based on fasting triglycerides. The data set was divided into three subsets, <250, 250-500, >500. For the sake of simplicity, only the <250 and > 500 subsets are shown in the following table (the 250-500 subset gives intermediate values for all the variables shown). The >500mg subset had higher levels of HbA1c at baseline and endpoint and used more insulin at endpoint than patients in the <250 subset. This finding is not surprising and reflects the insulin resistance that often accompanies hypertriglyceridemia. In both subsets, the reduction in HbA1c was about 60% greater with NPH than Detemir. Thus the decreased effectiveness of Detemir appears to occur across the board and is not specifically seen in patients with hypertriglyceridemia.

Insulin Dose and HbA1c by Baseline Triglyceride

	Triglyceride <250 mg/dl			Triglyceride > 250 mg/dl	
Detemir,	N	U/kg		N	U/kg
Baseline	172	0.2		25	0.2
EOS	180	0.5		26	0.8
Insulin NPH					
Baseline	94	0.2		11	0.2
EOS	101	0.4		11	0.7

Detemir	N	HbA1c(chng		N	HbA1c(chng
Baseline	179	9.3		27	10.3
EOS	171	8.4 **(-0.9)**		26	9.0 **(-1.3)**
Insulin NPH					
Baseline	101	9.4		11	9.6
EOS	95	8.0 **(-1.4)**		11	7.5 **(-2.1)**

Summary of Subset Analyses by race/ethnicity done by DMEDP
- complete analyses found in review by Lee Pian,. Biostatistics

Change in HbA1c (baseline to EOS) by Race

		Insulin Detemir			NPH Insulin	
Caucasian	Baseline	172	9.28		86	9.33
	EOS		8.40			7.74
	Change		-0.88			-1.61
Others	Baseline	91	9.70		49	9.42
	EOS		8.42			8.11
	Change		-1.28			-1.30

The category "others" is broken down into black and Hispanic in the table below. (Asians and others are omitted because the numbers are too small.)

Black	Baseline	16	9.64		8	9.54
	EOS		8.14			8.19
	Change		-1.50			-1.35
Hispanic	Baseline	64	9.85		36	9.48
	EOS		8.50			8.09
	Change		-1.32			-1.38

Mean Dose of Insulin at Endpoint (by Race)

	Insulin Detemir, units			NPH Insulin, IU	
Caucasian	N=190	61.04		N=90	50.07
Others	N=116	37.17		N=65	31.58

The mean dose of metformin at endpoint was about 2200 mg in all subsets.

Conclusion:

Trial 1337 failed to establish to equivalence of Insulin Detemir to NPH Insulin when used in combination with metformin in patients with type 2 diabetes. Although lower levels of HbA1c were achieved with NPH, levels of FPG at endpoint were the same in both treatments. This apparent discrepancy between HbA1c and FPG
is consistent with the slower action of Detemir. The most important finding was the difference in response between Caucasian and non-Caucasian patients. Insulin Detemir and NPH insulin had the same efficacy in black and Hispanic patients. But Detemir was inferior to NPH in Caucasian patients. The efficacy of Detemir relative to NPH did not appear to be influenced by the fasting triglyceride level.

Trial 1530

The trial was conducted at 58 centers throughout Europe.

This was a 24 week randomized open label trial comparing Insulin Detemir to NPH insulin in insulin-naïve patients with type 2 diabetes. The 24-week comparison was preceded by a two-week run-in in patients with type 2 diabetes who had been inadequately controlled on one or two oral antidiabetic drugs (OAD), excluding thiazolidinediones. The starting dose of both insulin products was 10 units in the morning and 10 units in the evening. The dose was titrated with a goal of plasma glucose concentration <6 mM before breakfast and dinner. The previous OAD regimen was continued.

The primary efficacy variable was HbA1c at end of treatment for the ITT population. Data are also presented for the per protocol population. The per protocol population excludes non-completers and patients with protocol violations, primarily change in oral antidiabetic agents during the trial. Other efficacy variables were FPG at endpoint and proportion of patients with HbA1c < 7% without symptomatic hypoglycemia confirmed by glucose < 4 mM and no single glucose < 3.1 mM. Other variables were self-measured glucose, and change in body weight.

475 patients were randomized and received treatment. This constitutes the ITT population. The completion rate was 96 % for Detemir and 94% for NPH. The patients were 99% white, 53% male, mean age 61 years, mean body weight 84.4 kg, BMI 28.9 and mean duration of diabetes 9.7 years. Combination therapy was used by 65% and metformin monotherapy by 28%. The two treatment arms were well matched. The ITT population was 237 for Detemir and 239 for NPH insulin. The per protocol population according to the text was 214 for Detemir and 214 for NPH insulin (n=213 is shown in table of data).

As shown in the table below for patients completing 24 weeks, reduction in HbA1c and final HbA1c were essentially the same for both Detemir and NPH, except that the Detemir patients required about 48% more insulin, expressed either as a mean dose of units per day or units/kg/day. The median insulin dose was 56 IU (30 in the morning plus 20 in the evening) for Detemir and 38 U (20 in the morning and 18 in the evening) for NPH.

Mean Efficacy Results, ITT

	Insulin Detemir n=227	NPH insulin n=227
HbA1c, %		
Baseline	8.61	8.51
EOS	6.58	6.46
Change	-1.84	-1.90
Final Insulin dose, U or IU	65.6	45.0
U or IU per kg	0.77	0.52

Insulin Detemir U = 24 nmol
NPH insulin IU= 6 nmol

The primary variable, HbA1c at EOS for the ITT population showed no difference between the two treatments. This was 6.58 (n=230) for Detemir and 6.46 (n=232 for NPN. The 95% CI for the difference Detemir – NPH was -0.002 to 0.254.

Mean FPG decreased from 11.1 mmol/l to 6.9 with Detemir and from 10.8 to 6.6 mmol/L with NPH. Mean weight gain on Detemir was 1.2 kg compared to 2.8 kg on NPH ($p<0.001$).

The proportion of "responders", reaching HbA1c of 7% without hypoglycemia was 26% for Detemir and 16% for NPH (p=0.008)

The change in HbA1c for the per protocol population is shown in the following table. There is little, if any, difference between Detemir and NPH.

Mean Efficacy Results, per protocol

	Insulin Detemir n=214	NPH insulin n=213
HbA1c, %		
Baseline	8.72	8.67
EOS	6.75	6.61
Change	-1.97	-2.06

Conclusion:

Trial 1530 appears to show that Detemir and NPH, each given twice daily, are equally effective in controlling type 2 diabetes. Good glycemic control was achieved with both drugs. That Detemir appeared to cause less weight gain is an advantage. That a larger dose of Detemir was required than NPH should not prevent approval. However, the label will need to make clear that somewhat more Detemir was required relative to NPH in patients with type 2 diabetes.

Appears This Way
On Original

Trial 1385

This non-pivotal trial compared Detemir plus insulin aspart to NPH plus human soluble insulin (HSI) in patients with type 2 diabetes who had previously been treated with insulin. Basal insulin, Detemir or NPH were given during the trial in accordance with patients' previous regimen. There was a six-week titration period followed by a 16 week maintenance period. The primary analysis was HbA1c at 22 weeks.

The ITT population was 58% male, 99.8% white, mean age 58 years and mean duration of diaebtes14 years. The mean BMI at baseline was 29.2, mean HbA1c was 8.12%. 64% had been taking two injections of basal insulin daily and 32% had been taking one injection of basal insulin daily. 46% had been on a basal/bolus regimen and 32% had been using insulin with oral hypoglycemic agent. The two treatment arms were well-matched at baseline. The doses of insulin at baseline do not appear to have been presented.

The trial was conducted in Europe and Argentina.

At 22 weeks, the mean total dose of insulin was 79 units in patients on the Detemir-aspart regimen and 64 units in patients on the NPH-HIS regimen. Mean dose of basal insulin was 48 U or Detemir and 37 IU (ratio=1.29). The mean dose of bolus insulin was 31 IU for aspart and 27 units of HSI (ratio=1.15).

At 22 weeks, mean HbA1c was 7.46 for Detemir/aspart and 7.52 for NPH/HSI. The criterion for superiority was not fulfilled. There was a mean reduction in HbA1c of about 0.6% units in both groups.

Comments on Efficacy:

Although the non-inferiority test with respect to HbA1c was nominally met in all phase 3 trials of insulin Detemir vs NPH in type 1 diabetes, methodological issues cloud interpretation of the results in all but one. The results of trial 1448, however, clearly demonstrate that patients given Insulin Detemir formulated at 2400 nmole/ml can achieve the same glycemic control as patients given NPH (600nmol/ml) without resorting to additional amounts of bolus insulin. Trial 1447 did not yield exactly the same finding, although both trials (1447 and 1448) compared NPH at breakfast and bedtime in protocols and patients populations that are nearly identical. Patients on Detemir in trial 1447 received somewhat more insulin than patients on NPH. However, both groups achieved the same degree of glycemic control and the amount of additional insulin was very small.

Although trial 1448 lasted only 16 weeks, earlier trials and extensions have demonstrated the durability of Insulin Detemir. The Sponsor has met the regulatory standard for efficacy for the population of patients with type 1 diabetes that was studied. One unit of Detemir (24 nmoles) had approximately the same activity as one unit on NPH (6 nmoles) in type 1 diabetes.

In the initial NDA submission, there were three phase 3 trials of Detemir vs NPH in type 2 diabetes. None established the non-inferiority of Detemir. Indeed, the weight of evidence suggested that Detemir was inferior to NPH, at least when given according to the schedule used in those studies. The problem seems to have been that the titration schedule was not aggressive enough to achieve the desired effect on hyperglycemia. Study 1530, in the resubmission, clearly establishes that Detemir is non-inferior to NPH with respect to HbA1c provided that enough Detemir is given.

The results of trial 1530 show that approximately 50% more "units" of Detemir than NPH are required in patients with type 2 diabetes. This finding is in agreement with the PK/PD study (trial 1439) described in an earlier section. The requirement that larger amounts of Detemir be used to achieve equivalent glycemic control as with NPH is over and above the insulin resistance usually seen in patients with type 2 diabetes. Because of obesity, patients with type 2 diabetes are often insulin resistant and therefore require more insulin of any type than patients with type 1 diabetes. With Detemir, the need for more insulin in patients with type 2 diabetes is even greater. Based on an FDA analysis of the PD data from trial 1439 (see Biopharm review fig 6 and accompanying text), the larger dose of Detemir vs NPH in type 2 diabetes does not appear to be due to obesity. The possible effects of hyperlipidemia on Detemir action has been discussed earlier (pages 15 and 53).

None of the trials of type 1 diabetes were done in the United States and there are virtually no black or Hispanic patients. Given that type 1 diabetes is much more common in Northern Europe than elsewhere, it is not surprising that few black or Hispanic patients with type 1 diabetes were studied in this application.* This is generally the case with trials of insulin products in type 1 diabetes. With respect type 2 diabetes, the one trial

conducted in the United States in the original NDA suggested a difference in response between white and non-white patients (black and Hispanic). Although unexpected, this finding was given plausibility by differences in species responses to Detemir but not to human insulin. On the other hand, the ethnic difference observed in trial 1337 came from a post hoc analysis. In my review of the initial NDA submission, I proposed that Novo Nordisk perform a clinical trial to test the hypothesis that ethnic differences exist for Detemir. In lieu of this proposal, Novo Nordisk was asked to perform a "clamp" study in patients with type 1 diabetes. For technical/feasibility reasons, this was later changed to type 2 diabetes. The resulting study, trial 1439, compared three doses of Detemir to NPH. The results of this trial have been discussed earlier. Consistent with results of other studies, NPH appeared to be about 50% more potent (on a unit basis) than Detemir. However, this trial did not reproduce the ethnic differences found in trial 1337. If anything, the difference between NPH and Detemir seemed greater in Black patients than in white patients. The reason for this discrepancy between the two trials is open to speculation. As noted earlier, the ethnic difference found in trial 1337 was based on a post-hoc analysis, and may be incorrect. On the other hand, a 16 hour clamp study (trial 1439) examines the acute actions of insulin (stimulation of glucose transport in muscle, suppression of glucose production in liver), and would not be expected to pick up possible differences in long-term actions of insulin (enzyme induction/repression) or adaptations that occur during long-term treatment (such as antibodies). Ordinarily, one would expect a six month clinical trial to more closely mimic the "real world" than a 16 hour clamp study. Thus, I believe it is still possible that ethnic differences in response to Detemir may still be present. Finally it must be born in mind that attempting to find differences based on "race" or "ethnicity" starts with the assumption that those terms can be defined. The use of self-identification to define race/ethnicity is clearly not adequate to capture the wealth of genetic and environment factors (diet for instance) that could be at play.

In short, the negative finding of trial 1439 provides some assurance that race/ethnicity is not an important factor in the use of Detemir, but does not, in my judgment, completely refute the previous finding from trial 1337.

*Although type 2 diabetes is more common in blacks and Hispanics, classical (autoimmune) type 1 diabetes is more common in whites, particular in whites of Northern European origin. The world's highest incidence is 35/100,000 in Finland, followed by Scandanavia and Scotland. By contrast, the incidences in Mexico City and Tanzania are less than 3/100,000. Within the United States, the incidence appears to follow the ethnic origin of the population. The US Virgin Islands is an interesting example. The incidence among whites during an epidemic in 1984 was 28/100,000 . By contrast, Hispanics and blacks in the US Virgin Islands have incidences of about 8 and 7/100,000 respectively. This contrast in less apparent elsewhere in the USA. In Allegheny County the incidence among whites and non-whites is 18 and 12/100,000 respectively and in Jefferson Co the incidence among whites and non-whites is 16 and 12/100,000 respectively (data taken from fig 2, page 91 of Textbood of Diabetes Mellitus, 2nd edition, Alberti, Zimmet and DeFronzo.). A second form of type 1 diabetes predominates in the tropics. It is not immune-mediated and is believed to represent from chronic pancreatitis with pancreatic insufficiency (both endocrine and exocrine) stemming from early mal-nutrition.

V11 Review of Safety

One study was performed whose primary endpoint was related to safety. This study, trial 1375, compared the incidence of hypoglycemia in patients with type 1 diabetes taking Detemir vs NPH insulin. This trial is reviewed first. The review of safety findings from efficacy trials follows.

Trial 1375

This is a comparison of Detemir to NPH insulin on self-reporting of hypoglycemia in patients with type 1 diabetes

Trial design

This was a 34-week randomized two periods crossover study in patients with type 1 diabetes. The two 16-week crossover periods are preceded by a 2-week run-in. During the run-in, patients were treated with a basal bolus regimen consisting of twice daily NPH insulin plus meal-time boluses of insulin aspart. The two treatment arms were Detemir twice daily plus aspart as bolus insulin and NPH twice daily plus aspart as bolus insulin. Each 16-week crossover period consisted of 6 weeks of titration followed by ten weeks of maintenance.

The patient population consisted of patients with type 1 diabetes, with HbA1c < 9% while taking less than 1.4 units /kg of insulin. Patients with hypoglycemia unawareness were excluded, as were patients with proliferative retinopathy or renal insufficiency but there was no exclusion based on history of hypoglycemia. The trial was done in Europe and South Africa.

The ITT dataset were 54 % male, 94% white, mean age 39 years, mean duration of diabetes 16.6 years, mean BMI 25.3 and mean HbA1c 7.9%. Mean dose of basal insulin was 27 units, mean dose of bolus insulin was 30 units. The two sequences were well matched with respect to baseline characteristics.

The objective was to show superiority of Detemir to NPH with respect to self-reported hypoglycemic episodes during the maintenance period of each cross over. Patients received basal insulin twice daily before breakfast and before dinner. The glycemic goals were pre-meal PG of < 6 mmol/L, pre bedtime 6-8 mmol/L and 90 min postprandial < 8 mmol/L. The protocol notes that an adjustment was made because glucose strips used for self-testing gave lower values than plasma. Thus, the plasma goals were reduced 10%. Adjustments in insulin dose were made by the investigator based on blood glucose measurement. A subset of patients used a Minimed continuous glucose monitoring system before each crossover endpoint.

A major hypoglycemic episode is one in which the patient was unable to treat himself/herself. A minor episode was one not requiring assistance but in which hypoglycemia was documented by PG< 3.1 mmol/L. The primary endpoint was incidence of self-reported hypoglycemia (all episodes, major, minor and symptoms only) during the last ten weeks of each crossover.

Results:

At the end of each crossover sequence, patients on Detemir took slightly more insulin than patients on NPH. The molar Detemir/NPH was 1.05 for basal insulin and 1.02 for bolus insulin. Mean HbA1c at the end of each treatment was 7.55 with both treatments.

The following are data for hypoglycemia during the last ten weeks of each cross-over. 92.8% of patients reported hypoglycemia while on Detemir compared 92.2% of patients on NPH. However, the number of events (1281 vs 1592) was lower on Detemir. Thus the Sponsor is claiming superiority with respect to the primary endpoint. The relative risk of hypoglycemia was 0.82 (95% CI 0.72-0.92).

82.4% of patients reported "minor" hypoglycemia episodes on Detemir compared to 84.4% on NPH. However, the number of events (699 vs 865) was lower on Detemir. Thus the Sponsor is claiming superiority with respect to this secondary endpoint. The relative risk of minor hypoglycemic episodes was 0.84 (95% CI 0.72-0.97).

12/125 (9.6%) reported 19 "major" hypoglycemic episodes on Detemir. 16/128 (12.5%) reported 33 major episodes on NPH. The relative risk of a "major" was 0.61 ((95% CI 0.27-1.36).

The relative risk of "nocturnal" hypoglycemia (all events) was 0.50 (0.38-0.65), but there were too few major events to evaluate.

In response to a question by FDA, the Sponsor provided (May 11, 2005) the following table to show that there were fewer hypoglycemic events with Detemir than NPH during both cross-over sequences:

Number of Hypoglycemic Episodes in Each Maintenance Period

		Period 1	**Period 2**
All episodes	Detemir/NPH	712	861
	NPH/Detemir	731	569
All nocturnal episodes	Detemir/NPH	75	142
	NPH/Detemir	153	70

Also, in response to a question by FDA, the Sponsor provided (May 11, 1005) the following table to show that that there were fewer hypoglycemic events with Detemir than NPH during the entire 16 week period (not just the 10 week maintenance):

Self-recorded Hypoglycemic Episodes during the Entire Treatment Period, ITT

	Detemir		NPH		Detemir/NPH Relative Risk	p-value
	N(%)	E	N(%)	E	95% CI	
All	123 (98.4)	2298	122 (95.3)	2735	0.86 [0.77; 0.95]	0.003
Nocturnal	80 (64.0)	277	100 (78.1)	506	0.55 [0.45; 0.67]	<0.001
Diurnal	119 (95.2)	1986	119 (93.0)	2185	0.93 [0.83; 1.04]	0.204
Major	15 (12.0)	27	21 (16.4)	47	0.62 [0.34; 1.14]	0.126
Nocturnal	4 (3.2)	7	10 (7.8)	18	NA	
Diurnal	14 (11.2)	20	17 (13.3)	29	NA	
Minor	119 (95.2)	1251	114 (89.1)	1439	0.90 [0.79; 1.01]	0.083
Nocturnal	68 (54.4)	159	82 (64.1)	284	0.56 [0.44; 0.72]	<0.001
Diurnal	111 (88.8)	1069	113 (88.3)	1126	0.99 [0.86; 1.14]	0.871
Symptoms Only	98 (78.4)	1012	100 (78.1)	1247	0.81 [0.70; 0.95]	0.008
Nocturnal	40 (32.0)	111	58 (45.3)	204	0.55 [0.40; 0.75]	<0.001
Diurnal	95 (76.0)	897	95 (74.2)	1030	0.87 [0.74; 1.03]	0.103

N: Number of subjects reporting at least one episode. %: Percentage of subjects in the ITT analysis set reporting at least one episode. E: number of reported episodes during the 32 week titration and treatment period. Diurnal: 06:00 to 23:00, Nocturnal: 23:00 to 06:00

Other safety data

One patient died of a myocardial infarction on NPH. Two patients had hypoglycemic coma on NPH. One patient on Detemir developed 'small red spots' the day after dosing. This was considered a possible allergic reaction and she was withdrawn. Two other patients on Detemir had transient rashes at the injection sites. One patient on Detemir and one on NPH reported lipodystrophy.

A sequence effect was observed with respect to body weight. During the first sequence both groups lost weight. However, during the second sequence, patients on Detemir lost weight (mean about 1 kg) while patients on NPH gained weight (mean about 1.5 kg). Therefore no conclusion could be drawn about body weight.

Conclusion:

The results of this trial support a conclusion that Detemir is less likely to cause hypoglycemia than NPH in patients with type 1 diabetes.

Safety Findings in Trials whose primary endpoint was related to efficacy

Type 1 Diabetes:

Trial 1181

One subject in the Detemir group died. This was a 34-year-old male who was found dead after 2 1/2 months of Detemir. His diary indicated that he had been experiencing "elevated glucose levels at night and as a consequence, had injected himself with bolus insulin at bedtime (in addition to the prescribed basal insulin) without simultaneous food." Serious AE's attributable to drug were 5 cases of hypoglycemia on Detemir (3 withdrawals due to hypoglycemia), one case of hyperglycemia on Detemir and 4 cases of hypoglycemia on NPH. Injection site reactions occurred in 4/236 patients on Detemir and 1/224 patient on NPH. None were severe. Retinal abnormalities were reported in 7 patients on Detemir and 6 patients on NPH.

Major hypoglycemia beyond the first month occurred in 20 (8.7%) of Detemir patients and 12(5.5%) of NPH patients. There were a total of 31 events with Detemir and 16 with NPH. The text states that the relative risk of major hypoglycemia Detemir/NPH is 2.01 (95% cI 0.88-4.62) p=0.098. Major hypoglycemia during the first month occurred in 8(3.4%) of Detemir patients and 4(1.8%) of NPH patients. There were 8 events with Detemir and 7 with NPH during the first month.

Mean body weight at baseline was 76.5 for Detemir and 75.5 for NPH. At 26 weeks, patients on Detemir lost an average of 0.5 kg while patients on NPH gained an average of 0.7 kg. ($p<0.001$ using ANOVA adjustment for baseline).

There were no other clinically relevant safety findings reported.

Extension:

There were no deaths during the 6-12 month extension. In the ITT population, 14 patients on Detemir had 17 major hypoglycemic events, compared to 9 patients on NPH with 9 events. Body weight increased an average of 0.1kg on Detemir and 0.6 kg on NPH. "Retinal disorder" occurred in 7 Detemir patients and 10 patients on NPH. One additional patient on Detemir had a "vitreous disorder". Injection site lipohypertrophy was reported in 6 patients on Detemir and 2 on NPH. 3 patients on Detemir developed otosalpingitis during the extension compared to 1 during the original 6 months on Detemir and none on NPH.

Antibodies (% B/T), ITT

	Insulin Detemir n=154	NPH insulin n=134
Detemir specific antibody		
Baseline	2.71	3.32
12 months	7.81	3.46
Insulin Antibodies		
Baseline	0.77	0.72
12 months	0.78	0.74
Cross-reacting antibodies		
Baseline	14.1	13.8
12 months	20.2	14.8

The rise in Detemir specific and cross –reacting antibody in Detemir-treated patients vs NPH was highly significant $p<0.001$.

There was no correlation between change in antibodies and change in HbA1c or FPG. But there was a correlation between change in antibodies and change in Detemir dose. The Spearman correlation coefficient was 0.20-0.21 for both antibodies. The p value was 0.0495 for anti-Detemir and 0.0289 for cross-reacting antibody. For patients on NPH the correlation coefficient between change in cross-reacting antibody was 0.35, p-0.0005. There was no other significant correlation for NPH patients.

Trial 1205 with extension trial 1316

There were no deaths. Two subjects on Detemir withdrew because of severe AE's. One of these was worsening of necrobiosis diabetocorum. Major hypoglycemic events occurred in 14% of patients on Detemir and 21% of patients on NPH.

AE's related to "application site' was reported in 1.9% of patients on Detemir and 1.0% on NPH. "Allergic" AE's were reported in 2.3% of patients on Detemir and 1.0% on NPH.

Clinically significant worsening of fundoscopy was reported in 1.4% of patients on Detemir and 3% of patients on NPH. There were no clinically relevant differences in laboratory safety evaluations.

Mean body weight at –3 weeks was about 71.4 kg in both groups. There was a loss of 0.1 kg in Detemir patients, and gain of 1.2 kg in NPH patients. This difference of 1.34 kg at 52 weeks was statistically significant ($p=0.001$)

Trial 1335

There were no deaths. 2 Detemir patients were withdrawn because of severe hypoglycemia (MVA in one, seizure/coma in the other). Beyond the first month, major hypoglycemic events were reported in 6.5% of patients on Detemir and 8.9% on NPH During the first month, major hypoglycemic events were reported in 1.3% of patients on Detemir and 2.4% on NPH. Beyond the first month, major hypoglycemic events were reported in 6.5% of patients on Detemir and 8.9% on NPH.

"Retinal disorder" was reported as an AE in 2.4% of patients on Detemir and 0.8% on NPH. Mean systolic blood pressure decreased 2.4 mm on Detemir and 1.6 on NPH. Mean weight loss on Detemir was 0.2 kg compared to a mean gain of 0.4 kg on NPH. Adjusting for baseline the mean difference between body weight at six months was –0.52 kg (p=0.024). " No clinically relevant findings were observed for any clinical laboratory or vital signs assessments."

Mean data on serum antibodies are shown in the table below. Of significance (p<0.001 vs NPH) was a rise of 3.4 % (B/T) in Detemir –specific antibodies in patients treated with Detemir and 3.7% in cross-reactive antibodies in patients treated with Detemir.

Antibodies (% B/T), ITT	Insulin Detemir	NPH insulin
Detemir specific antibody		
Baseline	1.55	1.83
6 months	4.88	1.85
Insulin Antibodies		
Baseline	0.98	1.06
6 months	1.04	1.14
Cross-reacting antibodies		
Baseline	12.9	12.2
6 months	16.6	12.2

No correlation between antibodies at six months and HbA1c or FPG at six months. However, significant correlations existed between dose of Detemir at six months and level of antibody. After adjusting for baseline characteristics, the correlation coefficient was 0.13 (p=0.009) for Detemir-specific antibody and 0.21 (p=0.0000) for cross-reactive antibody.

Study 1447

One subject in the Detemir group died. This was a 22-year-old male who was found dead after three months of Detemir. His diary indicated that he had been experiencing

frequent episodes of hypoglycemia. 9/171(3.3%) had a serious AE. 2/129(1.6%) of patients on NPH had a serious AE. Six subjects were withdrawn from Detemir because of an AE (death, three injection site reactions, CVA, allergic reaction). None were withdrawn from NPH.

Major hypoglycemic events occurred during the last 12 weeks of treatment in 3.6% of patients on Detemir morning/dinner, 3.2% of patients on NPH and 3.9% of patients on Detemir morning + hs. Expressed as total number of episodes, 12 major hypoglycemic episodes occurred in the 100 patients on Detemir morning/dinner, 5 major hypoglycemic episodes occurred in the 100 patients on NPH, and 6 major hypoglycemic episodes occurred in the 92 patients on Detemir morning + hs.

From table 10.5 - 19/271(7%) of patients on Detemir experienced visual AE's compared to 3/129 (2.3%) on NPH. 9 patients on Detemir reported "retinal disorder" compared to one patient on NPH. Retinal hemorrhage/edema, vitreous detachment and abnormal vision were reported by 6 patients on Detemir and none on NPH. The text describes three subjects (all on Detemir) who experienced deterioration in retinal examination from baseline to endpoint. In one case this was attributed to a marked decrease in HbA1c from 9.2% to 6.9%. One patient on Detemir developed cataract.

Four subjects (1.5%) on Detemir had an injection site reaction compared to 1 (0.8%) on NPH.

Body Weight:

Body weight changes little during the trial. However, patients on Detemir with dinner lost 0.4 kg on average compared to gains of 0.4 kg in patients on Detemir bedtime and 0.8 kg in patients on NPH bedtime.

Body weight for ITT

Body weight, kg	Detemir dinner	NPH bedtime	Detemir bedtime
Baseline	75.9	74.5	76.7
16 weeks	75.5	75.3	77.1

Pairwise comparison for this change is:

Detemir dinner-NPH bedtime	-1.3	p<0.0001
Detemir Bedtime – NPH bedtime	-0.5	p=0.081
Detemir dinner-Detemir bedtime	-0.7	p=0.015

There were "no clinically relevant differences" in clinical laboratory measurements including lipids

Trial 1448

There were no deaths. Serious AE's were reported in 5.1% of Detemir subjects and 3.0% of NPH. Hypoglycemia was reported as serious events in 4 patients on Detemir (3 coma, one hypoglycemia reaction resulting in an MVA) and 1 patient on NPH (coma). 3 of the Detemir patients with severe hypoglycemia were in the q 12-hr arm and one in the am/hs arm. Major hypoglycemic events over the entire study were reported in 6.6% of patients on Detemir q 12 hr, 10.6 on NPH am/hs and 10.8% of patients on Detemir am/hs. Minor hypoglycemic events over the entire study were reported in 88% of patients n Detemir q 12 hr, 89% on NPH am/hs and 88% of patients on Detemir am/hs. Major hypoglycemic events occurred during the last 12 weeks of treatment in 4.4% of patients on Detemir q12, 7.8% of patients on NPH and 8.0% of patients on Detemir morning + hs. Expressed as total number of episodes, 9 major hypoglycemic episodes occurred in the 127 patients on Detemir q12hr, 12 major hypoglycemic episodes occurred in the 120 patients on NPH, and 24 major hypoglycemic episodes occurred in the 127 patients on Detemir morning + hs. Overall, there was little, if any, difference in hypoglycemia between Detemir and NPH.

Injection site reactions were reported by 2.9% of patients on Detemir and no patients on NPH.

There were 3 subjects in the Detemir group found to have progression of retinopathy by fundoscopy. There were none with NPH. 1.4% on Detemir reported "retinal disorder" as an AE compared to 3.8% on NPH.

Body Weight:

Body weight changes little during the trial. There was no change for patients on Detemir compared to gains of 0.2 kg in patients on Detemir am/bedtime and 0.7 kg in patients on NPH am/bedtime.

Body weight for ITT (from table 4.32

Body weight, kg	Detemir q 12 hr	NPH am/hs	Detemir am/hs
<-2 weeks	74.5	75.7	75.2
16 weeks	74.5	76.4	75.4

Pairwise comparison for this change is:

Detemir 12 hr-NPH am/hs	-0.8	p<0.0061
Detemir am/hs – NPH am/hs	-0.6	p=0.04
Detemir dinner-Detemir bedtime	-0.2	p=0.4

There were "no clinically relevant differences" in clinical laboratory measurements including lipids.

Trial 1374

There was one death, due to a lung tumor, in a patient taking NPH insulin plus HSI.

SAE's related to hypoglycemia was reported in four patients on Detemir + aspart and one on NPH + HSI. These include two cases of hypoglycemic coma on Detemir and one on NPH. Two patients on Detemir plus aspart withdrew because of injection site reactions. Hypoglycemia (all types) was reported by 75% of Detemir patients compared to 83% of patients on NPH. There were 2497 events for Detemir and 3192 for NPH ($p=0.036$). 19 patients on Detemir reported 40 major hypoglycemic events compared to 18 patients on NPH who reported 45 events. Four episodes of major nocturnal hypoglycemia was reported by 3 patients on Detemir. 12 patients reported 24 events on NPH ($p<0.001$). A major event was one in which the patient was unable to treat himself/herself.

Change in body weight: On Detemir plus aspart, patients lost a mean of 0.8 kg over 18 weeks compared to a mean gain of 0.1 kg ($p< 0.001$) with NPH + HSI.

Trial 1372

There were no deaths. SAE's classified is probably/possibly related to trial product were as follows: One patient on Detemir was hospitalized because hypoglycemia after 116 days of treatment. Three patients on Glargine were hospitalized because of hypoglycemia after 37, 68, and 152 days of treatment. One patient on Glargine was hospitalized because of proliferative retinopathy and withdrew from the study. There were two additional cases of hypoglycemic coma where attribution to trial product was considered "unlikely". There was one patient on Detemir (subject 12308) and one subject on Glargine (13006).

During the 20 week maintenance phase, 3 (1.9%) patients on Detemir reported 4 episodes of major hypoglycemia and 12 (7.8%) patients on Glargine reported 15 events. The relative risk of a major episode during the 20 week maintenance was calculated by the Sponsor to be 0.28 ($p<0.047$). During the first six weeks, 5 patients on Detemir reported 6 events and 7 patients on Glargine reported 9 events.

Patients on Detemir gained a mean of 0.5 kg. Patients on Glargine gained a mean 1.0 kg ($p=0.193$).

Application site disorder was reported by 4/161 (2.5%) patients on Detemir and 2/159 (1.3%) patients on Glargine. Retinal disorder was reported by 1/161 (0.6%) patients on Detemir and 4/159 (2.5%) patients on Glargine.

Safety - Type 2 diabetes:

Trial 1166

There was one death in each arm, but neither appeared to be drug-related. One severe hypoglycemic event characterized as serious AE's occurred in each arm. Two patients on Detemir withdrew because of hyperglycemia and one because of injection site reaction. Other withdrawals (4 on Detemir, 2 on NPH did not appear to be related to study drugs. Major hypoglycemic events occurred in 1% of patients on Detemir and 2% in patients on NPH.

The number of subjects judged to have clinically significant change in fundoscopy at 6 months vs baseline was 4 subjects on Detemir and 6 on NPH. Patients on Detemir lost an average of 0.4 kg compared to an average gain of 1.8 kg on NPH. There were no clinically significant changes identified in routine safety monitoring including lipids.

Trial 1336

There was one episode of sudden death on Detemir, a 69-year-old male who was found dead in his hotel bed on day 97. He had had a coronary bypass previously. In addition to the death, seven other patents on Detemir withdrew because of an AE compared to one on NPH. One patient on Detemir withdrew because of pruritits. The other withdrawals did not appear to be drug related. Major hypoglycemic events occurred in 1.8% of patients on Detemir and 1.9% on NPH. Body weight before and after the trial are shown in the table below.

Body weight for ITT

Body weight, kg	Detemir	NPH
<-3weeks	85.4	89.7
26 weeks	85.8	91.0

There were no clinically significant changes identified in routine safety monitoring including lipids.

Trial 1337

There were 3/309 deaths on Detemir and 0/158 on NPH. Two of the deaths were CVA's. The third was a patient who was found with agonal respiration. He was presumed to have died of underlying cardiac disease. In addition to the three deaths, serious AE's were reported in 18 Detemir patients, none of which could reasonably be attributed to the drug. Serious AE's were reported in 10 NPH patients, one case of hypoglycemic coma which could reasonably be attributed to the drug. Adverse event leading two withdrawals occurred in 9 Detemir patients and 5 NPH patients. In two of the Detemir patients, the AE was an injection site reaction that could reasonably be attributed to the study drug. Application site hematomas were reported in 5.2% of Detemir patients and 3.2% on NPH. Application site reactions were reported in 5.5% of Detemir patients and 5.7% on NPH.

Major hypoglycemic reaction occurred in no Detemir patients and one patient on NPH. Triglyceride > 1000 mg/dl developed in 2 Detemir patients and no NPH patients. Worsening of fundoscopy occurred in 3.6% of Detemir patients and 3.2% NPH. The mean weight change in the Detemir group was –0.4 kg compared to +0.4 kg for the NPH group (p=.014). According to Novo Nordisk, this difference persisted even after adjusting for change in differences HbA1c. There were decreases in FFA and triglycerides in both groups. Otherwise there were no clinically significant changes in any of the safety measurements.

Trial 1530

There were two deaths, both on NPH insulin. Neither death appeared related to study drug.

Severe adverse events: One patient had an accidental overdose of Detemir. By mistake, he took his morning dose of 66 units in the evening instead of the prescribed 10 units. He was admitted to the hospital with a glucose of 8.1 mM, treated with intravenous glucose, and discharged. This case was scored as major hypoglycemia even though the patient never became hypoglycemic*. Eight major hypoglycemic episodes were experienced by 6 patients on NPH. Five of the NPH patients were hospitalized with seizure or loss of consciousness and recovered. The sixth NPH patient had a seizure and recovered but was not hospitalized. 908 hypoglycemic episodes were experienced by 151 (64%) patients on Detemir. 1688 hypoglycemic episodes were experienced by 191(80.3) patients on NPH. The relative risk of an episode (Detemir/NPH) was 0.53, 95% CF 0.42-0.68).

The following table gives the findings for hypoglycemia. All comparisons favor Detemir with $p<0.001$. A "major" event is when a patient requires assitance. A 'minor" event is symptoms suggesting hypoglycemia documented with BG, 3.1mM.

	Insulin Detemir			NPH Insulin			
	N=	%	episodes	N=	%	episodes	Rel Risk
All Episodes	151	64%	908	191	80%	1688	0.53
Nctrnl	71	30%	160	112	47%	349	0.45
MAJOR	1*	0.4%	1*	6	2.5%	8	
Nctrn	0	0	0	1	0.4%		
MINOR	96	40%	387	153	64%	755	0.48
Nctrnl	40	17%	74	84	35%	187	0.39

Nctrnl=nocturnal; N=number of patients and % with at least one episode;

Mean weight gain on Detemir was 1.2 kg compared to 2.8 kg on NPH ($p<0.001$).

Application site AE's were reported in 5.5% of patients on Detemir and 2.5% of patients on NPH. One patient on Detemir withdrew because of "insulin allergy" and one patient on NPH withdrew because of an application site AE.

Appears This Way
On Original

Summary of median antibody levels are shown in the table that follows. These values are specific binding (%bound/total) from which non-specific binding has been subtracted. This explains some slightly negative values, which should be interpreted as zero. The results indicate that Detemir stimulates production of specific antibodies to itself more than NPH stimulates antibodies to human insulin. Production of cross-reacting antibodies is much greater with Detemir and than with NPH. The finding of specific anti-Detemir antibodies at baseline is an enigma because patients had never previously been exposed to Detemir.

	Baseline Median (p5%-p95%)	24 week, EOS Median (p5%-95%)
INSULIN DETEMIR:		
Detemir specific	1.6 (0.8-2.8)	3.7 (1.1-24.4)
Human Insulin specific	0.1 (-0.3-0.7)	0.1 (-0.4 – 0.8)
Cross-reacting	-0.2 (-0.7-0.5)	10.7 (-0.3-52.5)
NPH Insulin		
Detemir specific	1.6 (0.8-3.0)	1.5 (0.7-2.6)
Human Insulin specific	0.1 (-0.4-0.8)	0.2 (-0.3-2.3)
Cross-reacting	-0.2 (-0.8-0.7)	1.7 (-0.5 – 63.2)

There was a positive correlation in both groups between antibody binding and final insulin dose but no correlation with change in HbA1c.

Conclusions from Trial 1530:

Detemir and NPH were equally effective at lowering Hb1c in these insulin-naïve patients with type 2 diabetes, although the dose of Detemir was approximately 50% greater than the dose of NPH. Patients on Detemir gained less weight and had fewer episodes of hypoglycemia. Of particular importance is that six patients on NPH suffered eight episodes of seizure or loss of consciousness related to hypoglycemia* compared to no patients on Detemir. Although the HbA1c reduction was equivalent, it is clear that Detemir was the better treatment.

Trial 1385

There was one episode of sudden death on Detemir/aspart.

SAE's possibly related to trial drug: One patient on Detemir/aspart had an accidental insulin overdose that was treated with glucose although he never had hypoglycemia. Two patients on NPH/HSI had hypoglycemic coma and a third temporarily discontinued study drugs because of severe hypoglycemia. During the maintenance period 2/65 patients on Detemir/aspart had 2 episodes of major hypoglycemia compared to 1/70 patients on NPH/HSI that had one episode.

Patients on Detemir/aspart gained a mean 0.52 kg vs a gain of 1.15 kg (p=0.036) on NPH/HSI.

Safety Update

The 120 Days Safety Update was submitted 4/4/05 and covered the period through January 15, 2005. The safety update contained information about patients in a recently completed comparison of Detemir to Glargine in type 2 diabetes (trial 1373) and patients in ongoing trials. The only noteworthy safety finding is that 5.8% of patients on Detemir compared to 3.4% of patients on Glargine reported "application site disorders".

Detemir is currently marketed in Europe and Australia. Through January 1, 2005, serious adverse events have been reported spontaneously in eight subjects. Two cases were noteworthy for swelling, reddening, and itching at the injection site. The other cases appeared unrelated to Detemir or consisted of fluctuations in glycemic control that are seen in patients with diabetes and are often attributed to changes in medication.

Comments on Safety:

There were two deaths among patients with type 1 diabetes treated with Detemir. The circumstances surrounding these cases suggest that the deaths may have been the consequence of poor glycemic control. There was one death in a NPH-treated patient. This death was due to lung cancer. Total exposure among patients with type 1 diabetes in phase 3 clinical trials was 1723 for Detemir and 1273 for NPH.* The death rate observed in these trials is not very different from the 1.2 deaths per 1000 patients years reported in the DCCT trial (NEJM 1993, 329:977-86). In patients with type 2 diabetes, there were 6/1293 deaths on Detemir and 3/966 on NPH in the phase 3 clinical trials. Underlying cardiovascular disease probably caused all of these deaths.

The number of serious adverse events was similar between Detemir and NPH.

The primary safety issues related to Detemir and all insulin products are hypoglycemia, weight gain, injection site reactions, and immunological issues. These issues must be evaluated in the context of specific trials. For insulin products, efficacy and safety cannot be evaluated independently. Hypoglycemia and weight gain are consequences of effective treatment of hyperglycemia. A more effective product would be expected to cause more hypoglycemia and more weight gain. The safety of an insulin product must therefore be evaluated in the context of the efficacy found in individual trials.

*Although not reviewed here in detail, there were no deaths among the 232 pediatric patients with type 1 diabetes treated with Detemir. There were no deaths in the 115 pediatric patients treated with NPH.

Appears This Way
On Original

Hypoglycemia:

The risk of hypoglycemia is the limiting factor that prevents patients with type 1 diabetes (and to a lesser extent type 2) from achieving diurnal glucose levels that are similar to normal. The central nervous system dysfunction caused by severe hypoglycemia can lead to coma or seizures. Hypoglycemia while driving can be a cause of automobile accidents in patients taking insulin.

Given the importance of hypoglycemia, it is not surprising that insulin manufacturers have developed products that they believe decrease the risk of hypoglycemia and have attempted to convince FDA to allow this information to be put in the product label. So far, none have made a convincing case. I have summarized some of the issues/problems relating to label claims about the risk of hypoglycemia:

Reporting bias: Insulin trials are unblinded. Thus, there is concern that knowledge of who is taking the test drug may influence reporting. Even with respect to hypoglycemia requiring assistance, someone has to make the judgment that an event was due to hypoglycemia and report that event to the investigator who then reports it to the Sponsor.

Trial design: Given the different time courses of different insulin preparations, it is possible to "stack the deck" to show an advantage of one product over another. For instance, if all the basal insulin were taken as a single dose at night, patients on a long-acting insulin would show less hypoglycemia than patients on NPH. But that difference would likely disappear if the NPH could be split. Also, patients taking short acting insulin before each meal will tend to have more hypoglycemia during the day and less at night than patients who take regular insulin before each meal. As noted in a recent paper by a workshop of the American Diabetes Association, a decrease in hypoglycemia at night is not an advantage if it is offset by increased hypoglycemia at other times of the day (Diabetes Care May 2005)

Definition: The less severe the event, the more likely that that event may be caused by something other than hypoglycemia. But limiting the definition to very severe episodes (seizure or coma) would require very large trials to detect a difference between treatments.

Clinical significance: Hypoglycemia commonly occurs at night. Sponsors have attempted to promote their products on the basis of a presumed advantage with respect to risk nocturnal hypoglycemia. But I have not heard a convincing argument why hypoglycemia at night is more important than hypoglycemia at other times of the day. To the contrary, I would expect that a hypoglycemic attack on the freeway at noon would be more likely to have irreversible consequences than a hypoglycemia attack in bed at midnight.

Statistical significance: Insulin trials generally have non-inferiority with respect to HbA1c as the primary objective. Hypoglycemia, like most safety measures, is a secondary endpoint. The use of multiple definitions of hypoglycemia invites Sponsors to "cherry pick" the definition that favors their product. The use of different doses of

different insulins in the same treatment arm (bolus + basal) makes attribution of a hypoglycemic event difficult. Finally, differences in hypoglycemia between treatments cannot be interpreted without reference to change in HbA1c.

Interpretation of hypoglycemia data from the Detemir trials have many of the problems outlined above. Of particular importance is that Detemir was not non-inferior to NPH with respect to HbA1c in some trials. In other trials, Detemir had to be "helped" to achieve non-inferiority by the use of extra amounts of bolus insulin. However, there are two Detemir trials in which the Sponsor's conclusions about hypoglycemia may be justified.

Trial 1530 was a head-on comparison of Detemir to NPH insulin in insulin-naïve patients with type 2 diabetes. Mean reduction of HbA1c was nearly 2% units in both groups. However, Detemir was superior to NPH in all comparisons regarding hypoglycemia. Even though the hypoglycemia measures were secondary variables, the very low p values ($p<0.001$) calculated by the Sponsor strongly suggest that the findings were real. There were too few major hypoglycemic events to permit statistical analysis, but 6/227 patients on NPH experienced seizures or loss of consciousness compared to none on Detemir. Even in an unblinded trial, the potential importance of these findings is inescapable.

Trial 1375 was a cross-over comparison of Detemir to NPH in patients with type 1 diabetes
earlier,

The hypoglycemia findings in trial 1448 are virtually the same for both Detemir and NPH. Although Detemir is favored by some measures of hypoglycemia in some of the other trials, the findings are inconsistent and/or not convincing.

In conclusion, I am not convinced that Detemir should be labeled
On the other hand, it would be inappropriate to require that the Sponsor withhold the potentially important data generated by trial 1530. As a way of reconciling these seemingly conflicting positions, I am recommending that data on hypoglycemic episodes in pivotal trials be presented

Weight gain:

On average, patients treated with Detemir either lost weight or gained less weight than patients treated with NPH. This was a consistent finding. In some trials, this difference in weight could reflect inferiority of Detemir to NPH with respect to treatment of hyperglycemia. In other trials, however, the relative lack of weight gain among Detemir-treated patients cannot be explained on the basis of inferior glycemic control. The following table shows changes in body weight for Detemir vs NPH is trials in which Detemir was clearly non-inferior to NPH with respect to HbA1c reduction.

	Trial #	Insulin	HbA1c change	Weight chng, kg
Type 1 diabetes	1447	Detemir/dinner	-0.53	-0.4
		NPH hs	-0.39	+0.8
		Detemir hs	-0.49	-0.4
	1448	Detemir q 12	-0.80	0
		NPH am/hs	-0.60	+0.7
		Detemir am/hs	-0.84	+0.2
	1474	Detemir/aspart	-0.66	-0.8
		NPH/regular	-0.37	+0.1
Type 2 diabetes	1530	Detemir	-1.84	+1.2
		NPH	-1.90	+2.8

The reason why Detemir is less likely to promote weight gain than NPH is not clear. One possible explanation is that greater reproducibility of absorption leads to more efficient eating behavior because of less variation in glucose levels. An other possibility, is that Detemir's fatty acid side chain makes it more likely than insulin to gain access to appetite satiety sites in the brain.** Regardless of mechanism, weight loss relative to NPH insulin would translate into a major clinical advantage if the effect were sustained over time.

** Insulin administration into the brain has been shown to decrease food intake (Nature 282,503, 1979).

Injection site findings

Injections site findings occurred in approximately 2% of patients on Detemir and 1% of patients on NPH in the trials of patients with type 1 diabetes. For insulin-naïve patients with type 2 diabetes, injections site findings occurred in approximately 5.5% of patients on Detemir and 4% of patients on NPH. In comparisons to Glargine, 2.5% of patients with type 1 diabetes who received Detemir had an injection site finding compared to 1.3% of patients on Glargine. From the safety update, 5.8% of patients on Detemir with type 2 diabetes in ongoing trial 1373 had an injection site finding compared to 3.4% of Glargine. From these results, it is reasonable to conclude that injection site findings are more frequent with Detemir than with other basal insulins. It is also worth noting that injection site findings were more frequent in insulin-naïve patients than in patients who had previously received insulin.

Immunological issues:

Insulin allergy:

Two patients withdrew because of "allergy" to Detemir. One patient had type 1 diabetes and had previously been on NPH insulin. The second patient had type 2 diabetes and had not previously taken insulin.

Insulin antibodies:

Insulin Detemir appeared to be more antigenic than NPH insulin. However, the difference appeared to have little, if any, clinical significance. There was a weak correlation (Spearman coefficient about 0.2) between antibodies and the dose of Detemir. There was no correlation between antibodies in HbA1c. Thus it appears that the possible effect of anti-Detemir antibodies could be overcome by a small increase in dose. A protocol for the method of detecting specific and cross-reacting antibodies is shown below. I believe this is sound methodology. Particularly important is subtraction of non-specific binding.

Methodology for Measuring Insulin Antibodies:

Series	Assay Mixture	Result represents the sum of:
A	Sample + buffer Insulin tracer	Background, insulin-specific and cross-reacting antibodies
B	Sample + cold Insulin + insulin tracer	Background with insulin tracer
C	Sample +cold Detemir +insulin tracer	Background and insulin specific antibodies
E	Sample +cold Detemir +Detemir tracer	Background with Detemir tracer
F	Sample +cold insulin +Detemir tracer	Background and Detemir antibodies

Insulin specific antibodies = C-B

Detemir-specific antibodies = F-E

Cross-reacting antibodies = A-C

2 Page(s) Withheld

____ § 552(b)(4) Trade Secret / Confidential

____ § 552(b)(5) Deliberative Process

✓ § 552(b)(5) Draft Labeling

Post-marketing Commitments:

IX. Use in Special Populations

Review of pediatric studies is pending

X. Conclusions and recommendation:

Insulin Detemir appears to be as effective as NPH insulin as long as patients receive adequate doses of Detemir. For patients with type 1 diabetes, one unit of Detemir is approximately equal to one unit of NPH. However, for patients with type 2 diabetes, the effectiveness of one unit of Detemir is less than one unit of NPH. Broadly speaking, the average patient with type 1 diabetes who is well controlled on 30 units of NPH can expect similar glycemic control if switched to 30 units of Detemir. By contrast, the average patient with type 2 diabetes who is well controlled on 30 units of NPH will probably require about 40-50 units of Detemir. This should not be a major problem, particularly with insulin-naïve patients, because there is no fixed dose for insulin. The doses of all insulin products are adjusted according to glucose levels.

The advantage of Detemir over NPH is that the action of Detemir probably has less intra-patient variability. At least for patients with type 2 diabetes, there appears to be less hypoglycemia with Detemir than with NPH at the same level of HbA1c. An additional advantage of Detemir is that it causes less weight gain than NPH. If sustained over the life of a patient, this weight-sparing effect of Detemir would be a major advantage over NPH.

The major competitor that Detemir will face is Insulin Glargline (Lantus). A study (trial 2175) comparing Detemir to Glargine is already underway in patients with type 2 diabetes. Of particular significance is that this trial is being conducted in the United States in order to provide data on the ethnic groups with type 2 diabetes that exist in the USA. This trial should answer the lingering question about ethnic differences in responsiveness to Detemir.

The efficacy and safety of Insulin Detemir has been established for patients with type 1 and type 2 diabetes. Pending revisions to the label, Insulin Detemir can be approved.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Robert Misbin
6/10/05 06:11:28 PM
MEDICAL OFFICER

Detemir NDA

David Orloff
6/13/05 04:42:57 PM
MEDICAL OFFICER

MEDICAL OFFICER REVIEW

Division of Metabolic and Endocrine Drug Products (HFD-510)

APPLICATION #:	**NDA 21536**	**APPLICATION TYPE:**	**New NDA.....**
SPONSOR:	**Novo Nordisk**	**PROPRIETARY NAME:**	**Levemir.....**
CATEGORY OF DRUG:	**Antidiabetic**	**USAN / Established Name:**	**Insulin Detemir.....**
MEDICAL REVIEWER:	**Robert I Misbin..**	**REVIEW DATE:**	**Sep 5, 2003.....**

SUBMISSIONS REVIEWED IN THIS DOCUMENT

Document Date:	CDER Stamp Date:	Submission Type:	Comments:
December 5 2002	December 9 2002	Original NDA	
April 7, 2003	April 8, 2003	Safety update	

The application contains data from ten phase 3 controlled clinical trials, seven trials (five original and two extension trials) in patients with type 1 diabetes and three trials in patients with type 2 diabetes.

Summary and Recommendation:

For patients with type 1 diabetes, Insulin Detemir appears to be as effective as NPH insulin. However, for patients with type 2 diabetes, the effectiveness of Detemir has not been convincingly demonstrated. Subset analysis of the data in type 2 diabetes suggests that the decreased efficacy of Detemir may be limited to white patients only. In black and Hispanic patients, Detemir and NPH gave similar results. This finding in type 2 diabetes calls into question the results of the trials in type 1 diabetes, because the trials of type 1 diabetes had virtually no black and Hispanic patients. If the ethnic/racial difference found in type 2 diabetes were true for patients with type 1 diabetes as well, black and Hispanic patients with type 1 diabetes patients would be at risk of hypoglycemia if dosed according to the proposed label. For these reasons, I believe that Detemir should not be approved until additional studies are performed with African American and Hispanic patients.

Signed: **Medical Reviewer:** **Robert I Misbin MD** **Date Sep 5, 2003**

Medical Team Leader: _____ **Date:** _____

Table of Contents: 2

Executive Summary:

1. Recommendations:

For patients with type 1 diabetes, Insulin Detemir appears to be as effective as NPH insulin. However, for patients with type 2 diabetes, the effectiveness of Detemir has not been convincingly demonstrated. Subset analysis of the data in type 2 diabetes suggests that the decreased efficacy of Detemir may be limited to white patients only. In black and Hispanic patients, Detemir and NPH gave similar results. This finding in type 2 diabetes calls into question the results of the trials in type 1 diabetes, because the trials of type 1 diabetes had virtually no black and Hispanic patients. If the ethnic difference found in type 2 diabetes were also present in type 1 diabetes, non-white patients with type 1 diabetes would be in danger of being overdosed if given Detemir according to a dosing regimen used for white patients.

Insulin Detemir does not offer any major advantage over NPH. Both need to be given twice daily in patients with type 1 diabetes to obtain good glycemic control. Therefore, a delay in the approval of Detemir will not deprive patients of the benefits of an improved insulin. For these reasons, I believe that Detemir should not be approved until additional studies are performed with African American and Hispanic patients.

2. Summary of Clinical Findings

The application contains data from ten phase 3 controlled clinical trials. There were seven trials (five original and two extension trials) in patients with type 1 diabetes and three trials in patients with type 2 diabetes. One of the trials in patients with type 2 diabetes took place in the United States. No American patients with type 1 diabetes were studied.

The studies were randomized open-label comparisons of Insulin Detemir to NPH insulin. Randomized comparison in two of the trials in type 1 diabetes lasted 16 weeks. In all other trials the duration of randomized comparison was six months.

Patients with type 1 diabetes received Detemir or NPH as basal insulin in addition to boluses of rapid acting insulin (regular human insulin or insulin aspart) before meals. A similar basal/bolus regimen was used in one of the trials of patients with type 2 diabetes.

The demonstration of efficacy was based on a non-inferiority comparison to NPH insulin with respect to HbA1c. But the concomitant use of rapid acting insulin complicates interpretation of the efficacy results.

Type 1 Diabetes:

Of the five phase 3 studies, only trial 1448 is clearly positive. I consider this to be the pivotal trial and describe it in detail below. Being only supportive, the other trials are summarized here only briefly.

Trials 1181 and 1243 were done with a formulation of Detemir that has half the concentration as the to-be-marketed formulation. Trial 1181 was a six month randomized comparison of Detemir and NPH. Trial 1243 was a 24-week extension of trial 1181 Although the non-inferiority test was nominally met, additional regular insulin was used in the Detemir group. Therefore this should not be used as a pivotal study to establish that Detemir is non-inferior to NPH for treatment of type 1 diabetes. The claim of durability appears to be valid.

Trial 1205 was a 24-week randomized comparison of Detemir and NPH. Trial 1316 was a 24-week extension of trial 1205. Trials 1205 and 1316 were done with a formulation of Detemir that has half the concentration of the to-be-marketed formulation. Although the non-inferiority test was nominally met, additional bolus insulin (insulin aspart) was used in the Detemir group. Therefore this should not be used as a pivotal study to establish to that Detemir is non-inferior to NPH for type 1 diabetes. However, the efficacy of Detemir does appear to last 12 months. An additional finding is that Detemir appeared more effective than NPH with respect to lowering FPG. This is consistent with the longer duration of action of Detemir, brought out in this study because the bolus insulin was the rapid acting insulin aspart (as opposed to trials 1181/1243 in which regular insulin was used)

Trial 1447 was a 16 week randomized comparison of Detemir with NPH. Patients used insulin aspart as bolus insulin before meals. Although insulin Detemir nominally met the test of non-inferiority to NPH insulin, patients on Detemir received somewhat more insulin than patients on NPH. Trial 1447 did not clearly establish the non-inferiority of Detemir relative to NPH.

Trial 1335 was a six month comparison of Detemir 2400 nmol/mL and NPH each given once daily at bedtime in patients with Type 1 diabetes who use boluses of regular insulin before meals. Detemir given once a day was approximately as effective as NPH once a day, but neither was effective in achieving good control. The glycemic goals were not met. The decrease in the dose of basal insulin given as Detemir was compensated for by an increase in the dose of regular. Therefore, the non-inferiority of Detemir relative to NPH was not clearly established. The results indicate that both Detemir and NPH need to be given more than once daily in order to achieve good glycemic control.

Trial 1448

This was a 16 week trial comparing NPH insulin to two regimens of insulin Detemir (2400 nmol/mL), and NPH insulin (600 nmol/mL). The NPH was given in the morning and at bedtime. In one arm, Detemir was given in the morning and at bedtime. In a second arm, Detemir was given every 12 hours. For the sake of simplicity, these arms are referred to as NPH am/hs, Detemir am/hs and Detemir q 12hr. All patients received boluses of insulin aspart before meals. This was designed to be a superiority trial. The

primary measure of efficacy was HbA1c at 16 weeks using the ITT population. The trial was conducted at 40 Centers in Europe, Australia, and New Zealand.

The trial population consisted of patients with type 1 diabetes, BMI < 35, HBA1c< 12%, basal insulin dose at least 30% of total insulin dose and total basal insulin requirement of 100 units or less.

Patients who were previously receiving once daily basal insulin were transferred to twice daily regimen with 25-30% in the morning and 70-75% pre-dinner/bedtime. The starting dose of Detemir (on a molar basis) was recommended to be 2.8 times the previous dose of basal insulin. The starting dose of NPH was recommended to be 70% the previous dose of basal insulin. There was an expectation that the doses of both basal insulins would be increased during the titration period and that the final dose of Detemir (on a molar basis) would be increased to approximately 4x the dose of NPH. This means that the expected final volume of NPH and Detemir would be approximately the same.

The insulin dose was titrated with the goal of premeal and night time (2:00-4:00 am) to be 72-126 mg/dl and 90 min post-prandial glucose to be < 180 mg/dl. During the first 4 weeks, it was recommended that the dose of basal insulin be adjusted while the dose of bolus insulin remained constant. The weeks following initial titration were used to finely adjust the doses of both bolus and basal insulin.

The ITT population was 53% male, 99% white (one black patient on Detemir and one on NPH), mean age about 40 years with 16 years of diabetes, mean BMI 25. At baseline mean HbA1c was about 8.6% and mean FPG was about 11.7 mM. The mean dose of basal insulin was bout 0.37 U/kg and the mean dose of bolus insulin was about 0.40 U/kg. 3/137 patients withdrew from the Detemir q 12 hour arm because of 'ineffective therapy", 1/133 from the NPH am/hs arm and zero from the Detemir am/hs arm.

HbA1c for ITT (from table 4.4)

HbA1c	Detemir q12	NPH am/hs	Detemir am/hs
<-3 weeks	8.56 (n=133)	8.51 (n=125)	8.71 (n=134)
16 weeks	7.76	7.91	7.87

Accounting for the slight differences in baseline, the change in HbA1c was -0.8 for Detemir 12 hr, -0.6 for NPH am/hs and -0.84 for Detemir am/hs. Nonoe of these were statistically different from each other.

Pre-study Dose of insulin for ITT

	Detemir q 12hr	NPH am/hs	Detemir am/hs
Basal U or IU	26.4	29.5	28.1
Bolus	30.9	30.5	29.4

Dose of insulin at end of 16 weeks: ITT

	Detemir q 12hr	NPH am/hs	Detemir am/hs
Basal U or IU	36.7	34.8	36.3
Bolus	27.9	29.4	29.4

Comparisons of Daily Dose of Insulin at 16 weeks

	Detemir q 12hr	NPH am/hs	Detemir am/hs
Basal U or IU	36.7	34.8	36.3
Ratio (Detmr/NPH)	1.06	1.00	1.04
	Detemir q 12hr	NPH am/hs	Detemir am/hs
Bolus U or IU	27.9	29.4	29.4
Ratio (Detmr/NPH)	0.95	1.00	1.00

Insulin Detemir U = 24 nmol
NPH insulin IU= 6 nmol
Insulin aspart IU = 6 nmol

Summary: Insulin Detemir met the test of non-inferiority to NPH insulin without additional amounts of bolus insulin. This is the pivotal study to support approval for type 1 diabetes. As is noted in other studies, Detemir is more effective than NPH at lowering FPG. This finding is consistent with Detemir's longer duration of action.

Type 2 diabetes:

Of the three phase 3 studies, none clearly establish the efficacy of Insulin Detemir. Trial 1337 is the only trial done in the United States and is the most informative of the three trials in type 2 diabetes. It is summarized here in detail. The two earlier trials are summarized only briefly.

Trial 1166 was a six-month comparison of Detemir and NPH as the only form of therapy in patients with type 2 diabetes. Detemir was found to be inferior to NPH insulin. But Detemir was administered at 1200 nmole/ml, one half the concentration of the to-be-marketed formulation. The Sponsor has argued that patients were reluctant to administer the large volumes of Detemir that would have been needed to demonstrate non-inferiority to NPH.

Trial 1336 was a six-month comparison of Detemir to NPH in patients with type 2 diabetes who had previously been on an insulin regimen. Insulin aspart was given before meals. Although Insulin Detemir nominally met the test of non-inferiority, patients on Detemir received additional amounts of bolus insulin (insulin aspart). Therefore, this should not be considered a pivotal trial to establish efficacy.

APPEARS THIS WAY
ON ORIGINAL

Trial 1337

This was a randomized six month trial of Detemir (2400 nM) vs NPH (2:1) in combination with metformin. The trial was performed at 72 sites in the USA and Puerto Rico.

The trial population was patients with type 2 diabetes who had been on metformin, either alone or in combination with other oral antidiabetic agents. There was a two-week washout of other oral agents during which time the dose of metformin was "optimized" to 2000-2550 mg/d or maximum tolerated dose. Patients who failed to reach FPG of 7 mM (126 mg/dl) were randomized to Detemir or NPH as a single evening dose. This regimen of metformin plus Detemir/NPH was maintained for six months.

The trial was designed to test non-inferiority of Detemir vs NPH. HbA1c at six months in the ITT population was the primary endpoint with a margin of 0.4% units.

467 patients were randomized (309 to Detemir and 158 to NPH), and 405 (266 and 139) completed the study. There were 12% withdrawals of Detemir and 11% on NPH. This difference in withdrawals was accounted for by "ineffective therapy" in 2.6% of patients on Detemir and none on NPH. Of the 8 patients who withdraw because "ineffective therapy", 5/8 had been on Met+TZD, 2/8 on Met w/o TZD, and 1/8 on Met alone. Randomized patients had a mean age of 56 years, 6 years of diabetes 60% Caucasian, 6% white, 30% Hispanic, mean body weight 90 kg, BMI 31.5. The Detemir group was 51% male. The NPH group was 59% male. Previous antidiabetic therapy was metformin alone, 19%, Met + TZD 37%, Met combo w/o TZD 44%. The mean dose of metformin was about 2200 mg.

Insulin Detemir (1U=24 nmol) or NPH (U=6nmol) were initiated at 0.1U/kg for FBG<180 mg/dl or 0.2 U/kg for FBG>180mg/dl. The dose was then increased every three days to achieve a goal of FBG of 7 mmol/L. The mean initial dose of insulin was 0.17 U/kg for Detemir and 0.16 U/kg for NPH, about 15 units in both groups. At endpoint the mean dose of Detemir was 0.57 U/kg (about 51 units), compared to 0.45 U/kg (about 41 units) for NPH. The molar ratio Detemir/NPH was 4.19 at baseline, 4.8 at 2 months, and 4.98 at endpoint.

As shown in the table below, HbA1c values fell significantly in both arms. But the HbA1c value at EOS was lower in the NPH group than in the Detemir group. Because the upper limit of the 95% CI is 0.78 (>0. 4% units), the predefined criterion for non-inferiority was not fulfilled.

HbA1c values in Modified ITT population

	Detemir	NPH	Diff (95% CI)
Baseline	9.5	9.4	0.01
EOS	8.5	8.0	0.56 (0.33- 0.78)
Change from baseline	-0.9	-1.5	
P value	<0.0001	<0.0001	

FPG was the same in both groups at baseline (246 mg/dl) and endpoint (154mg/dl).

HbA1c response based on subgroups:

The Sponsor performed the following sub-set analysis based on pretrial antidiabetic medication (metformin only, metformin plus TZD, metformin combo w/o TZD).

Metformin Only

	Detemir	NPH	Diff (95% CI)
Baseline	9.4	9.6	
EOS	7.8	7.7	-0.307,0.853
Change from baseline	-1.5	-2.0	
P value	<0.0001	<0.0001	
Metformin Dose	2065(1000-2550)	2112(1500-2550)	

Metformin Combo with TZD

	Detemir	NPH	Diff (95% CI)
Baseline	9.4	9.4	
EOS	8.7	8.0	0.23,1.15
Change from baseline	-0.6	-1.4	
P value	<0.0001	<0.0001	
Metformin Dose	2173(1000-2550)	2201(1000-2550)	

Metformin Combo without TZD

	Detemir	NPH	Diff (95% CI)
Baseline	9.6	9.4	
EOS	8.6	8.1	0.076, 0.81
Change from baseline	-0.9	-1.4	
P value	<0.0001	<0.0001	
Metformin Dose	2201(1500-2550)	2252(1000-2550)	

Based on this subset analysis, the Sponsor contends that Detemir met the test of non-inferiority to NPH in the metformin-only subset. However, this contention, upon further analysis, seems poorly founded:

At the request of DMEDP, the Sponsor provided the doses of metformin at screening, baseline, and endpoint as well as the HbA1c at screening and baseline. As shown in the tables below, there was an increase in the dose of metformin from screening to baseline in all groups. This is referred to as "optimization of metformin therapy" in the protocol. In the metformin-only subset, this change represented intensification of therapy and is manifested by fall in HbA1c and FPG **before** randomization. Thus some of the efficacy attributed to Detemir and NPH was probably a delayed effect of the increased dose of metformin. The claim of non-inferiority of Detemir to NPH is not valid because the contribution to total efficacy of the increased dose of metformin cannot be quantitated. By contrast, discontinuation of the other oral hypoglycemic agents in the metformin combo subsets led to exacerbation of hyperglycemia. Under these circumstances, Detemir was clearly inferior to NPH.

Mean doses of Metformin, mg

	INSULIN DETEMIR					NPH INSULIN			
	Met	w/oTZD	TZD	total		Met	w/oTZD	TZD	total
Screening	1768	1962	1889	1896		1743	2002	1907	1921
Baseline	2044	2201	2179	2163		2112	2245	2203	2206
EOS	2198	2235	2176	2205		2241	2243	2220	2234

Mean FPG mM

	INSULIN DETEMIR					NPH INSULIN			
	Met	w/oTZD	TZD	total		Met	w/oTZD	TZD	total
Screening	12.75	12.00	11.95	12.12		13.04	12.13	11.60	12.12
Baseline	12.00	14.07	13.91	13.61		12.26	13.85	13.70	13.51

HbA1c

	INSULIN DETEMIR					NPH INSULIN			
	Met	w/oTZD	TZD	total		Met	w/oTZD	TZD	total
Screening	9.76	9.56	9.32	9.51		9.76	9.46	9.48	9.52
Baseline	9.51	9.58	9.40	9.49		9.60	9.37	9.45	9.44

Detemir is the only insulin product that shows variability in potency in different mammalian species. For this reason, it was speculated that there might be variability among different human populations. A subset analysis based on race/ethnicity was done by DMEDP. As shown below, Detemir was inferior to NPH in Caucasian patients but similar to NPH in other patients.

Change in HbA1c (baseline to EOS) by Race/ethnicity

		Insulin Detemir			NPH Insulin	
Caucasian	Baseline	172	9.28		86	9.33
	EOS		8.40			7.74
	Change		-0.88			-1.61
Others	Baseline	91	9.70		49	9.42
	EOS		8.42			8.11
	Change		-1.28			-1.30

The mean dose of metformin at endpoint was about 2200 mg in all groups.

In summary, trial 1337 failed to establish the non-inferiority of Insulin Detemir to NPH Insulin when used in combination with metformin in patients with type 2 diabetes. Although lower levels of HbA1c were achieved with NPH, levels of FPG at endpoint were the same in both treatments. This apparent discrepancy between HbA1c and FPG is consistent with the longer duration of action of Detemir. The most important finding was the difference in response between Caucasian and non-Caucasian patients.

Integrated Safety (all phase 3 trials):

There was little difference in reporting of major hypoglycemic episodes between patients on Detemir and patients on NPH. Patients with type 1 diabetes reported more local reactions to Detemir than to NPH, but this finding was not reproduced in insulin-naïve patients with type 2 diabetes. Insulin Detemir appears somewhat more antigenic than NPH, but I did not find evidence of clinically significant consequences.

Clinical Review

I Introduction and Background

Insulin Detemir is an analog of human insulin in which a c14 fatty acid (myristic acid) is covalently bound to B29 LYS and position B30 is omitted. The fatty acid associates with albumin in plasma and tissues. Approximately 98-99% of Insulin Detemir is bound to albumin and its protracted course of action is due to slow release from the albumin molecule. Delayed absorption from subcutaneous injection and slower clearance may also contribute to its protracted course.

Insulin products are currently formulated as U100 (100 units per ml). Although a unit of insulin was originally derived from animal bioassays, a modern definition applicable to pure insulin is that 1 unit=6nmoles=0.036mg. These relationship holds for the human insulin and synthetic insulin analogs that are currently in use as well as the beef and pork insulins that had been widely used in the past. But these relationships will break down if applied to insulin Detemir. In one in vitro system, the affinity of Detemir for insulin receptors was approximately 46% that of human insulin. Based on this estimate, Detemir was initially formulated to have twice the molar concentration of other insulin products. But studies in vivo suggested that a 4:1 ratio would be a better estimate.

Defining a unit of potency for Detemir, that will be useful clinically, presents a challenge. To dose patients based on nanomoles or milligrams would cause great confusion. On the other hand, DMEDP should be reluctant to allow the Sponsor to define a "unit" of insulin that would apply solely to Detemir. In consultation with DMEDP, NovoNordisk attempted to adjust the molar concentration of Detemir so that patients taking NPH insulin could be switched to an equal volume of Detemir. Based on preliminary data, the initial concentration of Detemir was 1200 nmol/ml (2x other insulin products). The concentration was later increased to 2400 nmol/ml. This is the concentration of the to-be-marketed formulation. The hope was that a patient who ordinarily takes 50 units (300 nmoles) or 0.5 ml of NPH insulin would get the same result if treated with 0.5 ml (1200nmoles) of Detemir.

II Chemistry and Pharmacology:

Chemistry:

The Chemistry reviewer has identified inadequate validation of a bioassay as a deficiency. The Sponsor has proposed that an in vitro assay in isolated rat fat cells replace the standard mouse bioassay based on glucose reduction. The Chemistry reviewer indicated that additional work was needed to demonstrate the correlation between the proposed in vitro assay and the standard in vivo assay.

As will be discussed below, Insulin Detemir is unlike all other insulin products in that its potency varies from species to species. Its activity in mice and rats is much less than in humans. It is my understanding that the purpose of a bioassay for insulin products is to demonstrate with certainty that the substance will lower glucose levels in vivo, even after its structure and purity has been demonstrated by standard chemical techniques. With respect to Insulin Detemir, I do not believe this purpose is served by a rodent-based assay. It would be preferable to develop a bioassay using cultured human or cells.

Pharmacology

Binding to albumin

Insulin Detemir is an analog of human insulin in which a c14 fatty acid (myristic acid) is covalently bound to B29 LYS and position B30 is omitted. The fatty acid associates with albumin in plasma and tissues. Approximately 98-99% of Insulin Detemir is bound to albumin and its protracted course is due to slow release from the albumin molecule. Delayed absorption from subcutaneous injection and delayed clearance may also contribute to its protracted course. Free Detemir is biologically active. The Detemir-albumin complex does not bind to the insulin receptor. Binding to albumin is not affected by 0.4-mM palmitic acid or myristic acid fatty acids.

FDA expressed the concern that binding of Detemir to albumin (and hence the ability of Detemir to bind with insulin receptors) might be affected by the lipid content of plasma. As stated by the Sponsor, these studies were done to address the possibility that in some patients with hyperlipidemia, there could displacement of insulin Detemir from the albumin binding site, with possible partitioning in the hydrophilic and lipophilic interphase, potential loss of biological activity, or unpredictable release of insulin Detemir.

The Sponsor performed a study of the binding of Detemir to plasma samples obtained from subjects with hyperlipidemia. An additional study was performed on the effect of a high fat meal on the binding of Detemir to plasma. The results of these studies (taken from the 6/4/02 briefing document) are shown below:

Group	Mean Chol, mg/dl	Mean Trigly, mg/dl	% binding, Mean(SD)
Hyperchol n=3	466	359	99.55(0.10)
Hypertrigly n=7	301	2001	99.61(0.10)
Normal n=3	167	77	99.3(0.31)
Normal n=3, after fatty mean	162	129	99.6(0.09)

As shown in the table above, binding was higher in the hyperlipidemic patients than in the normal controls and binding went up 0.3 (SD=0.23) in the normal controls following a fatty meal. This increase in binding in the three normals was associated with a rise in triglycerides. But the hypertriglyceridemia achieved is very much less than the fasting levels in the 7 hypertriglyceridema subjects, even though the % binding was the same. Thus, there was no correlation between binding and triglyceride levels. This latter finding was confirmed in a pooled study of 31 subjects. There was no correlation between fasting triglycerides and Detemir binding (Spearman Correlation Coef = 0.16, p=0.38). However, there was a correlation with fasting cholesterol (Spearman =0.38, p=0.08). Two/nine normal subjects had large increases in binding following a fatty meal (99.0 to 99.5).

In considering the possible significance of these results, it must be borne in mind that the **unbound** Detemir is what is physiologically active. A change in binding from 99.0% to 99.5% would seem more important if expressed as a decrease in **unbound** Detemir from 1.0% to 0.5%. I am also concerned about the technological limitations of these experiments (counting radioactive samples to detect small differences, intactness of the ligand , etc).

Defining Potency:

Insulin products are currently formulated as U100 (100 units per ml). Although a unit of insulin was originally derived from animal bioassays, a modern definition applicable to pure insulin is that 1 unit=6nmoles=0.036mg. This relationship holds for the human insulin and synthetic insulin analogs that are currently in use as well as the beef and pork insulins that had been widely used in the past. But these relationship will break down if applied to insulin Detemir. As shown in the table below, there exists a wide range of potencies for Detemir among various mammalian species. It is problematic to accept results of a mouse bioassay, given that Detemir has so little potency in that species. Defining a unit of potency that will be useful clinically presents an even greater challenge. To dose patients based on nanomoles or milligrams would cause great confusion. On the other hand, FDA was reluctant to allow the Sponsor to define a "unit" of insulin that would apply solely to Detemir. In consultation with FDA, NovoNordisk attempted to adjust the molar concentration of Detemir so that patients taking NPH insulin could be switched to an equal volume of Detemir. Based on preliminary data, the initial concentration of Detemir was 1200 nmol/ml (x2 other insulin products). The

concentration was later increased to 2400 nmol/ml. The hope was that a patient who ordinarily takes 50 units (300 nmoles) or 0.5 cc of NPH insulin would get the same result if treated with 0.5 cc (1200nmoles) of Detemir.

Overview of Potency of Detemir relative to human insulin in mammals*

Mouse	6%	Detemir compared to soluble human insulin by SC injection
Mouse	approx 5%	compared to insulin using fat cells in vitro
Rabbit	<5%	Detemir compared to NPH insulin by SC injection
Rat	15%	Detemir compared to soluble human insulin by IV injection
Dog	approx 100%	Detemir compared to soluble human insulin by IV injection
Pig	approx 100%	Detemir compared to NPH insulin by SC injection
Human	25%	Detemir compared to NPH insulin by SC injection

*from submission of Feb 13, 2002

Based on early studies, the Sponsor believed that approximately twice the molar dose of Detemir would be required to achieve the same glucodynamic effect as NPH. This higher dose reflects the lower affinity (46%) of Detemir for the human insulin receptor. As noted above, the estimate was later revised to 4:1. The concentration of Detemir used in the phase 3 program was 1200 or 2400 nmole/ml. But the to-be-marketed formulation will be 2400 nmole/ml.

Drug Metabolism:

It is generally recognized that the rate-limiting step in insulin degradation is binding of insulin to its receptor. The bound insulin is metabolized by protease(s) associated with the cell surface and the internalized insulin fragment(s) are metabolized by lysosomes.

The Sponsor has incubated Detemir and insulin with liver and kidney cytosol and concluded that their metabolic pathways are similar and that the first step is degradation is cleavage of the disulfide bonds. Although this conclusion may be correct with respect to degradation in unpurified cellular extracts in vitro, no evidence is provided that these results have anything to do with the physiological relevant pathway(s) of insulin degradation. The concentration at which these experiments were performed was over a thousand-fold higher than one might expect in vivo. No explanation is offered about the lack of species specificity that one might expect to observe if degradation and metabolic

action were related (see below). No controls were included to see if the reaction was specific for insulin or if any S-S containing peptide would be similarly degraded.
In short, NovoNordisk has been uncritical in evaluating the physiological relevance its studies of the metabolism of insulin Detemir. The data put forward should not be accepted by FDA as providing an adequate description of the mechanism by which insulin Detemir is degraded in vivo.

III Pharmacokinetic/Pharmacodynamic study in patients with Type 1 and Type 2 Diabetes

Additional information about the relative potency of Detemir comes form a PK/PD study 1221 performed in Austria during 2000 and submitted with the NDA. This utilized a euglycemic clamp. Regular insulin and two doses of Detemir were infused. The FPG level was brought down from a mean baseline of about 11mM and "clamped" at about 5 mM by infusion of glucose for 600 minutes. In this model, the effectiveness of the insulin preparation can be judged from the amount of glucose necessary to maintain euglycemia. The steady state insulin concentration of about 60 uU/ml is in the range of what is observed in normal subjects after eating. Although not actually measured, this insulin level would be expected to shut off hepatic glucose output, therefore what is being measured is insulin-stimulated glucose uptake by muscle and fat.

The authors had to reject data from a few "outliers" among the patients with type 2 diabetes. The explanation given was interference with endogenous antibodies, although antibodies levels were not actually presented. For this reason I am skeptical about the validity of some of the measurements and the parameters derived from them.* However, comparison of the glucose infusion rates and drug doses still lead to some interesting results. The insulin infusion rate (6 pmol/kg/min, 6 pmol=0.001Unit) appears to have been chosen to give an insulin level that would be sub-maximal with respect to response. The doses of Detemir (18 and 30 pmol/kg/min) appear to have been chosen to bracket the insulin response, assuming that it would take about 4 times as much Detemir (24 pmol/kg/min of Detemir) to give the same response as insulin (6 pmol/kg/min). As shown in the following tables, the effectiveness of Detemir fell short of expectations. Even 30 pmol/kg/min of Detemir did not have the same effect as 6 pmol/kg/min of insulin. The Sponsor estimated that the potency of Detemir to insulin was 1:10 in type 1 diabetes. In type 2 diabetes, they estimated that the potency of Detemir to insulin was 1:12, but commented on the large confidence interval and that this estimate might still be too low.

Glucose infusion rate to maintain FPG=5mM during infusion of Insulin or Detemir

Glucose infusion rate, mg/kg.min	Human insulin, 6 pmol/kg/min	Detemir 18 pmol/kg/min	Detemir 30 pmol/kg/min
Type 1 diabetes	6.36	3.46	4.79
Type 2 diabetes	4.32	2.38	3.12

From PK section of NDA vol 35

It should be noted that the glucodynamic activity of both insulin and Detemir was greater in type 1 diabetes than in type 2 diabetes. This is an expected finding and reflects the insulin resistance that is usually present in type 2 diabetes. But the effect of Detemir relative to insulin appears to be the same in both type 1 and type 2 diabetes.

*Measurement of insulin and insulin Detemir were based on binding to monoclonal antibodies. The Sponsor has stated that the presence of endogenous antibodies (in insulin-treated patients) did not interfere with this assay (NDA 5.3.1.4 validation study 960214, module5, vol12, pp7-67). However, data from a few patients with type 2 diabetes had to be rejected because of endogenous antibodies. This inconsistency casts doubt on the validity of conclusions from this study and needs to be explained.

IV Description of Clinical data and Sources

The application contains data from ten phase 3 controlled clinical trials. There were seven trials (five original and two extension trials) in patients with type 1 diabetes and three trials in type 2 diabetes. One of the trials in patients with type 2 diabetes took place in the United States. No American patients with type 1 diabetes were studied.

The studies were randomized comparisons of Insulin Detemir to NPH insulin. Detemir is a clear solution and NPH is a suspension. Because patients taking NPH must be sure that the suspension is homogeneous, blinding of NPH and Detemir was not feasible. For this reason the trials were open label. Randomized comparison in two of the trials in type 1 diabetes lasted 16 weeks. In all other trials, the duration of randomized comparison was 6 months.

Patients with type 1 diabetes received Detemir or NPH as basal insulin in addition to boluses of rapid acting insulin (regular human insulin or insulin aspart) before meals. A similar basal/bolus regimen was used in one of the trials of patients with type 2 diabetes.

The demonstration of efficacy was based on a non-inferiority comparison to NPH insulin with respect to HbA1c. As will be discussed later, the concomitant use of regular insulin complicates interpretation of the efficacy results.

V Clinical Review Methods:

The review was conducted of the hard copy of the NDA. No routine inspections of the sites were performed. Although the consent document was not reviewed, the trials appear to have been conducted in accordance with acceptable ethical standards. The financial disclosure documentation appears adequate.

Documents submitted:

NDA 21-536, submitted December 11, 2002

Response to request for information (fax from FDA March 26, 2003) submitted by Sponsor on April 2, 2003

Regulatory statements regarding submission of documents;

The Sponsor, Novo Nordisk submitted debarment and financial disclosure documents December 5, 2002. I have examined these documents and found them to be acceptable. The debarment statement indicated that Novo Nordisk had not and will not use the services of any person debarred under section 306 of the Federal Food, Drug and Cosmetic Act.

The following financial disclosure information has been submitted:

1 Form OMB No. 0910-0396. The applicant certifies that Novo Nordisk has not entered into any financial arrangement with the clinical investigators named in the lists included in the NDA whereby the value of compensation to the investigator could be affected by the outcome of the study.

2 The applicant further certifies that none of the listed clinical investigators disclosed a proprietary interest in the product or an equity interest in Novo Nordisk.

3 The applicant certifies that no listed investigator was the recipient of other payments such as honoraria, consultation fees, research grants, or compensation in the form of equipment from Novo Nordisk .

4 Analyses of efficacy data in this NDA did not reveal any significant effect of center on outcomes. Furthermore, the data on both safety and effectiveness were consistent across the multiple trials submitted to the NDA. Thus a potential conflict of interest from any investigator does not call into question the overall integrity of the data submitted.

V1 – Review of Efficacy

Unlike other insulin products, Insulin Detemir shows a marked variation in potency in different species. The initial estimate was that Detemir was half as potent (on a weight or molar basis) as human insulin. But studies in isolated systems suggested the same effect could be achieved with Detemir as with human insulin provided that enough Detemir was given.

FDA has never previously had to face the situation of an insulin product that was substantially less potent that other insulin products. There is no fixed dose for insulin. The correct dose of insulin in any given patient is determined by titration. Given that the dose of insulin in the pivotal trials was titrated to optimize effect on glycemia, it seemed reasonable to set a standard for approval of Detemir based on glycemic control alone.*

Patients with type 1 diabetes (and some with type 2 diabetes) are generally treated with two insulin products. A basal insulin (NPH, Lente or Glargine) is given once or twice a day and boluses of a fast-acting insulin (regular insulin or one of the fast acting analogs, Lispro or Aspart) are given before meals.

All phase 3 trials were designed to compare Insulin Detemir to NPH respect with respect to HbA1c. It was recognized that the dose of Detemir (on a molar basis) would be greater than the dose of NPH insulin. Initially, the phase three trials were done with a Detemir preparation that contained 1200 nmoles/ml. The concentration was later increased to 2400 nmoles/ml. Because of this change in concentration, the definition of a "unit" of Detemir also changed. The concentration in all other insulin products is 600 nmoles/ml. What remains constant in all insulins used in these trials is the number of units per volume of product. This is 100 units per ml for Detemir, NPH insulin, regular insulin, and insulin aspart.

Unlike the situation with previously approved insulin products, the dose of test product required to achieve glycemic control was not considered an important variable in these trials. However the dose of bolus insulin (regular or Aspart) took on special significance. Recognizing that Detemir is so much less potent than the bolus insulins, a small amount additional bolus insulin in Detemir-treated patients could potentially give the impression that Detemir was more effective than it really was.

*This is not unlike the situation with sulfonylureas. Glyburide, Glipizide, Chlorpropamide and other sulfonylureas have the nearly the same efficacy, but the mg doses required to achieve the same amount of glucose lowering are different. A larger tablet does not of itself constitute a disadvantage.

Type 1 Diabetes:

Trial 1181

Six month trial of Detemir + regular insulin vs NPH+ regular insulin in patients with type 1 diabetes

This trial was conducted in 55 sites in Australia, New Zealand, Germany, Switzerland and Austria.

The trial population was adults with type 1 diabetes BMI< 35, total insulin requirement no greater than 100 units/d and HbA1c no greater than 12%. Patients had to have been on a regimen of basal insulin (twice daily) plus pre-meal boluses for at least 2 months. This was designed as a non-inferiority trial with a margin of 0.4% units using the ITT population. The dose of insulin Detemir was initiated at twice the patient's previous dose of NPH, so that the volume of basal insulin was the same in both groups at the start of the trial. Basal insulin was administered twice daily in the morning and at bedtime.

The ITT population was defined as all randomized patients who received at least one dose of trial product. The per protocol population was defined as subjects who completed the trial, did not have protocol violations that could potentially affect the efficacy results.

Treatments: Insulin Detemir, 1200 nmol/mL 1 unit=12 nmol
NPH insulin, 600nmol/mL 1 unit= 6 nmol
Human soluble insulin, 600nmol/mL – all given in 3 ml pens
Glycemic goals: FBG 4-7 mM(72-126 mg/dl)
90 min Postprandial blood glucose < 10 mm(180 mg/dl)
BG 2:00-4:00 am 4-7 mM(72-126 mg/dl)

Safety Assessment:

Major hypoglycemia – severe CNS symptoms consistent with hypoglycemia in which patients requires assistance, with BG<2.8 mM (50 mg/dl) or reversal by food or glucagon

Minor hypoglycemia- episode with BG< 2.8 handled by patient or asymptomatic

237 patients were randomized to Detemir and 224 to NPH. The withdrawal rate was 10.5% for Detemir and 6.7% for NPH. Withdrawal due to "ineffective therapy" was 3.4% for Detemir and 4% for NPH. Non-compliance, unwillingness to continue and "other" reasons accounted for 5.1% for Detemir and 1.8% for NPH. The ITT population was 62% male, 99% white, mean age 39 years (15 years of diabetes), BMI 25.3, HbA1c 7.7%, Mean basal insulin dose was 26.5 units for Detemir patients and 26.3 units for NPH patients. Mean bolus insulin dose was 29 units for Detemir patients and 26.4 units for

NPH patients. Thus, Detemir patients were using approximately 10% more bolus insulin than NPH patients at baseline.

Efficacy results are shown in the next few tables. With respect to HbA1c, the two groups were well matched at baseline. There was a very small rise in the mean HbA1c in the Detemir group and a very small fall in the NPH group. At 26 weeks, HbA1c were not statistically different either in the ITT or per protocol populations. With respect to plasma glucose, there was a dip in the NPH group at 13 weeks. However, by 26 weeks there was no difference between Detemir and NPH.

HbA1c at Baseline and 26 weeks for ITT population

	Detemir n=210	NPH n=206
<-3 weeks	7.63	7.68
26 weeks	7.66	7.61

HbA1c at Baseline and 26 weeks for per protocol population

	Detemir n=136	NPH n=146
<-3 weeks	7.73	7.63
26 weeks	7.74	7.59

FPG for ITT population

	Detemir n=209	NPH n=204
<-3 weeks	10.7	10.6
13 weeks	10.2	9.81
26 weeks	10.5	10.6

FPG for PP population

	Detemir n=135	NPH n=143
<-3 weeks	11.0	10.5
13 weeks	10.2	9.69
26 weeks	10.5	10.2

Although Detemir and NPH gave similar efficacy results, the patients on Detemir required more insulin. This result is seen in the following tables.

Insulin Dose at 26 weeks

	Detemir	NPH
Basal U or IU	44.1	28.5
Ratio (Detmr/NPH)	1.54	1.00

	Detemir	NPH
Bolus U or IU	33.0	27.9
Ratio (Detmr/NPH)	1.18	1.00

Insulin Detemir U = 12nmol
NPH insulin IU= 6 nmol
Insulin aspart IU = 6 nmol

The volume ratio of Detemir to NPH at EOS was 1.54 while the molar ratio of Detemir to NPH at EOS was 3.09. Detemir patients used 18% more regular insulin than NPH patients. But some of this difference had been present at baseline.

Trial 1243

This was a 6 month extension trial of Detemir vs NPH for patients who completed trial 1181. The purpose of the trial was to examine the 12-month safety of Detemir and to determine if efficacy could be maintained long-term.

HbA1c at 6 and 12 months for ITT population

	Detemir n=139	NPH n=124
6 months	7.63	7.57
12 months	7.73	7.67

HbA1c at 6 and 12 months for per protocol population

	Detemir n=86	NPH n=81
6 months	7.70	7.54
12 months	7.80	7.62

The doses of basal and bolus insulins are given in the following tables:

Basal Insulin, Detemir (U) or NPH (IU), ITT population

	Detemir	NPH
6 months	44.9	29.4
12 months	46.7	29.8

Bolus Regular Insulin (IU)

	Detemir	NPH
6 months	33.1	27.7
12 months	33.4	29.2

Insulin Detemir U = 12nmol
NPH insulin IU= 6 nmol
Regular insulin IU = 6 nmol

Basal Insulin, Detemir (U) or NPH (IU), pp population

	Detemir	NPH
6 months	46.0	29.5
12 months	48.2	30.5

Bolus Regular Insulin (IU)

	Detemir	NPH
6 months	34.0	28.0
12 months	33.8	30.1

Conclusion:

Trials 1181 and 1243 were done with a formulation of Detemir that has half the concentration as the to-be-marketed formulation. Although the non-inferiority test was nominally met, additional regular insulin was used in the Detemir group. Therefore this cannot be used as a pivotal study to establish to that Detemir and NPH are equally effective. However, the glucose–lowering effect of Detemir appears to be last 12 months.

Trial 1205

Six month trial of Detemir + insulin aspart vs NPH+ insulin aspirate in patients with type 1 diabetes. This trial was conducted in 45 sites in France, Belgium, Luxembourg, Netherlands, and Norway

The trial population was adults with type 1 diabetes BMI< 35, total insulin requirement no greater than 100 units/d and HbA1c no greater than 12%. Patients had to have been on a regimen of basal insulin (once or twice daily) plus pre-meal boluses for at least 2 months. This was designed as a non-inferiority trial with a margin of 0.4% units using the ITT population. The dose of insulin Detemir was initiated at twice the patient's previous dose of NPH, so that the volume of basal insulin was the same in both groups at the start of the trial. Basal insulin was administered twice daily in the morning and at bedtime.

The ITT population was defined as all randomized patients who received at least one dose of trial product. The per protocol population was defined as subjects who completed the trial, did not have protocol violations that could potentially affect the efficacy results.

Treatments: Insulin Detemir, 1200 nmol/mL 1 unit=12 nmol
NPH insulin, 600nmol/mL 1 unit= 6 nmol
Human soluble insulin, 600nmol/mL – all given in 3 ml pens
Glycemic goals: FBG 4-7 mM(72-126 mg/dl)
90 min Postprandial blood glucose < 10 mM(180 mg/dl)
BG 2:00-4:00 am 4-7 mM(72-126 mg/dl)
Safety Assessment:

Major hypoglycemia – severe CNS symptoms consistent with hypoglycemia in which patients requires assistance, with BG<2.8 mM (50 mg/dl) or reversal by food or glucagon

Minor hypoglycemia- episode with BG< 2.8 handled by patient, or asymptomatic

301 patients were randomized to Detemir and 147 to NPH. The withdrawal rate was 5.6% for Detemir and 4.1% for NPH. Withdrawal due to "ineffective therapy" was 1.7% for Detemir and 1.4% for NPH. Non-compliance unwillingness to continue and "other" reasons accounted for 3.4% for Detemir and 2.7% for NPH. The ITT population was 53% male, 99.5% white, mean age 40 years (17 years of diabetes), BMI 24.6, HbA1c 8.27%, Mean basal insulin dose was 27.4 units for Detemir patients and 25.2 units for NPH patients. Mean bolus insulin dose was 30.9 units for Detemir patients and 29.6 units for NPH patients.

Efficacy results are shown in the next few tables. With respect to HbA1c, the two groups were well matched at baseline. There was a fall in the mean HbA1c both groups which probably reflects intensification of the insulin regimen during the trial (twice daily basal with aspart instead of regular insulin). At 26 weeks, there were no statistically significant differences between Detemir and NPH either in the ITT or per protocol populations. With

respect to plasma glucose, there was a trend for lower glucose with Detemir in the ITT population. In the per protocol population, the difference between Detemir and NPH at 26 weeks (-1.82 by ANOVA) was statistically significant (p=0.012)

HbA1c at Baseline and 26 weeks for ITT population

	Detemir n=280	NPH n=139
<-3 weeks	8.18	8.11
26 weeks	7.62	7.61

HbA1c at Baseline and 26 weeks for Per protocol population

	Detemir n=123	NPH n=55
<-3 weeks	8.09	8.31
26 weeks	7.38	7.59

FPG for ITT population

	Detemir n=274	NPH n=138
<-3 weeks	11.7	11.6
13 weeks	10.8	11.0
26 weeks	9.60	10.3

FPG for PP population

	Detemir n=120	NPH n=54
<-3 weeks	11.6	13.3
13 weeks	10.6	10.2
26 weeks	9.33	11.1

Although Detemir and NPH gave similar efficacy results, the patients on Detemir required more bolus insulin. This result is seen in the following tables.

Pre-study Insulin Dose for ITT

	Detemir	NPH
Basal U or IU	27.4	25.2
Bolus	30.9	29.6

Insulin Dose at 26 weeks for ITT

	Detemir	NPH
Basal U or IU	59.2	31.7
Ratio (Detmr/NPH)	3.74	1.00

	Detemir	NPH
Bolus U or IU	30.7	26.0
Ratio (Detmr/NPH)	1.18	1.00

Insulin Detemir U = 12nmol
NPH insulin IU= 6 nmol
Insulin aspart IU = 6 nmol

The volume ratio of Detemir to NPH at EOS was 1.87 while the molar ratio of Detemir to NPH at EOS was 3.74. Detemir patients used 18% more insulin aspart than NPH patients.

Trial 1316

This was a 6-month extension trial of Detemir vs NPH for patients who completed trial 1205. The purpose of the trial was to examine the 12-month safety of Detemir and to determine if efficacy could be maintained long-term. Patients continued to be treated with twice daily basal insulin and insulin aspart before meals. As shown below, there was little of no change in HbA1c or insulin dose between 6 and 12 months.

HbA1c at 6 and 12 months for ITT population

	Detemir n=210	NPH n=96
6 months	7.50	7.46
12 months	7.51	7.47

HbA1c at 6 and 12 months for per protocol population

	Detemir n=87	NPH n=33
6 months	7.27	7.41
12 months	7.30	7.52

Basal Insulin, Detemir (U) or NPH (IU), ITT population

	Detemir	NPH
6 months	58.3	32.6
12 months	60.8	33.6

Bolus Regular Insulin (IU)

	Detemir	NPH
6 months	30.2	27.1
12 months	31.7	27.3

Insulin Detemir U = 12nmol
NPH insulin IU= 6 nmol
Regular insulin IU = 6 nmol

Conclusion:

Trials 1205 and 1316 were done with a formulation of Detemir that has half the concentration as the to-be-marketed formulation. Although the non-inferiority test was nominally met, additional bolus insulin (insulin aspart) was used in the Detemir group. Therefore this cannot be used as a pivotal study to establish to that Detemir and NPH are equally effective. The claim of durability is supported by the data. An additional finding is that Detemir appeared more effective than NPH with respect to lowering FPG. This is consistent with the slower action of Detemir, brought out in this study because the bolus insulin was the rapid acting insulin aspart (as opposed to trials 1181/1243 in which regular insulin was used)

Trial 1335

Six month comparison of Detemir 2400 nmol/mL and NPH each given once daily at bedtime in patients with Type 1 diabetes who use boluses of regular insulin before meals The trial was conducted in Europe and Australia

The trial population was adults with type 1 diabetes, for at least 1 year, with HbA1c of no more than 12% taking no more than 100 units of basal insulin once daily in the evening.

Patients randomized to NPH were started on their previous dose of NPH, but patients on Detemir started at ½ the previous dose of NPH. The dose of NPH or Detemir was then increased as needed to achieve the glucose targets described for previous studies. The bolus insulin dose was kept constant for the first two weeks to allow the basal insulin to be titrated.

The trial was designed to test non-inferiority in the ITT population using HbA1c at endpoint with a non-inferiority margin or 0,.4%.

Withdrawals were 5.5% in the Detemir arm and 8.6% in the NPH arm. 3/492 patients on Detemir withdrew for "lack of efficacy" and none on NPH. "Other" reasons for withdrawal constituted 3.5% for Detemir and 5.8% for NPH.

Of the ITT population about 63% were male, all but six patients were white. The mean age was 40 years, 17 years of diabetes, mean BMI about 25.2.

HbA1c at baseline and 26 weeks are shown in the tables below for the ITT and per protocol populations. There was little change in HbA1c over the course of the study and no statistically significant differences between Detemir and NPH.

HbA1c at Baseline and 26 weeks for ITT population

	Detemir n=464	NPH n=236
<-3 weeks	8.35	8.35
26 weeks	8.30	8.41

HbA1c at Baseline and 26 weeks for Per protocol population

	Detemir n=447	NPH n=227
<-3 weeks	8.34	8.34
26 weeks	8.29	8.40

With respect to FPG, there was a dip in the Detemir group at 13 weeks, which was partially maintained at 26 weeks. The difference in FPG (Detemir-NPH) of –1.16 mM was significant (p=0.001). But both groups fell far short of the glycemic goal which was FBG 4-7 mM.

FPG for ITT population

	Detemir n=453	NPH n=230
<-3 weeks	11.9	11.6
13 weeks	9.8	11.3
26 weeks	10.3	11.4

As shown in the table below, both groups were well matched with respect to insulin dose before initiation of treatment.

Insulin Dose at <-3 weeks

	Detemir n=478	NPH n=250
Basal	23.5	24.1
Bolus	33.7	33.7

Insulin Dose at 26 weeks

	Detemir	NPH
Basal	20.9	25.6
Ratio Detemir/NPH	0.82	1.00
Bolus	35.6	33.5
Ratio Detemir/NPH	1.06	1.00

Insulin Detemir U = 24nmol
NPH insulin IU= 6 nmol
Regular insulin IU=6 nmol

According to the protocol, patients on NPH started on their previous dose of NPH, but patients on Detemir started at ½ the previous dose of NPH. The dose of NPH or Detemir was then increased as needed. By endpoint, there was a small net rise in the NPH dose (24.1 to 25.6); however, the Detemir patients never caught up, so their mean dose of Detemir at 26 weeks (20.9) was still less than their pre-study dose of NPH (23.5). At EOS, the ratio of basal insulins by volume, Detemir/NPH, was 0.82 and the molar ratio was 3.27. The dose of regular insulin changed little in the NPH group, but the dose of regular insulin in the Detemir group rose from 33.7 to 35.6. Thus, the relative decrease in dose of basal insulin in the Detemir group was compensated for by a small increase in the dose of regular.

Conclusion: Detemir given **once a day** was approximately as effective as NPH once a day, **but neither was effective in achieving good control**. The glycemic goals were not met. The decrease in the dose of basal insulin given as Detemir was compensated for by an increase in the dose of regular. Therefore, the non-inferiority of Detemir relative to NPH was not clearly established

Study 1447

This was a 16 week trial comparing NPH insulin (600 nmol/mL) to two regimens of insulin Detemir (2400 nmol/mL). NPH was given in the morning and at bedtime. Detemir was given in the morning with a second injection either at bedtime or before dinner. For the sake of simplicity, these arms are referred to as NPH bedtime, Detemir bedtime and Detemir dinner. All patients received boluses of insulin aspart before meals. This was designed to be a superiority trial. The primary measure of efficacy was HbA1c at 16 weeks using the ITT population. The trial was conducted at 52 Centers in Europe.

The trial population consisted of patients with type 1 diabetes, BMI < 35, HBA1c< 12%, basal insulin dose at least 30% of total insulin dose and total basal insulin requirement of 100 units or less. Patients with known hypoglycemia unawareness were excluded, as were patients with creatinine over 1.7 mg/dl, ALT greater than 2x ULN or NYHA class 111 or 1V heart failure. Use of corticosteroids or beta blockers were also prohibited.

Patients who were previously receiving once daily basal insulin were transferred to twice daily regimen with 25-30% in the morning and 70-75% pre-dinner/bedtime. The starting dose of Detemir (on a molar basis) was recommended to be 2.8 times the previous dose of basal insulin. The starting dose of NPH was recommended to be 70% the previous dose of basal insulin. There was an expectation that the doses of both basal insulins would be increased during the titration period and that the final dose of Detemir (on a molar basis) would be increased to approximately 4x the dose of NPH. This means that the expected final volume of NPH and Detemir would be approximately the same.

The insulin dose was titrated with the goal of premeal and night time(2:00-4:00 am) to be 72-126 mg/dl and 90 min post-prandial glucose to be < 180 mg/dl. During the first 4 weeks, it was recommended that the dose of basal insulin be adjusted while the dose of bolus insulin remained constant. The weeks following initial titration were used to finely adjust the doses of both bolus and basal insulin. The injection site area was to remain constant but the exact site within the area was rotated to prevent lipohypertrophy. All insulin injections were given with 3 ml Penfill.

The ITT population was about 60% male, 100% white, mean age 40 years (15 years of diabetes), BMI 25.2, HbA1c 8.07, FPG 10.4 mM. 62% had been taking 2 or more injections of basal insulin per day. The mean pre-study daily doses of insulin were and bolus insulin was 0.34 U/kg and 0.39 U/kg respectively.

Results:

As shown in the table below, the primary measure of efficacy, HbA1c at endpoint for the ITT population, was not statistically different among the three groups

HbA1c for ITT

HbA1c	Detemir dinner	NPH bedtime	Detemir bedtime
Baseline	8.01 (n=133)	8.09 (n=125)	8.13 (n=123)
16 weeks	7.58 (n=133)	7.70 (n=125)	7.64 (n=123)

Accounting for the slight differences in baseline, the change in HbA1c was -0.53 for Detemir dinner, -0.39 for NPH bedtime and -0.49 for Detemir bedtime. The results with the per protocol population (shown below) is essentially the same as for the ITT population.

HbA1c for per protocol

HbA1c	Detemir dinner	NPH bedtime	Detemir bedtime
Baseline	8.09 (n=112)	8.08 (n=105)	8.11 (n=105)
16 weeks	7.57 (n=112)	7.69 (n=105)	7.62 (n=105)

Within subject variation by self-testing of fasting glucose and 10 point glucose profiles were lower in the two Detemir arms than in the NPH arm.

Insulin doses before the study and at endpoint are shown in the tables below. Mean basal insulin and total insulin rose in all three groups. The dose of bolus insulin was essentially unchanged in the Detemir bedtime group but fell in the other two groups. In comparisons to the NPH patients, Detemir patients took on average about 5-10% more insulin at baseline and about 10-20% more insulin endpoint.

Pre-study Dose of insulin for ITT

	Detemir dinner	NPH bedtime	Detemir bedtime
Basal U or IU	26.3	24.1	26.7
Bolus	29.1	27.9	30.5
Total	55.4	52	57.2

Dose of insulin at end of 16 weeks: ITT

	Detemir dinner	NPH bedtime	Detemir bedtime
Basal U or IU	34	28.6	31.7
Bolus	28.7	25.6	30.6
Total	62.7	54.2	62.3

Comparisons of Daily Dose of Insulin at 16 weeks

	Detemir dinner	NPH bedtime	Detemir bedtime
Basal U or IU	34	28.6	31.7
Ratio (Detmr/NPH)	1.19	1.00	1.11

	Detemir dinner	NPH bedtime	Detemir bedtime
Bolus U or IU	28.7	25.6	30.6
Ratio (Detmr/NPH)	1.12	1.00	1.20

Insulin Detemir U = 24 nmol
NPH insulin IU= 6 nmol
Insulin aspart IU = 6 nmol

Conclusion: Trial 1447 did not clearly establish the non-inferiority of Detemir relative to NPH. Although insulin Detemir nominally met the test of non-inferiority to NPH insulin, patients on Detemir received somewhat more insulin than patients on NPH.

Study: 1448

This was a 16 week trial comparing NPH insulin to two regimens of insulin Detemir (2400 nmol/mL), and NPH insulin (600 nmol/mL). The NPH was given in the morning and at bedtime. In one arm, Detemir was given in the morning and at bedtime. In a second arm, Detemir was given every 12 hours. For the sake of simplicity, these arms are referred to as NPH am/hs, Detemir am/hs and Detemir q 12hr. All patients received boluses of insulin aspart before meals. This was designed to be a superiority trial. The primary measure of efficacy was HbA1c at 16 weeks using the ITT population. The trial was conducted at 40 Centers in Europe, Australia, and New Zealand.

The inclusion/exclusion criteria dose selection, titration and conduct of the trial are the same as in trial 1447. For France a local amendment, dated 30 August 2001, was made to the final protocol:

Glucose metabolism and especially insulin sensitivity varies upon patients ethnic origins. Health Authorities request that subjects in a phase III programme with a new insulin reflect the principal ethnic groups of a patient's population. Patients will have to approve recording of his/her ethnic origin.

The ITT population was 53% male, 99% white (one black patient on Detemir and one on NPH), mean age about 40 years with 16 years of diabetes, mean BMI 25. At baseline mean HbA1c was about 8.6% and mean FPG was about 11.7 mM. The mean dose of basal insulin was bout 0.37 U/kg and the mean dose of bolus insulin was about 0.40 U/kg. 3/137 patients withdrew from the Detemir q 12 hour arm because of 'ineffective therapy", 1/133 from the NPH am/hs arm and zero from the Detemir am/hs arm.

Average timing of Dose of insulin for ITT

	Detemir q 12hr	NPH am/hs	Detemir am/hs
Basal	7:55/19:56	7.56/22:30	7:42/22:36
Bolus	7:38/12:32/18:42	7:54/12:35/18:48	7:49/12;42/1842

HbA1c for ITT (from table 4.4)

HbA1c	Detemir q12	NPH am/hs	Detemir am/hs
<-3 weeks	8.56 (n=133)	8.51 (n=125)	8.71 (n=134)
16 weeks	7.76	7.91	7.87

Accounting for the slight differences in baseline, the change in HbA1c was -0.8 for Detemir 12 hr, -0.6 for NPH am/hs and -0.84 for Detemir am/hs. The results with the per protocol population (shown below) is essentially the same as for the ITT population.

HbA1c for per protocol (from table 4.5)

HbA1c	Detemir q 12	NPH am/hs	Detemir am/hs
<-3weeks	8.62 (n=111)	8.51 (n=117)	8.73 (n=124)
16 weeks	7.82	7.84	7.88

The change in HbA1c was -0.8 for Detemir 12 hr, -0.67 for NPH am/hs and -0.85 for Detemir am/hs. A combined ANOVA analysis of final HbA1c pooling the two Detemir arms (from table 9.3) is shown below:

Insulin Detemir Mean (SE)	NPH insulin Mean (SE)	Detemir-NPH Mean (95% CI)	p value
7.76	7.94	-0.18 (-0.34, -0.02)	0.0269

Mean FPG was higher ($p<0.0001$ for the comparison of NPH vs Detemir in the NPH am/hs arm (11.24 mM) than in the Detemir q12 hr arm (9.75mM) and in the Detemir am/hs arm (8.94 mM). Within subject day to day variation for FBG (home) was reported to be significantly lower with Detemir. These results are shown below:

	Mean FPG	SD	CV,%
Detemir 12 hr	8.23	2.95	35.9
Detemir morning/bedtime	8.20	2.91	35.5
NPH morning/bedtime	8.96	3.49	39.0

Pre-study Dose of insulin for ITT

	Detemir q 12hr	NPH am/hs	Detemir am/hs
Basal U or IU	26.4	29.5	28.1
Bolus	30.9	30.5	29.4

Dose of insulin at end of 16 weeks: ITT

	Detemir q 12hr	NPH am/hs	Detemir am/hs
Basal U or IU	36.7	34.8	36.3
Bolus	27.9	29.4	.29.4

Comparisons of Daily Dose of Insulin at 16 weeks

	Detemir q 12hr	NPH am/hs	Detemir am/hs
Basal U or IU	36.7	34.8	36.3
Ratio (Detmr/NPH)	1.06	1.00	1.04
	Detemir q 12hr	NPH am/hs	Detemir am/hs
Bolus U or IU	27.9	29.4	29.4
Ratio (Detmr/NPH)	0.95	1.00	1.00

Insulin Detemir U = 24 nmol
NPH insulin IU= 6 nmol
Insulin aspart IU = 6 nmol

Conclusion:

In trial 1448, insulin Detemir meets the test of non-inferiority to NPH insulin without additional amounts of bolus insulin. This is the pivotal study to support approval for type 1 diabetes. As is noted in other studies, Detemir is more effective than NPH at lowering FPG. This finding is consistent with Detemir's slower action.

Type 2 diabetes

Trial 1166

This trial was conducted in five countries in Asia and four in Scandanavia
This was an open label 6 month trial comparing Detemir to NPH insulin each given twice daily. Inclusion characteristics were type 2 diabetes on a regimen or insulin and./or oral hypoglycemia agent for at least 12 months., aged 35 or greater, BMI< 35, HBA1c between 8-12%. Patients with total daily insulin dose> 120 units were excluded.

Study drug was Detemir 1200 nmol/ml or NPH 600 nMol/ml. Patients discontinued their usual antidaibebtic medications at screening which was < 3 weeks from randomization. Insulin-treated patients randomized to Detemir were started on twice (molar basis) their previous dose NPH,. This meant that the starting volume of study drug was the same for both Detemir and NPH The insulin dose was titrated with the goal of premeal and nigh time(2:00-4:00 am) to be 72-126 mg/dl and 90 min post-prandial glucose to be < 180 mg/dl. Insulin was given with breakfast and bedtime. The dose was made at the investigators discretion based results of home blood glucose monitoring. Fundoscopy was done at screening and endpoint.

The trial was to test non-inferiority based on the primary endpoint, HbA1c after 6 months for the ITT population, with a margin of 0.4% units.

Results:

There were 24/224 (11%) patients who dropped out of the Detemir arm because of "ineffective therapy" compared to 2/221(1%) with NPH. Patients in the ITT population were about 55% male, 65% white, 35% Asian, mean age about 59 years, mean duration of diabetes about 11 years, mean BMI about 27.6, HbA1c 8.8 and FPG 10.4 mM. Approximately 74% where taking a combination of insulin plus oral hypoglycemic agent, 45% insulin only and 25% oral agent only. Among the insulin users, the mean dose at screening was about 40 units.

Results for HbA1c at endpoint show that Detemir was inferior to NPH by 0.66 (95% cf 0.44, 0.89). There was a small decrease (-0.25) in HbA1c in patients on NPH and a small rise (0.34) in patients on Detemir. The noninferiority test was not met. Exploratory ANOVA by country, age, sex and BMI did not yield any interesting results.

HbA1c - ITT (all exposed patients)

	ITT n=221	n= 218
	Detemir n=178	NPH n=203
<-3 weeks	8.93	8.78
26 weeks	9.26	8.53

The mean FPG at endpoint for the ITT population was 9.79 for Detemir compared to 8.50 for NPH.

HbA1c - Per protocol

	n= 155	n=169
	Detemir n=153	NPH n=166
<-3 weeks	8.91	8.74
26 weeks	9.35	8.56

The mean insulin dose at 6 months for NPH was 59.8 IU (359 nmol) compared to 124 U (1493 nmoles). The molar ratio of Detemir to NPH was 4.2

Conclusion:

Trial 1166 demonstrated that Detemir at 1200 nmole/ml is inferior to NPH insulin.

Trial 1336

This was a 6-month open label trial conducted in five countries in Europe to compare Insulin Detemir to NPH insulin when used as the basal insulin in a basal/ bolus regimen. The preparation of insulin Detemir is this trial was 2400 nmol/ml. The preparation of NPH insulin is 600 nmol/ml.

Patients where age 35 years or more and were using a basal insulin dose of at last 30% of their total insulin dose and had HbA1 no greater than 12% on a total insulin dose of no more than 100 units. Patients taking oral agents within two months were excluded. After a three-week run-in patients were randomized to Insulin Detemir (2:1 randomization) or NPH. The initial dose of Detemir was taken to be half the volume of the previous dose of NPH (half the volume but twice the molar dose). Patients randomized to NPH started the same dose that they were taking previously. Insulin aspart was given as pre-meal bolus. The glycemic goals were the same as previous in studies. Patients/investigators were given discretion about insulin regimen. The initial dose of basal insulin was given at bedtime. A second dose of basal insulin could be added if glycemic goal could not be safely achieved with a single dose.

The primary variable was HbA1c at six months. This was designed as a non-inferiority trial with a margin of 0.4% units.

The ITT population was 506 patients. They were 51% male, 99% white, had a mean age of 60.4 years, 13 years of diabetes, mean BMI 30.4. Withdrawals due to ineffective therapy were 2.3% for Detemir compared to 1.2% for NPH. Withdrawals due to adverse event were 2.3% for Detemir compared to 0.6% for NPH.

HbA1c - ITT (all exposed patients)

	ITT n=341	n= 164
	Detemir n=315	NPH n=155
<-3 weeks	7.87	7.76
26 weeks	7.61	7.40

The mean change from baseline was -0.26 % units for Detemir compared to -0.36 % units for NPH.

The primary analysis ANOVA of HbA1c for Detemir –NPH at 26 weeks was 0.16 with a 95% confidence interval of 0.003-0.312. Thus the test of non-inferiority, based on a margin of 0.4 was met.

Exploratory analysis showed little difference between patients on once daily or twice daily basal insulin in HbA1c at six months as shown below:

	Detemir n=315	NPH n=155
Once daily	7.64 (n=155)	7.56(n=72)
Twice daily	7.61 (n=160)	7 41(n=83)

The mean FPG at endpoint for the ITT population was 9.73 mM for Detemir compared to 9.61 for NPH.

HbA1c - Per protocol

	n= 297	n=148
	Detemir n=297	NPH n=147
<-3 weeks	7.87	7.79
26 weeks	7.61	7.43

The mean change from baseline was -0.26 % units for Detemir compared to -0.36 % units for NPH.

The mean pretrial dose of basal insulin was 27.8U in the Detemir group and 28.0 units in the NPH arm. The mean pretrial dose of bolus insulin was 33.6U in the Detemir group and 34.8 units in the NPH arm. For the ITT population, the mean dose of basal insulin at 26 weeks was 36.4U in the Detemir group and 35.3 units in the NPH arm. The mean dose of bolus insulin at 26 weeks was 40.2U in the Detemir group and 35.8 units in the NPH arm. The ratio of insulin dose at 26 weeks, Detemir/NPH was 1.03 for basal insulin and 1.12 for bolus insulin. These results are essentially the same for the Per protocol population.

Conclusion: Trial 1336 should not be considered a pivotal trial to establish efficacy. Although Insulin Detemir nominally met the test of non-inferiority, patients on Detemir received additional amounts of bolus insulin (insulin aspart).

Trial 1337

This was a randomized six month trial of Detemir (2400 nM) vs NPH (2:1) in combination with metformin. The trial was performed at 72 sites in the USA and Puerto Rico.

The trial population was patients with type 2 diabetes who had been on metformin, either alone or in combination with other oral antidiabetic agents. There was a two-week washout of other oral agents during which time the dose of metformin was "optimized" to 2000-2550 mg/d or maximum tolerated dose. Patients who failed to reach FPG of 7 mM (126 mg/dl) were randomized to Detemir or NPH as a single evening dose. This regimen of metformin plus Detemir/NPH was maintained for 24 weeks.

The trial was designed to test non-inferiority of Detemir vs NPH. HbA1c at 24weeks in the ITT population was the primary endpoint with a margin of 0.4% units.

467 patients were randomized (309 to Detemir and 158 to NPH), and 405 (266 and 139) completed the study. There were 12% withdrawals of NPH and 11% on NPH. This difference in withdrawals was accounted for by "ineffective therapy" in 2.6% of patients on Detemir and none on NPH. Of the 8 patients who withdraw because "ineffective therapy", 5/8 had been on Met+TZD, 2/8 on Met w/o TZD, and 1/8 on Met alone. Randomized patients had a mean age of 56 years, 6 years of diabetes 60% Caucasian, 6% white, 30% Hispanic, mean body weight 90 kg, BMI 31.5. The Detemir group was 51% male. The NPH group was 59% male. Previous antidiabetic therapy was metformin alone, 19%, Met + TZD 37%, Met combo w/o TZD 44%. The mean dose of metformin was about 2200 mg.

Insulin titration:

Insulin Detemir (1U=24 nmol) or NPH (U=6nmol) were initiated at 0.1U/kg for FBG<180 mg/dl or 0.2 U/kg for FBG>180mg/dl. The dose was then increased to every three days to achieve a goal of FBG of 7 mmol/L. The mean initial dose of insulin was 0.17 U/kg for Detemir and 0.16 U/kg for NPH, about 15 units in both groups. At endpoint the mean dose of Detemir was 0.57 U/kg (about 51 units), compared to 0.45 U/kg (about 41 units) for NPH. The molar ratio Detemir/NPH was 4.19 at baseline, 4.8 at 2 months, and 4.98 at endpoint.

As shown in the table below, HbA1c values fell significantly in both arms. But the HbA1c value at EOS was lower in the NPH group than in the Detemir group. Because the upper limit of the 95% CI is 0.78 (>0. 4% units), the predefined criterion for non-inferiority was not fulfilled.

HbA1c values in Modified ITT population

	Detemir	NPH	Diff (95% CI)
Baseline	9.5	9.4	0.01
EOS	8.5	8.0	0.56 (0.33- 0.78)
Change from baseline	-0.9	-1.5	
P value	<0.0001	<0.0001	

FPG was the same in both groups at baseline (246 mg/dl) and endpoint (154mg/dl).

HbA1c response based on subgroups

The Sponsor performed the following sub-set analysis based on pretrial antidiabetic medication (metformin only, metformin plus TZD, metformin combo w/o TZD).

Metformin Only

	Detemir	NPH	Diff (95% CI)
Baseline	9.4	9.6	
EOS	7.8	7.7	-0.307,0.853
Change from baseline	-1.5	-2.0	
P value	<0.0001	<0.0001	
Metformin Dose	2065(1000-2550)	2112(1500-2550)	

Metformin Combo with TZD

	Detemir	NPH	Diff (95% CI)
Baseline	9.4	9.4	
EOS	8.7	8.0	0.23,1.15
Change from baseline	-0.6	-1.4	
P value	<0.0001	<0.0001	
Metformin Dose	2173(1000-2550)	2201(1000-2550)	

Metformin Combo without TZD

	Detemir	NPH	Diff (95% CI)
Baseline	9.6	9.4	
EOS	8.6	8.1	0.076, 0.81
Change from baseline	-0.9	-1.4	
P value	<0.0001	<0.0001	
Metformin Dose	2201(1500-2550)	2252(1000-2550)	

Based on this subset analysis, the Sponsor contends that Detemir met the test of non-inferiority to NPH in the metformin-only subset. However, this contention upon further analysis, seems poorly founded:

At the request of DMEDP, the Sponsor provided the doses of metformin at screening, baseline, and endpoint as well as the HbA1c ant screening and baseline. As shown in the tables below, there was an increase in the dose of metformin from screening to baseline in all groups. This is referred to as "optimization of metformin therapy" in the protocol. In the metformin-only subset, this change represented intensification of therapy and is manifested by fall in HbA1c and FPG **before** randomization. Thus some of the efficacy attributed to Detemir and NPH was probably a delayed effect of the increased dose of metformin. The claim of non-inferiority of Detemir to NPH is not valid because the contribution to total efficacy of the increased dose of metformin cannot be quantitated. By contrast, discontinuation of the other oral hypoglycemic agents in the metformin combo subsets led to exacerbation of hyperglycemia. Under these circumstances, Detemir was clearly inferior to NPH.

Mean doses of Metformin, mg

	INSULIN DETEMIR					NPH INSULIN			
	Met	w/oTZD	TZD	total		Met	w/oTZD	TZD	total
Screening	1768	1962	1889	1896		1743	2002	1907	1921
Baseline	2044	2201	2179	2163		2112	2245	2203	2206
EOS	2198	2235	2176	2205		2241	2243	2220	2234

Mean FPG mM

	INSULIN DETEMIR					NPH INSULIN			
	Met	w/oTZD	TZD	total		Met	w/oTZD	TZD	total
Screening	12.8	12.0	12.0	12.1		13.0	12.1	11.6	12.1
Baseline	12.0	14.1	13.9	13.6		12.3	13.8	13.7	13.5

HbA1c

	INSULIN DETEMIR					NPH INSULIN			
	Met	w/oTZD	TZD	total		Met	w/oTZD	TZD	total
Screening	9.8	9.6	9.3	9.5		9.8	9.5	9.5	9.5
Baseline	9.5	9.6	9.4	9.5		9.6	9.4	9.5	9.5

Effect of Hypertriglyceridemia

The Sponsor submitted a subset analysis based on fasting triglycerides. The data set was divided into three subsets, <250, 250-500, >500. For the sake of simplicity, only the <250 and > 500 subsets are shown in the following table (the 250-500 subset gives intermediate values for all the variables shown). The >500mg subset had higher levels of HbA1c at baseline and endpoint and used more insulin at endpoint than patients in the <250 subset. This finding is not surprising and reflects the insulin resistance that often accompanies hypertriglyceridemia. In both subsets, the reduction in HbA1c was about 60% greater with NPH than Detemir. Thus the decreased effectiveness of Detemir appears to occur across the board and is not specifically seen in patients with hypertriglyceridemia.

Insulin Dose and HbA1c by Baseline Triglyceride

	Triglyceride <250 mg/dl			Triglyceride > 250 mg/dl	
Detemir,	N	U/kg		N	U/kg
Baseline	172	0.2		25	0.2
EOS	180	0.5		26	0.8
Insulin NPH					
Baseline	94	0.2		11	0.2
EOS	101	0.4		11	0.7

Detemir	N	HbA1c(chng		N	HbA1c(chng
Baseline	179	9.3		27	10.3
EOS	171	8.4 **(-0.9)**		26	9.0 **(-1.3)**
Insulin NPH					
Baseline	101	9.4		11	9.6
EOS	95	8.0 **(-1.4)**		11	7.5 **(-2.1)**

Appears This Way
On Original

Summary of Subset Analyses by race/ethnicity done by DMEDP
- complete analyses found in review by Lee Pian,. Biostatistics

Change in HbA1c (baseline to EOS) by Race

		Insulin Detemir			NPH Insulin	
Caucasian	Baseline	172	9.28		86	9.33
	EOS		8.40			7.74
	Change		-0.88			-1.61
Others	Baseline	91	9.70		49	9.42
	EOS		8.42			8.11
	Change		-1.28			-1.30

The category "others" is broken down into black and Hispanic in the table below. (Asians and others are omitted because the numbers are too small.)

Black	Baseline	16	9.64		8	9.54
	EOS		8.14			8.19
	Change		-1.50			-1.35
Hispanic	Baseline	64	9.85		36	9.48
	EOS		8.50			8.09
	Change		-1.32			-1.38

Mean Dose of Insulin at Endpoint (by Race)

	Insulin Detemir, units			NPH Insulin, IU	
Caucasian	N=190	61.04		N=90	50.07
Others	N=116	37.17		N=65	31.58

The mean dose of metformin at endpoint was about 2200 mg in all subsets.

Conclusion: Trial 1337 failed to establish to equivalence of Insulin Detemir to NPH Insulin when used in combination with metformin in patients with type 2 diabetes. Although lower levels of HbA1c were achieved with NPH, levels of FPG at endpoint were the same in both treatments. This apparent discrepancy between HbA1c and FPG is consistent with the slower action of Detemir. The most important finding was the difference in response between Caucasian and non-Caucasian patients. Insulin Detemir and NPH insulin had the same efficacy in black and Hispanic patients. But Detemir was inferior to NPH in Caucasian patients. The efficacy of Detemir relative to NPH did not appear to be influenced by the fasting triglyceride level.

Comments on Efficacy:

Although the non-inferiority test with respect to HbA1c was nominally met in all phase 3 trials of insulin Detemir vs NPH in type 1 diabetes, methodological issues cloud interpretation of the results in all but one. The results of trial 1448, however, clearly demonstrate that patients given Insulin Detemir formulated at 2400 nmole/ml can achieve the same glycemic control as patients given NPH (600nmol/ml) without resorting to additional amounts of bolus insulin. Trial 1447 did not yield exactly the same finding, although both trials compared NPH at breakfast and bedtime in protocols and patients populations that are nearly identical. Patients on Detemir in trial 1447 received somewhat more insulin than patients on NPH. However, both groups achieved the same degree of glycemic control and the amount of additional insulin was very small.

Although trial 1448 lasted only 16 weeks, earlier trials and extensions have demonstrated the durability of Insulin Detemir. When taken as a whole, I believe that the Sponsor has met the regulatory standard for efficacy for the population of patients with type 1 diabetes that was studied. Unfortunately, the study population was largely Caucasian. None of the trials of type 1 diabetes were done in the United States and there are virtually no black or Hispanic patients.

The lack of black and Hispanic patients with type 1 diabetes would not necessarily prevent approval were it not for the findings with type 2 diabetes. Although three trials of Detemir vs NPH were done in type 2 diabetes, none establish the non-inferiority of Detemir. Indeed, the weight of evidence suggests that Detemir may indeed be inferior to NPH, at least as administered in these studies. The results of the American study, trial 1337 are particularly important and suggest a difference in response between white and non-white patients (black and Hispanic). The reason for this difference is open to speculation. A genetic basis is possible but I suspect that environmental factors (diet for instance) are equally likely. If the ethnic difference found in type 2 diabetes were also present in type 1 diabetes, non-white patients with type 1 diabetes would be in danger of being overdosed if given Detemir.

Some background on ethnic factors relating to type 1 diabetes is provided in the footnote below*. Without wishing a lengthy digression, I believe a few points should be made here regarding the Detemir application:

Given that type 1 diabetes is much more common in Northern Europe than elsewhere, it is not surprising that few black or Hispanic patients with type 1 diabetes were studied in this application. This is generally the case with trials of insulin products in type 1 diabetes. One trial of patients with type 2 diabetes in the United States might ordinarily have been expected to provide adequate exposure to black and Hispanic patients. But the discrepancy in response between white and non-white patients with type 2 diabetes needs to be further examined and explained.

The evidence suggests that a dosing regimen for Detemir that may be appropriate for white patients with type 1 diabetes and non-white patients with type 2 diabetes would

leave white type 2 patients inadequately treated and non-white type 1 patients over-treated. The white type 2 patients could potentially compensate by increasing the dose of Detemir or taking an additional medication, but the non-white type 1 patients would be at risk of hypoglycemia.

Finally it must be stressed that no advantage of Detemir over NPH has been demonstrated in any population. At best, once daily Detemir gives the same result as once daily NPH and twice daily Detemir gives the same result as twice daily NPH.

*Although type 2 diabetes is more common in blacks and Hispanics, classical (autoimmune) type I diabetes is more common in whites, particular in whites of Northern European origin. The world's highest incidence is 35/100,000 in Finland, followed by Scandanavia and Scotland. By contrast, the incidences in Mexico City and Tanzania are less than 3/100,000. Within the United States, the incidence appears to follow the ethnic origin of the population. The US Virgin Islands is an interesting example. The incidence among whites during an epidemic in 1984 was 28/100,000 . By contrast, Hispanics and blacks in the US Virgin Islands have incidences of about 8 and 7/100,000 respectively. This contrast in less apparent elsewhere in the USA. In Allegheny County the incidence among whites and non-whites is 18 and 12/100,000 respectively and in Jefferson Co the incidence among whites and non-whites is 16 and 12/100,000 respectively (data taken from fig 2, page 91 of Textbood of Diabetes Mellitus, 2nd edition, Alberti, Zimmet and DeFronzo.). A second form of type 1 diabetes predominates in the tropics. It is not immune-mediated and is believed to represent from chronic pancreatitis with pancreatic insufficiency (both endocrine and exocrine) stemming from early mal-nutrition.

V11 Review of Safety

Type 1 Diabetes:

Trial 1181

One subject in the Detemir group died. This was a 34-year-old male who was found dead after 2 1/2 months of Detemir. His diary indicated that he had been experiencing "elevated glucose levels at night and as a consequence, had injected himself with bolus insulin at bedtime (in addition to the prescribed basal insulin) without simultaneous food." Serious AE's attributable to drug were 5 cases of hypoglycemia on Detemir (3 withdrawals due to hypoglycemia), one case of hyperglycemia on Detemir and 4 cases of hypoglycemia on NPH. Injection site reactions occurred in 4/236 patients on Detemir and 1/224 patient on NPH. None were severe. Retinal abnormalities were reported in 7 patients on Detemir and 6 patients on NPH.

Major hypoglycemia beyond the first month occurred in 20 (8.7%) of Detemir patients and 12(5.5%) of NPH patients. There were a total of 31 events with Detemir and 16 with NPH. The text states that the relative risk of major hypoglycemia Detemir/NPH is 2.01 (95% cI 0.88-4.62) p=0.098. Major hypoglycemia during the first month occurred in 8(3.4%) of Detemir patients and 4(1.8%) of NPH patients. There were 8 events with Detemir and 7 with NPH during the first month.

Mean body weight at baseline was 76.5 for Detemir and 75.5 for NPH. At 26 weeks, patients on Detemir lost an average of 0.5 kg while patients on NPH gained an average of 0.7kg. ($p<0.001$ using ANOVA adjustment for baseline).

There were no other clinically relevant safety findings reported.

Extension:

There were no deaths during the 6-12 month extension. In the ITT population, 14 patients on Detemir had 17 major hypoglycemic events, compared to 9 patients on NPH with 9 events. Body weight increased an average of 0.1kg on Detemir and 0.6 kg on NPH.

Retinal disorder occurred in 7 Detemir patients and 10 patients on NPH. One additional patient on Detemir had a "vitreous disorder". Injection site lipohypertrophy was reported in 6 patients on Detemir and 2 on NPH. 3 patients on Detemir developed otosalpingitis during the extension compared to 1 during the original 6 months on Detemir and none on NPH.

Antibodies (% B/T), ITT

	Insulin Detemir n=154	NPH insulin n=134
Detemir specific antibody		
Baseline	2.71	3.32
12 months	7.81	3.46
Insulin Antibodies		
Baseline	0.77	0.72
12 months	0.78	0.74
Cross-reacting antibodies		
Baseline	14.1	13.8
12 months	20.2	14.8

The rise in Detemir specific and cross –reacting antibody in Detemir-treated patients vs NPH was highly significant $p<0.001$.

There was no correlation between change in antibodies and change in HbA1c or FPG. But there was a correlation between change in antibodies and change in Detemir dose. The Spearman correlation coefficient was 0.20-0.21 for both antibodies. The p value was 0.0495 for anti-Detemir and 0.0289 for cross-reacting antibody. For patients on NPH the correlation coefficient between change in cross-reacting antibody was 0.35, p-0.0005. There was no other significant correlation for NPH patients.

Trial 1205 with extension trial 1316

There were no deaths. Two subjects on Detemir withdrew because of severe AE's. One of these was worsening of necrobiosis diabetocorum. Major hypoglycemic events occurred in 14% of patients on Detemir and 21% of patients on NPH.

AE's related to "application site' was reported in 1.9% of patients on Detemir and 1.0% on NPH. "Allergic" were reported in 2.3% of patients on Detemir and 1.0% on NPH.

Clinically significant worsening of fundoscopy was reported in 1.4% of patients on Detemir and 3% of patients on NPH. There were no clinically relevant differences in laboratory safety evaluations.

Mean body weight at <- 3weeks was about 71.4 kg in both groups. The was a loss of 0.1 kg in Detemir patients, and gain of 1.2 kg in NPH patients. This difference of 1.34 kg at 52 weeks was statistically significant ($p=0.001$)

Trial 1335

There were no deaths. 2 Detemir patients were withdrawn because of severe hypoglycemia (MVA in one, seizure/coma in the other). Beyond the first month, major hypoglycemic events were reported in 6.5% of patients on Detemir and 8.9% on NPH

During the first month, major hypoglycemic events were reported in 1.3% of patients on Detemir and 2.4% on NPH. Beyond the first month, major hypoglycemic events were reported in 6.5% of patients on Detemir and 8.9% on NPH.

"Retinal disorder" was reported as an AE in 2.4% of patients on Detemir and 0.8% on NPH. Mean systolic blood pressure decreased 2.4 mm on Detemir and 1.6 on NPH. Mean weight loss on Detemir was 0.2 kg compared to a mean gain of 0.4 kg on NPH. Adjusting for baseline the mean difference between body weight at six months was –0.52 kg (p=0.024). " No clinically relevant findings were observed for any clinical laboratory or vital signs assessments."

Mean data on serum antibodies are shown in the table below. Of significance (p<0.001 vs NPH) was a rise of 3.4 % (B/T) in Detemir –specific antibodies in patients treated with Detemir and 3.7% in cross-reactive antibodies in patients treated with Detemir.

Antibodies (% B/T), ITT	Insulin Detemir	NPH insulin
Detemir specific antibody		
Baseline	1.55	1.83
6 months	4.88	1.85
Insulin Antibodies		
Baseline	0.98	1.06
6 months	1.04	1.14
Cross-reacting antibodies		
Baseline	12.9	12.2
6 months	16.6	12.2

No correlation between antibodies at six months and HbA1c or FPG at six months. However, significant correlations existed between dose of Detemir at six months and level of antibody. After adjusting for baseline characteristics, the correlation coefficient was 0.13 (p=0.009) for Detemir-specific antibody and 0.21 (p=0.0000) for cross-reactive antibody.

Study 1447

One subject in the Detemir group died. This was a 22-year-old male who was found dead after three months of Detemir. His diary indicated that he had been experiencing frequent episodes of hypoglycemia. 9/171(3.3%) had a serious AE. 2/129(1.6%) of patients on NPH had a serious AE. Six subjects were withdrawn from Detemir because of an AE (death, three injection site reactions, CVA, allergic reaction). None were withdrawn from NPH.

Major hypoglycemic events occurred in 3.7% of Detemir patients and 3.1% of NPH.

From table 10.5 - 19/271(7%) of patients on Detemir experienced visual AE's compared to 3/129 (2.3%) on NPH. 9 patients on Detemir reported "retinal disorder" compared to one patient on NPH. Retinal hemorrhage/edema, vitreous detachment and abnormal vision were reported by 6 patients on Detemir and none on NPH. The text describes three subjects (all on Detemir) who experienced deterioration in retinal examination from baseline to endpoint. In one case this was attributed to a marked decrease in HbA1c from 9.2% to 6.9%. One patient on Detemir developed cataract.

Four subjects (1.5%) on Detemir had an injection site reaction compared to 1 (0.8%) on NPH.

Body Weight:

Body weight changes little during the trial. However, patients on Detemir with dinner lost 0.4 kg on average compared to gains of 0.4 kg in patients on Detemir bedtime and 0.8 kg in patients on NPH bedtime.

Body weight for ITT

Body weight, kg	Detemir dinner	NPH bedtime	Detemir bedtime
Baseline	75.9	74.5	76.7
16 weeks	75.5	75.3	77.1

Pairwise comparison for this change is:

Detemir dinner-NPH bedtime	-1.3	p<0.0001
Detemir Bedtime – NPH bedtime	-0.5	p=0.081
Detemir dinner-Detemir bedtime	-0.7	p=0.015

There were "no clinically relevant differences" in clinical laboratory measurements including lipids

Trial 1448

There were no deaths. Serious AE's were reported in 5.1% of Detemir subjects and 3.0% of NPH. Hypoglycemia was reported as serious events in 4 patients on Detemir (3 coma, one hypoglycemia reaction resulting in an MVA) and 1 patients on NPH (coma). 3 of the Detemir patients with severe hypoglycemia were in the q 12-hr arm and one in the am/hs arm. Major hypoglycemic events over the entire study were reported in 6.6% of patients on Detemir q 12 hr, 10.6 on NPH am/hs and 10.8% of patients on Detemir am/hs. Minor hypoglycemic events over the entire study were reported in 88% of patients n Detemir q 12 hr, 89% on NPH am/hs and 88% of patients on Detemir am/hs. Overall, there was little difference in hypoglycemia between Detemir and NPH.

Injection site reactions were reported by 2.9% of patients on Detemir and no patients on NPH.

There were 3 subjects in the Detemir group found to have progression of retinopathy by fundoscopy. There were none with NPH. 1.4% on Detemir reported "retinal disorder" as an AE compared to 3.8% on NPH.

Body Weight:

Body weight changes little during the trial. There was no change for patients on Detemir compared to gains of 0.2 kg in patients on Detemir am/bedtime and 0.7 kg in patients on NPH am/bedtime.

Body weight for ITT (from table 4.32

Body weight, kg	Detemir q 12 hr	NPH am/hs	Detemir am/hs
<-2 weeks	74.5	75.7	75.2
16 weeks	74.5	76.4	75.4

Pairwise comparison for this change is:

Detemir 12 hr-NPH am/hs	-0.8	p<0.0061
Detemir am/hs – NPH am/hs	-0.6	p=0.04
Detemir dinner-Detemir bedtime	-0.2	p=0.4

There were "no clinically relevant differences" in clinical laboratory measurements including lipids.

Safety - Type 2 diabetes:

Trial 1166

There was one death in each arm, but neither appeared to be drug-related. One severe hypoglycemic event characterized as serious AE' occurred in each arm. Two patients on Detemir withdrew because of hyperglycemia and one because of injection site reaction. Other withdrawals (4 on Detemir, 2 on NPH did not appear to be related to study drugs. Major hypoglycemic events occurred in 1% of patients on Detemir and 2%in patients on NPH.

The number of subjects judged to have clinically significant change in fundoscopy at 6 months vs baseline was 4 subjects on Detemir and 6 on NPH. Patients on Detemir lost an average of 0.4kg compared to an average gain of 1.8 kg on NPH. There were no clinically significant changes identified in routine safety monitoring including lipids.

Trial 1336

There was one episode of sudden death on Detemir, a 69-year-old male who was found dead in his hotel bed on day 97. He had had a coronary bypass previously. In addition to the death, seven other patents on Detemir withdrew because of an AE compared to one on NPH. One patient on Detemir withdrew because of pruritits. The other withdrawals did not appear to be drug related. Major hypoglycemic events occurred in 1.8% of patients on Detemir and 1.9% on NPH. Body weight before and after the trial are shown in the table below.

Body weight for ITT

Body weight, kg	Detemir	NPH
<-3weeks	85.4	89.7
26 weeks	85.8	91.0

There were no clinically significant changes identified in routine safety monitoring including lipids and fundoscopy.

Trial 1337

There were 3/309 deaths on Detemir and 0/158 on NPH. Two of the deaths were CVA's. The third was a patient who was found with agonal respiration. He was presumed to have died of underlying cardiac disease. In addition to the three deaths, serious AE's were reported in 18 Detemir patients, none of which could reasonably be attributed to the drug. Serious AE's were reported in 10 NPH patients, one case of hypoglycemic coma which could reasonably be attributed to the drug. Adverse event leading two withdrawals occurred in 9 Detemir patients and 5 NPH patients. In two of the Detemir patients, the AE was an injection site reaction that could reasonably be attributed to the study drug.

Application site hematomas were reported in 5.2% of Detemir patients and 3.2% on NPH. Application site reactions were reported in 5.5% of Detemir patients and 5.7% on NPH.

Major hypoglycemic reaction occurred in no Detemir patterns and one patient on NPH. Triglyceride>1000developed in 2 Detemir patients and no NPH patients. Worsening of fundoscopy occurred in 3.6% of Detemir patients and 3.2% NPH. The mean weight change in the Detemir group was –0.4kg compared to +0.4 kg for the NPH group (p=.014). According to Novo Nordisk , this difference persisted even after adjusting for change in differences HbA1c. There were decreases in FFA and triglycerides in both groups. Otherwise there were no clinically significant changes in any of the safety measurements.

Safety Update

The 120 Days Safety Update submitted 4/7/03 provided little new information. Three deaths occurred in Detemir patients >30 days after completion of the trials. All three occurred in patients with type 2 diabetes and the trial medications cannot reasonably be implicated. In the ongoing trials, there have been two deaths on NPH and none on Detemir.

As with all insulin products, hypoglycemia is the greatest concern. 150/2641 (5.7%) of patients on Detemir reported at least one episode of major hypoglycemia compared to 109/1626 (6.7) patients on NPH. There were 328 episodes with Detemir than 180 with NPH. The Sponsor has calculated a rate of 0.3 episodes per patients year of exposed subjects for Detemir and 0.2 for NPH.

Summary of safety:

There were two deaths among patients with type 1 diabetes treated with Detemir. The circumstances surrounding these cases suggest that the deaths may have been the consequence of poor glycemic control. Although there were no deaths among NPH-treated patients, it must be born in mind that the trials had an unequal randomization. Total exposure among patients with type 1 diabetes was 1528 for Detemir and 865 for NPH. The two deaths on Detemir in approximately 1000 patient years is not very different from the 1.2 deaths per 1000 patients years reported in the DCCT trial (NEJM 1993, 329:977-86). In patients with type 2 diabetes there were 5/802 deaths on Detemir and 1/531 on NPH. Underlying cardiovascular disease probably caused all of these deaths, although two episodes of sudden death could possibly have been related to hypoglycemia.

The number of serious adverse events was similar between Detemir and NPH. The proportion of patients reporting serious hypoglycemic episodes was also similar, although the number of episodes per patient was slightly greater with Detemir. Injections site reactions were more common with Detemir in the trials of patients with type 1 diabetes only. For insulin-naïve patients with type 2 diabetes, there was no difference between Detemir and NPH with respect to injection site reactions.

Patients treated with Detemir either lost weight or gained less weight than patients treated with NPH. In some cases (trial 1166 for example), this difference in weight change reflected the inferiority of Detemir to NPH with respect to treatment of hyperglycemia. In trials 1447 and 1448, however, the relative lack of weight gain among Detemir-treated patients cannot be explained on the basis of poor glycemic control.

Insulin Detemir appeared to be more antigenic than NPH insulin. However, the difference appeared to have little, if any, clinical significance. There was a weak correlation (Spearman coefficient about 0.2) between antibodies and the dose of Detemir. There was no correlation between antibodies in HbA1c. Thus it appears that the possible effect of anti-Detemir antibodies could be overcome by a small increase in dose. A protocol for the method of detecting specific and cross-reacting antibodies is shown below. I believe this is sound methodology, and would like to see it applied to insulin-naïve patients with type 2 diabetes.

APPEARS THIS WAY
ON ORIGINAL

Methodology for Measuring Insulin Antibodies:
(answer to questions submitted 4/16/2003)

Series	Assay Mixture	Result represents the sum of:
A	Sample + buffer Insulin tracer	Background, insulin-specific and cross-reacting antibodies
B	Sample + cold Insulin + insulin tracer	Background with insulin tracer
C	Sample +cold Detemir +insulin tracer	Background and insulin specific antibodies
E	Sample +cold Detemir +Detemir tracer	Background with Detemir tracer
F	Sample +cold insulin +Detemir tracer	Background and Detemir antibodies

Insulin specific antibodies = C-B

Detemir-specific antibodies = F-E

Cross-reacting antibodies = A-C

V111 Dosing, Regimen, and Administrative Issues:

Proposed label

Description: The text should make it clear that

PD: The adjective ' should be deleted from the description of Detemir's action. should be deleted, or revised in a way that would be understandable to practicing physicians. Fig 1 should not include the ' but should include the comparable data for NPH.

PK The claim o should be deleted.

Distribution and Elimination: It is generally recognized that the rate-limiting step in insulin degradation is binding of insulin to its receptor. The bound insulin is metabolized by protease(s) associated with the cell surface and the internalized insulin fragments are metabolized by lysosomes. ' l are not informative and should not be referred to in the label. Studies of receptor-mediated degradation should be performed.

How supplied:

The Sponsor wishes to market 10 ml vials, 3 ml pre-filled syringes, and 3 ml cartridges/pens. Patients using vials often mix their basal and bolus insulins in the same syringe. It is likely that patients using Detemir will use NovoNordisk's insulin aspart as their bolus insulin. Mixing of Detemir with insulin aspart changes the absorption properties of both and should not be done.

1X. Use in Special Populations

The Sponsor should request a deferral of pediatric studies.

Demographic Worksheet

Application Information *(Enter all identifying information for the submission pertaining to this summary)*

NDA Number: 21536 Submission Type: N/A (pilot) Serial Number: N/A (pilot)

Populations Included In Application *(Please provide information for each category listed below from the primary safety database excluding PK studies)*

Category		Number Exposed To Study Drug		Number Exposed To Study Drug		Number Exposed To Study Drug
Gender	Males	1402	All Females	1044	Females >50	463
Age:	0-≤1 Mo.	0	>1 Mo.-≤2Year	0	>2-≤12	0
	12-16	0	17-64	2150	≥65	296
Race:	White	2239	Black	23	Asian	88
	Other	10 (86 Hispanic)				

Gender-Based Analyses *(Please provide information for each category listed below.)*

Category	Was Analysis Performed?				Was gender-based analysis included in labeling?	
			If no is checked, indicate which applies or provide comment below		Yes	No
Efficacy	☐ Yes	☑ No	☐ Inadequate #'s	☐ Disease Absent	☐	☑
Safety	☐ Yes	☑ No	☐ Inadequate #'s	☐ Disease Absent	☐	☑

Is a dosing modification based on gender recommended in the label? ☐ Yes ☑ No

If the analysis was completed, who performed the analysis ☐ Sponsor ☐ FDA

Age-Based Analyses *(Please provide information for each category listed below)*

Category	Was Analysis Performed?				Was age-based analysis included in labeling?	
			If no is checked, indicate which applies or provide comment below		Yes	No
Efficacy	☐ Yes	☑ No	☐ Inadequate #'s	☐ Disease Absent	☐	☑
Safety	☐ Yes	☑ No	☐ Inadequate #'s	☐ Disease Absent	☐	☑

Is a dosing modification based on age recommended in the label? ☐ Yes ☑ No

If the analysis was completed, who performed the analysis ☐ Sponsor ☐ FDA

Race-Based Analyses *(Please provide information for each category listed below)*

Category	Was Analysis Performed?				Was race-based analysis included in labeling?	
			If no is checked, indicate which applies or provide comment below		Yes	No
Efficacy	☐ Yes	☐ No	☒ Inadequate #'s	☐ Disease Absent	☐	☑
Safety	☐ Yes	☐ No	☒ Inadequate #'s	☐ Disease Absent	☐	☑

Is a dosing modification based on race recommended in the label? ☐ Yes ☑ No

If the analysis was completed, who performed the analysis ☐ Sponsor ☑ FDA

In the comment section below, indicate whether an alternate reason (other than "inadequate numbers" or "disease absent") was provided for why a subgroup analysis was NOT performed, and/or if other subgroups were studied for which the metabolism or excretion of the drug might be altered (including if labeling was modified).

Comment:

FDA performed an efficacy analysis according to race/ethnicity for the trial in which it there were data.

X. Conclusions and recommendation:

For patients with type 1 diabetes, Insulin Detemir appears to be as effective as NPH insulin. However, for patients with type 2 diabetes, the effectiveness of Detemir has not been convincingly demonstrated. Even when more is used, equivalent HbA1c reduction is not achieved with Detemir. Subset analysis of the data in type 2 diabetes suggests that the decreased efficacy of Detemir may be limited to white patients only. In black and Hispanic patients, Detemir and NPH gave similar results. This finding in type 2 diabetes calls into question the results of the trials in type 1 diabetes, because the trials of type 1 diabetes had virtually no black and Hispanic patients. If the ethnic/racial difference found in type 2 diabetes were true for patients with type 1 diabetes as well, black and Hispanic patients with type 1 diabetes patients would be at risk of hypoglycemia if dosed according to the proposed label. For these reasons, I believe that Detemir should not be approved until additional clinical studies are performed with African American and Hispanic patients (see appendix).

Other points:

The Sponsor should be encouraged to improve its methodology. It would be highly desirable to have a valid system with which to study Detemir action and degradation in vitro. It would be highly desirable to be able to predict the clinical response to Detemir based on short-term studies.

Appendix: Need for additional clinical studies

The efficacy of Detemir in type 2 diabetes has not been demonstrated. At best, it appears to be non-inferior to NPH in non-white patients only. Although the efficacy/safety of Detemir appears to be non-inferior to NPH in patients with type 1 diabetes, there was little, if any, exposure to black and Hispanic patients.

Additional studies should be done in the United States and should have exposure to African American, Latino and Caucasian patients in roughly equal proportions. In addition to classifying patients by race/ethnicity, data on genetic markers should be obtained. Patients should also be queried about environmental factors (diet especially) that could affect insulin action.

For patients with type 1 diabetes, information is needed about correct dosing for non-white patients. For patients with type 2 diabetes, a pivotal trial is needed to establish efficacy. I believe the following proposals would provide the information needed for approval

Type 1 diabetes:

The study should have two parts: part A and part B. Part A consists of open-label treatment with Detemir. To be enrolled, patients should have HbA1c of at least 7.5% at baseline. The dose of Detemir should be given twice daily and titrated to achieve a goal of HbA1c of 7.0%. Bolus therapy with regular insulin or aspart is maintained throughout and is not adjusted except for safety. Part A should last 3 months. Patients who complete part A with HbA1c of 7.5% or less are eligible to be enrolled into Part B. Part B is an open-label randomized comparison of Detemir to NPH with respect to change in HbA1c. It should last at least three months. Patients are randomized to Detemir vs NPH insulin (1:1) with stratification based on race/ethnicity (African American, Latino, Caucasian, other).

For part B, a positive result would be non-inferiority of Detemir to NPH for change in HbA1c with a margin of 0.4%.

Patients who drop out of part A because of "lack of efficacy" should be switched to NPH insulin and observed for an additional three months. Patients who fail to achieve the goal of HbA1c <7.5% at the end of part A should be treated with NPH insulin and observed for an additional three months. The treatment regimen used for NPH should be the same as the regimen used earlier for Detemir.

Data analysis for part A should be descriptive. It should consist of the HbA1c and insulin dose at baseline and endpoint. Mean data for the group as a whole and for the racial/ethnic subsets should be presented. For patients who are unable to achieve glycemic control on Detemir, HbA1c and insulin dose should be determined after three months of treatment with NPH.

Type 2 diabetes:

This should be a six-month comparison of Detemir to NPH. Patients taking other antidiabetic medications should have HbA1c of at least 7.5% at screening. The other antidiabetic medications should be discontinued during a 1-2 week run-in. Treatment naïve patients should have HbA1c of at least 8% at screening. To be eligible for randomization, patients should have FPG of at least 10 mM (180 mg/dl) at baseline. Patients should be randomized to Detemir vs NPH insulin (2:1) with stratification based on FPG, and race/ethnicity. Study drugs can be given once daily or twice daily and titrated to achieve a goal of FPG =7 mM. No other antidiabetic medications should be allowed. The primary endpoint measure should difference in HbA1c at endpoint with a non-inferiority margin of 0.4% to NPH. For the study to be considered analyzable, the mean reduction in HbA1c on NPH should be at least 1%. In addition, comparisons among the different ethnic/racial groups should be made for HbA1c, insulin dose, and antiinsulin/Detemir antibodies.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Robert Misbin
9/5/03 09:59:35 AM
MEDICAL OFFICER

David Orloff
9/16/03 05:51:52 PM
MEDICAL OFFICER

MEDICAL OFFICER REVIEW

Division of Metabolic and Endocrine Drug Products (HFD-510)

APPLICATION #:	21-536	APPLICATION TYPE:	New NDA.....
SPONSOR:	Novo Nordisk	PROPRIETARY NAME:	
CATEGORY OF DRUG:	Antidiabetic	USAN / Established Name:	Insulin Detemir
		ROUTE:	Injection.....
MEDICAL REVIEWER:	Robert I Misbin..	REVIEW DATE:	January 31, 2003.....

SUBMISSIONS REVIEWED IN THIS DOCUMENT

Document Date:	CDER Stamp Date:	Submission Type:	Comments:
Dec 5, 2002	Dec 9 2002	New NDA	

FILING MEMO

Signed: Medical Reviewer: Robert I Misbin MD Date: January 31, 2003

Medical Team Leader: _____ Date: _____

Filing Memo from Medical Officer:

The NDA can be filed

An advisory committee meeting is not recommended

Routine inspections should be done from studies 1447 and 1448. The specific sites can be selected by DSI.

Comments to be sent to the Sponsor:

The efficacy results in Type 1 patients are potentially confounded by the increased use of bolus doses of insulin in detemir-treated patients compared to the control (NPH). The Division's concern is the purported demonstration of non-inferiority for detemir may be the result of bias induced by a mean 6-18% relative increase in bolus insulin. This issue will be reviewed thoroughly from both clinical and statistical perspectives.

The Type 2 efficacy results are, on face, not encouraging. Only one of the three trials demonstrated non-inferiority of detemir to NPH. The efficacy for the single positive trial is potentially confounded by a mean 12% greater use of bolus doses of insulin in the detemir treatment group compared to NPH.

Exposure of "black" patients to detemir is small, only about 1% of the total patient population.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Robert Misbin
1/31/03 02:48:31 PM
MEDICAL OFFICER

David Orloff
1/31/03 04:55:15 PM
MEDICAL OFFICER