

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
21-536

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

**OFFICE OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS
REVIEW**

NDA: 21-536	Submission Date(s): December 20, 2004
Brand Name	Insulin detemir
Generic Name	Recombinant DNA origin injection
Reviewer	Wei Qiu, Ph.D., Jim (Xiaoxiong) Wei, MD, Ph.D.
Team Leader	Hae-Young Ahn, Ph.D.
OCPB Division	DPEII
ORM division	Metabolic and Endocrine Drug Products
Sponsor	Novo Nordisk
Submission Type	Resubmission
Formulation; Strength(s)	Injection; 100 Unites per mL (U-100); 10 mL vial, 3 mL PenFill® cartridges, 3 mL InnoLet®, and 3 mL FlexPen®
Indication	For once or twice-daily subcutaneous administration in the treatment of patients with diabetes mellitus who require basal (long acting coverage) insulin for the control of hyperglycemia

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1 Executive Summary

1.1 Recommendation

The Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation 2 (OCPB/DPE-2) has reviewed NDA 21-536 submitted on December 20, 2004 and finds it acceptable. Recommendation and labeling comments should be conveyed to the sponsor as appropriate.

1.2 Phase IV Commitments

None.

1.3 Summary of Clinical Pharmacology and Biopharmaceutics Findings

Race Effect

The dose-exposure and dose-response relationships for insulin detemir and NPH insulin in 14 Blacks, 15 Hispanics, and 14 Whites with type 2 diabetes were evaluated in an iso-glycaemic clamp trial. Over the dose ranges of 0.3 to 1.2 U/kg for insulin detemir and 0.3 to 1.2 IU/kg for NPH insulin, statistical analysis demonstrated no significant difference between the three ethnic groups with regards to AUC_{0-16h} or C_{max} values of insulin detemir and NPH insulin, respectively. In addition, the dose-response relationships for the three ethnic groups in terms of $AUC_{GIR,0-16h}$ were not significant different for both insulin detemir and NPH insulin.

Molar Dose Ratio of Insulin Detemir and NPH Insulin

Type 1 diabetes:

The molar dose ratio of insulin detemir and NPH insulin over the dose ranges of 0.15 to 0.6 U/kg for insulin detemir and 0.15 to 0.6 IU/kg for NPH insulin was evaluated in an iso-glycaemic clamp trial with 12 White type 1 diabetic patients. Results showed that the pharmacodynamic response ($AUC_{GIR,0-24h}$) of 1 unit (U) of insulin detemir was not different from 1 unit (IU) of NPH insulin. Therefore, the molar dose ratio of insulin detemir versus NPH insulin was 4.

Type 2 diabetes:

The molar dose ratio of insulin detemir and NPH insulin over the dose ranges of 0.3 to 1.2 U/kg for insulin detemir and 0.3 to 1.2 IU/kg for NPH insulin was evaluated in an iso-glycaemic clamp trial with 43 patients with type 2 diabetes (14 Blacks, 15 Hispanics, and 14 Whites). The pharmacodynamic response ($AUC_{GIR,0-16h}$) of 1.57 unit (U) of insulin detemir was similar to 1 unit (IU) of NPH insulin. The molar dose ratio of insulin detemir versus NPH insulin was 6.28.

2 Question Based Review

2.1 General Attributes of the Drug

1. What pertinent regulatory background or history contributes to the current assessment of the clinical pharmacology and biopharmaceutics of this drug?

The original new drug application was submitted on December 5, 2002 and was acceptable from the Clinical Pharmacology and Biopharmaceutics perspective. However, it was approvable due to the failure to consistently demonstrate efficacy (as defined by non-inferiority to NPH insulin). An approvable letter was issued on October 2, 2003. Although not approvability issues, the Clinical Pharmacology and Biopharmaceutic reviewer recommended the following in the approvable letter: (1) Develop improved methodology in order to achieve a valid system with which to study insulin detemir action and degradation in vitro; (2) The activity of insulin detemir with regard to CYP induction should be further investigated in humans. Studies should include in vitro induction study using human hepatocytes; (3) Establish a valid in vitro metabolic profile of insulin detemir.

The sponsor was also recommended to address the race/ethnicity issue using a clamp study (Study 1439) involving type 2 patients, equally divided among Blacks or African Americans, Whites of Hispanic or Latino origin, and Whites not of Hispanic or Latino origin during the meeting held on December 9, 2003 and following discussions on December 10, 16, and 17, 2003. The racial ethnic differences in pharmacodynamic response to NPH insulin and insulin detemir needed to be explored.

In August 2004, Dr. Jim Wei suggested the sponsor to provide an information package giving the rationale as to why the log-transformation method used in Trial NN304-1450 is valid for calculating Coefficient of Variation.

The re-submission included three PK/PD studies (Trials 1491, 1538, and 1439). The race/ethnicity issue was addressed in study 1439. In addition, the sponsor addressed the biopharm comments stated in the approvable letter as well as provided rationale for the log-transformation method used for the calculation of coefficient of variation.

2. How different is the in vitro insulin detemir degradation profiles compared to human insulin?

In the original submission, data obtained from cell homogenates or the cytosol fraction systems showed that the metabolism pathways of insulin detemir and human insulin were similar but not identical. The degradation pathways of human insulin in the cytosol fraction system were not in accordance with the widely accepted pathways in whole cell systems or in vivo. The difference between the sponsor's evaluation and literature data might be due to the exposure of human insulin to some enzymes in the cytosol fraction system but not in the whole cell systems or in vivo. Preliminary studies in whole cell systems (hepatocytes) were not informative because of very low recovery.

In this re-submission, the in vitro degradation of insulin detemir and human insulin was studied following incubation with Cathepsin D, an acidic endopeptidase isolated from hepatic endosomes. Literature data suggested that Cathepsin D may be identical to endosomal acidic insulinase (EAI), an acidic endopeptidase responsible for the metabolism of human insulin in vivo. Cathepsin D has the same cleavage specificity as EAI and the same initial cleavage products are found after incubation of human insulin.

For both insulin detemir and human insulin, the initial metabolites were $A^{1-21}-B^{1-24}$ and $A^{1-21}-B^{1-25}$ corresponding to a cleavage at residues $Phe^{B24}-Phe^{B25}$ and $Phe^{B25}-Tyr^{B26}$, respectively (**Figure 1**). The same initial metabolites for human insulin have previously been described in the literature and have been found both in vivo and in vitro. A few more metabolites were detected in both human insulin and insulin detemir and their molecular weight were calculated to be in the range of 3000 -3600 g/mol. However, the structures of these metabolites have not been assigned.

Based on Cathepsin D degradation study, the metabolic pathway of insulin detemir and human insulin were found to be the same. The initial steps of metabolism are the cleavages at residues $Phe^{B24}-Phe^{B25}$ and $Phe^{B25}-Tyr^{B26}$.

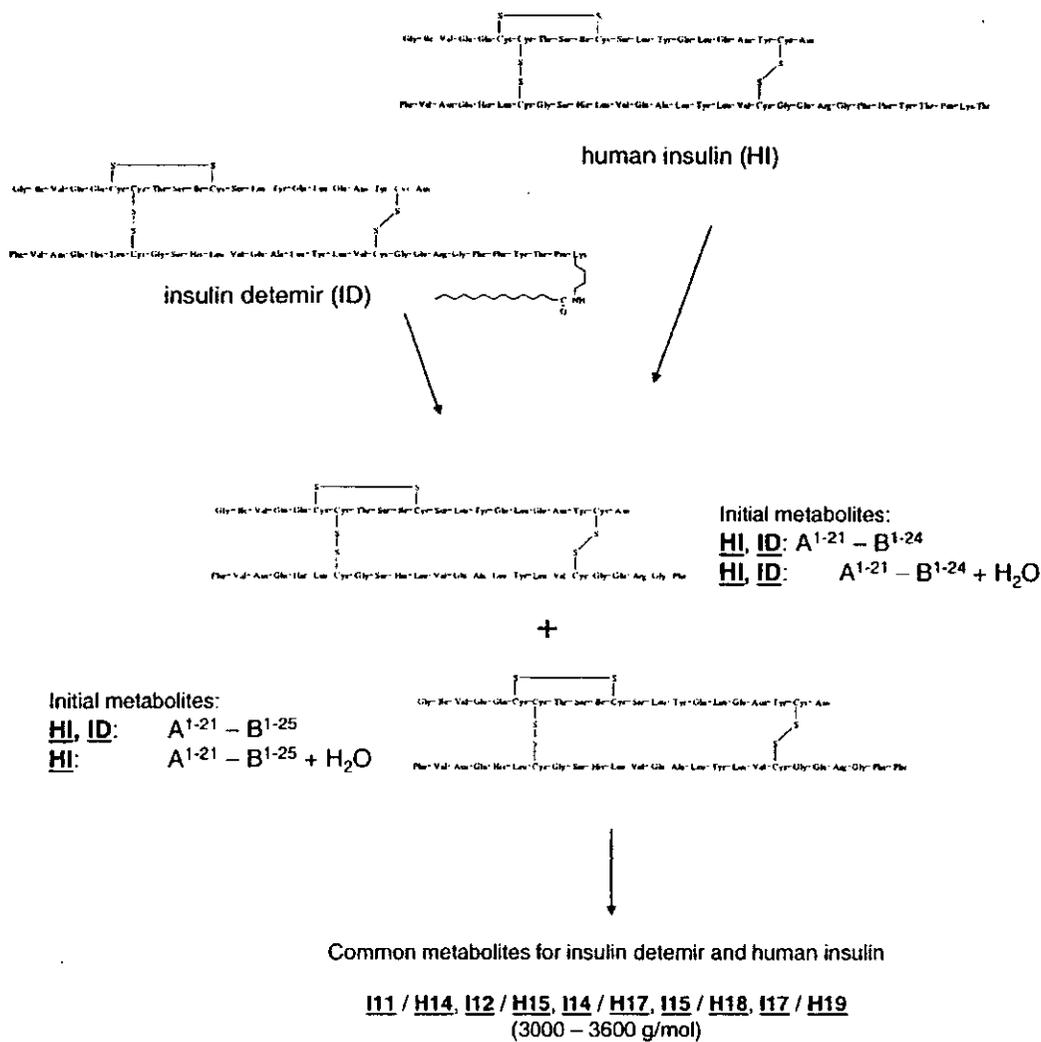


Figure 1. In vitro (Cathepsin D degradation) metabolic pathway of insulin detemir or human insulin (incubated separately)

2.2 General Clinical Pharmacology

1. What is the molar dose ratio of insulin detemir compared to NPH insulin in patients with type 1 and type 2 diabetes? If the dose ratio of insulin detemir to NPH insulin is different in type 1 and type 2 diabetes, what is the possible reason?

Type 1 diabetes:

In an iso-glycaemic clamp trial (Study 1419), twelve white patients with type 1 diabetes received two of the three doses of insulin detemir (0.15, 0.3, and 0.6 U/kg) and two of the three doses of NPH insulin (0.15, 0.3, and 0.6 IU/kg). Mean glucose infusion rate - time profiles are shown in **Figure 2**.

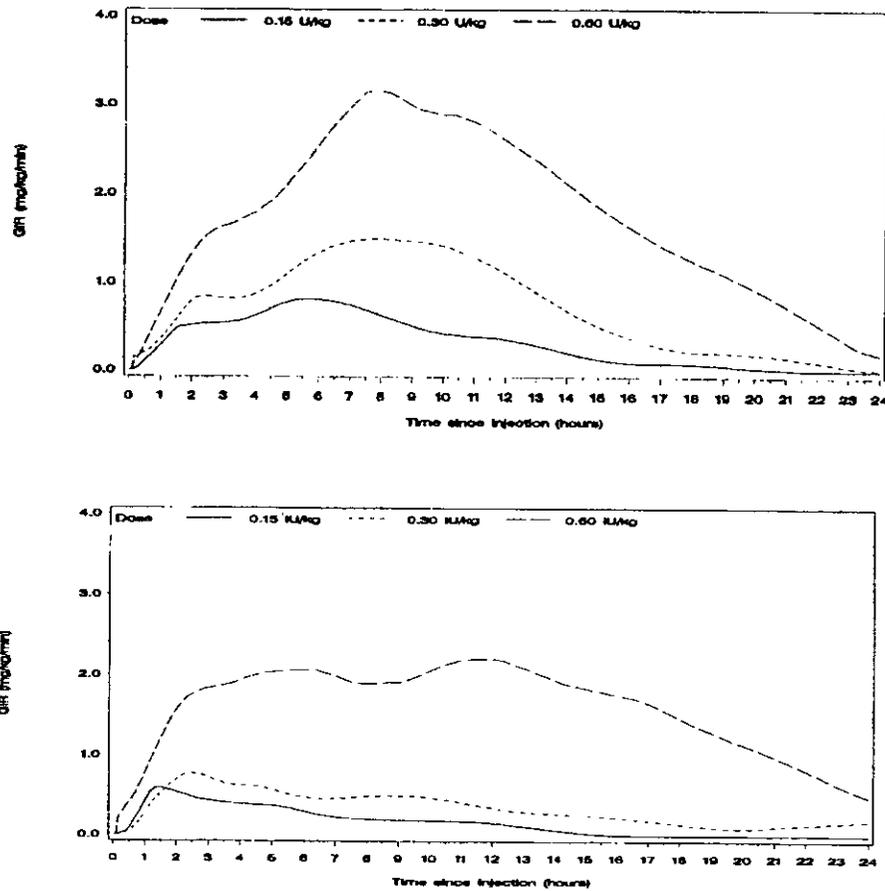


Figure 2. Mean GIR - time profiles for Insulin Detemir (Upper panel) and NPH insulin (Lower panel) in type 1 diabetes

Statistical analysis demonstrated that the dose-response with regard to $\log(AUC_{GIR,0-24h})$ versus $\log(Dose)$ could be described by a straight line. The intercept and slope for insulin detemir were 8.52 and 1.72, respectively. The intercept and slope for NPH insulin were 8.57 and 2.34, respectively. No statistical significant differences with regard to either the slope or intercept were found between insulin detemir and NPH insulin. Therefore, 1 U of insulin detemir was not different from 1 IU of NPH insulin. Since the molar concentration of the insulin detemir formulation was four times higher than the molar concentration of the NPH insulin (2400 versus 600 nmole/mL), the molar dose ratio between insulin detemir and NPH insulin is 4.

Type 2 diabetes:

In an iso-glycaemic clamp trial (1439), forty-three patients with type 2 diabetes (14 Blacks, 15 Hispanics, and 14 Whites) 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). Mean glucose infusion rate-time profiles are shown in Figures 3, 4, and 5.

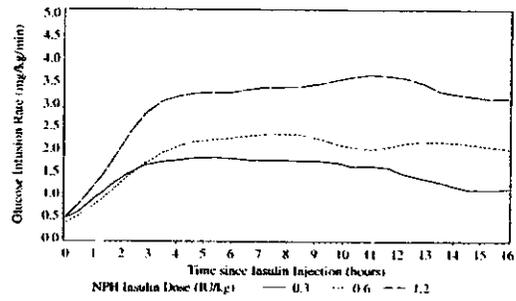
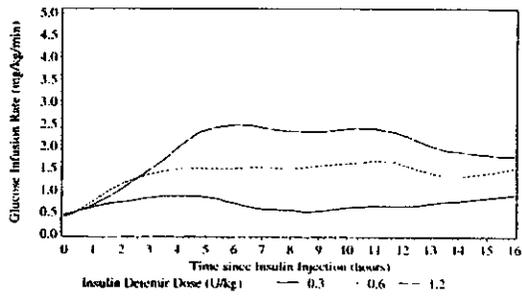


Figure 3 Mean GIR curves for insulin detemir (Left panel) and NPH insulin (Right panel) in Blacks with type 2 diabetes.

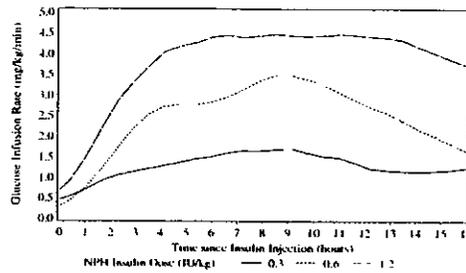
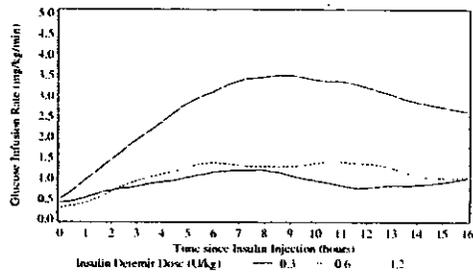


Figure 4. Mean GIR curves for insulin detemir (left panel) and NPH insulin (right panel) in Hispanics with type 2 diabetes

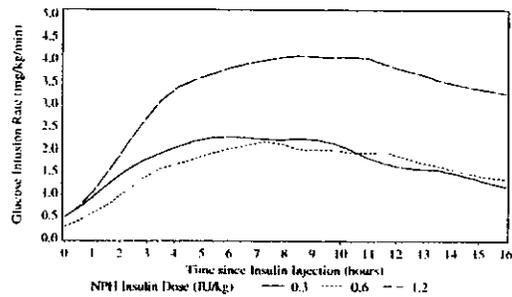
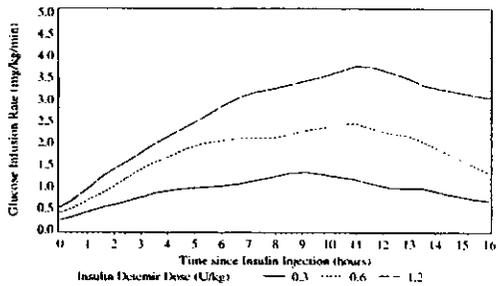


Figure 5. Mean GIR curves for insulin detemir (left panel) and NPH insulin (right panel) in Whites with type 2 diabetes

Statistical analysis showed that the dose-response relationship with regards to $\log(AUC_{GIR,0-16h})$ versus $\log(Dose)$ was linear for both insulin detemir and NPH insulin among the three ethnic groups. The regression lines for insulin detemir and NPH insulin were not parallel in the original analysis. When three of the 267 clamps showing zero or negative values for $AUC_{GIR,0-16h}$ were included and the values of $AUC_{GIR,0-16h}$ were set to 1, the regression lines between $\log(AUC_{GIR,0-16h})$ and $\log(Dose)$ were parallel for insulin detemir and NPH insulin. The common slope was 1.14. The intercept for insulin detemir and NPH insulin were 7.79 and 7.28, respectively. The dose ratio of insulin detemir versus NPH insulin on a unit scale was 1.57 U/IU with 95% confidence interval of 1.12 to 2.33. Thus, one unit of insulin detemir was less potent than one unit of NPH insulin. Since the molar concentration of the insulin detemir formulation was four times higher than the molar concentration of the NPH insulin (2400 versus 600 nmole/mL), the dose ratio between insulin detemir and NPH insulin on a molar scale was 6.28 with 95% confidence interval of 4.48 to 9.32.

In summary, the dose ratios of insulin detemir to NPH insulin in type 1 and type 2 diabetes were 4 and 6.28, respectively. Generally type 2 diabetes patients have greater Body Mass Index (BMI) than type 1 patients. In the above mentioned studies 1419 and 1439, type 2 patients had BMI values between 22.2 and 36.5 kg/m^2 while type 1 patients had BMI values in the range of 19 to 27 kg/m^2 . To further explore whether the dose ratio difference observed in type 1 and type 2 patients was caused by the different values of BMI in these two patient populations, the pharmacodynamic response ($AUC(GIR,0-16h)$) was plotted with BMI using the data obtained from type 2 diabetes enrolled in study 1439. Results (Figures 6) showed that for both insulin detemir and NPH insulin, the pharmacodynamic response tended to decrease as BMI increased. It appeared that the regression lines for insulin detemir and NPH insulin were parallel. Therefore, this finding suggested that the dose ratio difference found in type 1 and type 2 diabetes patients would not be explained by the different BMI values for these patient populations. Medical Officer (Dr. Robert Misbin) and Statistician (Dr. Lee Ping Pian) were involved in this analysis.

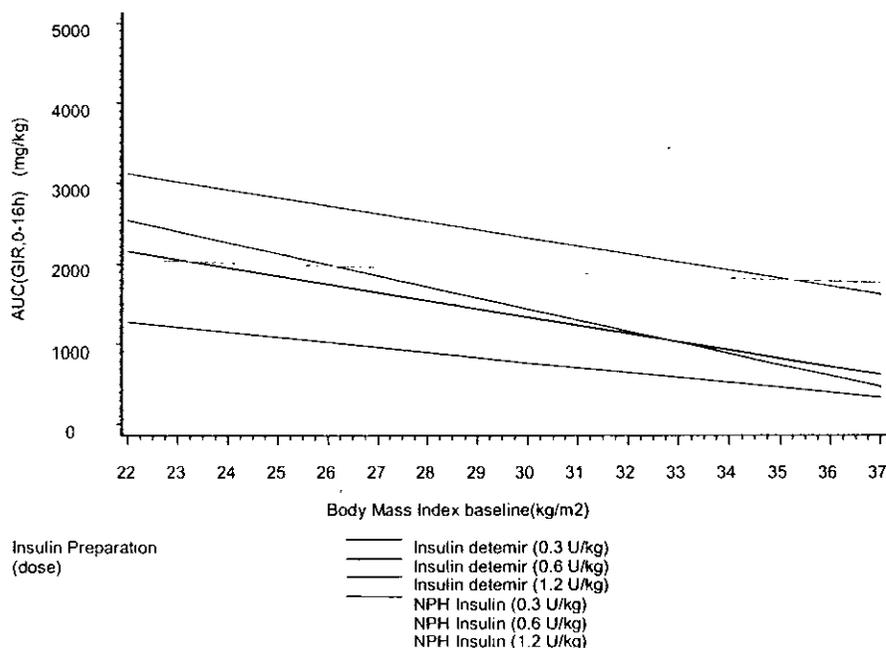


Figure 6. Relationship of $AUC(GIR,0-16h)$ and Body Mass Index (BMI) for Insulin Detemir and NPH insulin (Study 1439)

2. Is the log-transformation method used in Trial NN304-1450 valid for calculating Coefficient of Variation (CV)?

To address the issue of validation of log-transformation method in calculating CVs, the sponsor conducted a simulation study to evaluate four methods calculating within-subject CV. The four methods are as follows:

Method 1: mean of individual CVs

Method 2: square-root of the mean individual squared CVs

Method 3: ANOVA standard deviation (σ) of the log-transformed observation

Method 4: ANOVA standard deviation (σ) of the log-transformed observation, corrected by square root of $\exp(\sigma^2)-1$.

The simulation study resembled the design of trial NN304-1450 using a parallel-group design with sixteen subjects in each of the three treatment groups and with four replications for each subject. The within-subject variances for the log-transformed observations are set to 0.1, 0.2, and 0.4 in the three different treatment groups, corresponding to true within-subject CVs of 0.324, 0.471, and 0.701 respectively. A total of 1000 datasets were simulated. Results are shown in Table 1. It was evident that Method 1 had the most bias compared to other methods. Thus method 1 should not be used for the calculation of the within-subject CV as it provides underestimated values. Method 2 could be used if the data can not be assumed to be log-normally distributed. If the data can be assumed to be log-normally distributed methods 3 or 4 should be employed, as they provide better estimates.

Table 1. Bias in Deriving the Coefficient of Variation from four different Methods

	True CV	Mean CV (STD) derived from simulations	Mean bias in CV (STD) from simulations	Frequency: estimated CV lower than the true CV
Method 1	0.324	0.285 (0.0294)	0.039 (0.0295)	89.6%
	0.471	0.403 (0.0431)	0.068 (0.0431)	93.7%
	0.701	0.550 (0.0589)	0.151 (0.0589)	99.4%
Method 2	0.324	0.308 (0.0314)	0.017 (0.0314)	69.7%
	0.471	0.435 (0.0475)	0.035 (0.0475)	77.3%
	0.701	0.594 (0.0633)	0.107 (0.0633)	95.0%
Method 3	0.324	0.312 (0.0308)	0.013 (0.0308)	66.8%
	0.471	0.446 (0.0465)	0.024 (0.0465)	71.4%
	0.701	0.629 (0.0650)	0.072 (0.0650)	86.4%
Method 4	0.324	0.319 (0.0331)	0.004 (0.0332)	57.2%
	0.471	0.470 (0.0541)	0.000 (0.0542)	52.4%
	0.701	0.699 (0.0882)	0.002 (0.0882)	52.9%

The distribution histogram of the primary endpoint $AUC_{GIR,0-12h}$ in trial NN304-1450 indicates that it is reasonable to assume log-normal distribution of $AUC_{GIR,0-12h}$. The estimates of the within-subjects CVs using all four methods are presented in Table 2. Method 3 corresponds to the approach taken in the integrated clinical trial report and results were incorporated in the labeling. Method 1 and 2 provides smaller within-subject CVs compared to methods 3 and 4.

Table 2. Coefficient of Variation for $AUC_{GIR,0-12h}$ Calculated using four Different Methods (Trial 1450)

	Insulin detemir	NPH insulin	Insulin glargine
Method 1	24%	36%	40%
Method 2	26%	41%	45%
Method 3	27%	59%	46%
Method 4	27%	65%	48%

In conclusion, the log-transformation method is valid in calculating within-subject CVs.

2.3 Intrinsic Factors

1. Does race influence exposure (PK) and response (PD) of insulin detemir?

The dose-exposure and dose-response relationships of insulin detemir and NPH insulin in Blacks, Hispanics, and Whites with type 2 diabetes were investigated in Study 1439. The dose-exposure relationships for the three ethnic groups with regards to AUC_{0-16h} and C_{max} values of insulin detemir and NPH insulin were similar. Based on the area under the curve of glucose infusion rate from 0 to 16 hour post dose, $AUC_{GIR,0-16h}$, the dose-response relationships for the three ethnic groups were similar for insulin detemir and NPH insulin.

Study 1439 was a randomized, single-center, double-blind, single-dose, six-period, cross-over, iso-glycaemic clamp trial. 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). Trial products were administered s.c. in the thigh. The clamp was stopped after 16 hours post dose.

Fifty patients (17 Blacks, 16 Hispanic, and 17 Whites) were randomized. The patients comprised 16 women and 34 men, and the ratio between men and women was approximately the same for the three ethnic groups. Patients were between 24 and 73 years and had a BMI between 22.2 and 36.5 kg/m². Duration of diabetes varied from 1 to 30 years. Individual HbA1c varied between 4.6% and 10.2% with a mean HbA1c of 8.0% (7.5% for Blacks, 8.3% for Hispanics and 8.1% for Whites). Forty-three patients completed the study with 14 Blacks, 15 Hispanics, and 14 Whites.

The pharmacokinetic data were collected up to 16 hour post dose. The mean serum concentration-time curves for insulin detemir and NPH insulin in the three ethnic groups are shown in **Figures 7 and 8**. Statistical analysis demonstrated that there was no difference between the three ethnic groups with regards to AUC_{0-16h} or C_{max} values of insulin detemir and human insulin for insulin detemir and NPH insulin, respectively.

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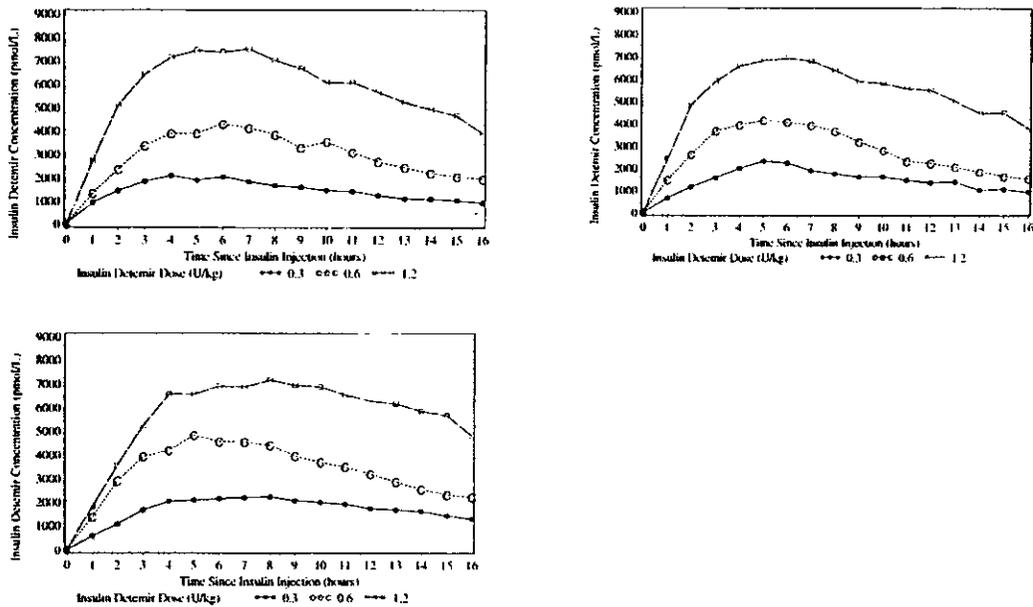


Figure 7. Mean insulin detemir concentration-time profiles in Blacks (Upper panel, left), Hispanics (Upper panel, right), and Whites (Lower panel)

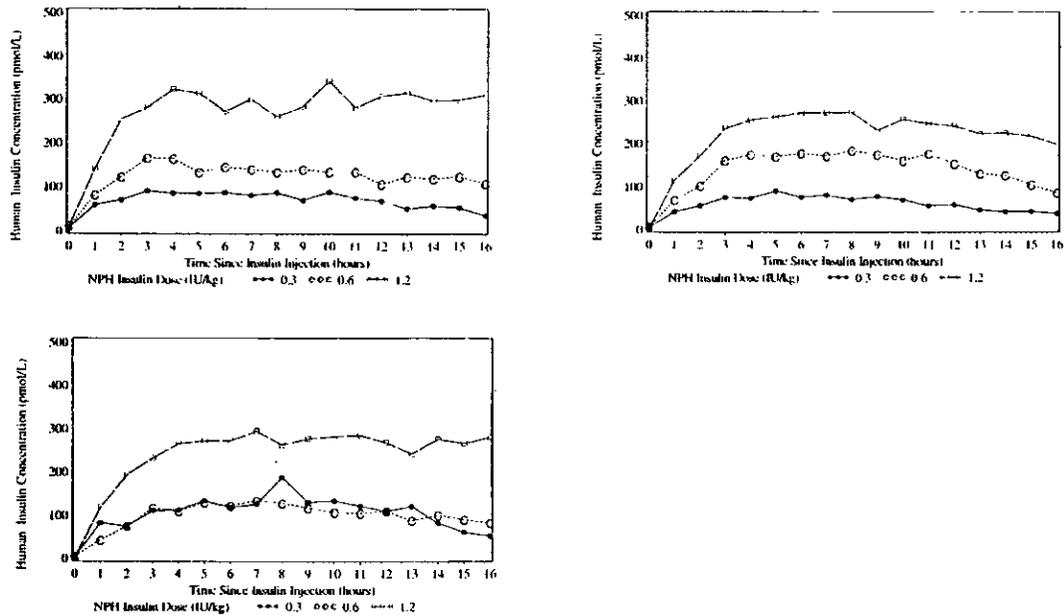


Figure 8. Mean human insulin concentration-time profiles in Blacks (Upper panel, left), Hispanics (Upper panel, right), and Whites (Lower panel)

Mean baseline-corrected glucose infusion rate (GIR) curves for insulin detemir and NPH insulin are shown in **Figure 9** and **10**. Statistical analysis of $AUC_{GIR,0-16h}$ suggested that the dose-response relationships for the three ethnic groups were similar for insulin detemir and NPH insulin.

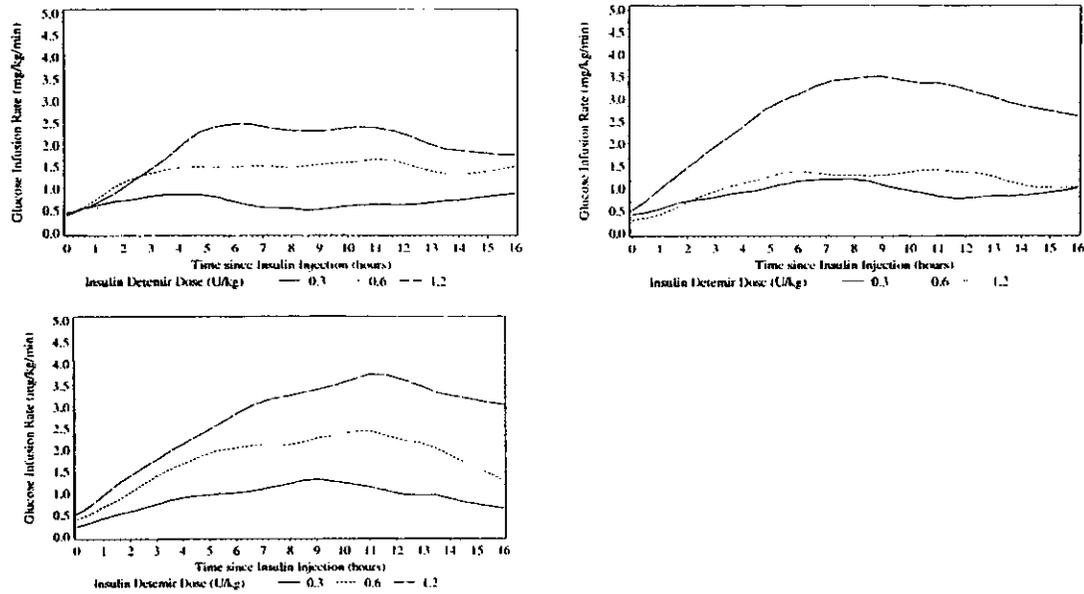


Figure 9. Mean GIR curves for Insulin Detemir in Blacks (Upper panel, left), Hispanics (Upper panel, right), and Whites (Lower panel)

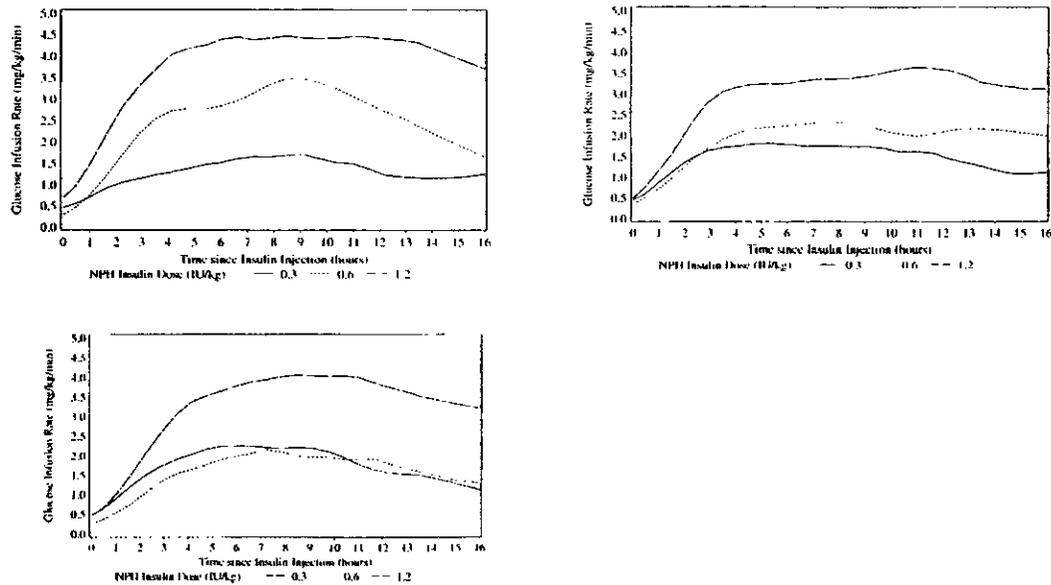


Figure 10. Mean GIR curves for NPH Insulin in Blacks (Upper panel, left), Hispanics (Upper panel, right), and Whites (Lower panel)

2.4 Extrinsic Factors

1. Drug-drug interactions

1) Is insulin detemir an inhibitor and/or an inducer of CYP2E1?

The effects of insulin detemir and human insulin on CYP2E1 activity was evaluated by incubating insulin detemir and human insulin with human hepatocytes from three donors (two lot cryopreserved plateable human hepatocytes and one lot freshly isolated human hepatocytes). Chlorzoxazone was used as the probe substrate of CYP2E1. Its concentrations were 40 and 200 μM which were in the reported range of K_m values. Results showed that insulin detemir and human insulin produced a concentration dependent decrease in CYP2E1 activity following 72 hours exposure to human hepatocytes in the presence of 1% human serum albumin. Study results were highly variable. Insulin detemir produced comparable maximal decrease (50% inhibition) in CYP2E1 activity as human insulin. Neither insulin detemir nor human insulin completely inhibited 6-hydroxylation of chlorzoxazone. Human insulin appeared to be more potent than insulin detemir. Taking the higher exposure to insulin detemir compared to human insulin, the inhibitions caused by insulin detemir and human insulin are not expected to be different.

2.5 General Biopharmaceutics

Not applicable.

2.6 Analytical Section

1. How are the active moieties identified and measured in the plasma in the clinical pharmacology and biopharmaceutics studies?

Insulin detemir was measured using a specific ELISA-assay not cross-reacting with human insulin. Total insulin detemir (free and albumin-bound) was measured. Lower limit of quantification (LLOQ) was —

3 Detailed Labeling Recommendations

Under **CLINICAL PHARMACOLOGY** section:



4 Page(s) Withheld

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

_____ § 552(b)(5) Deliberative Process

_____ § 552(b)(5) Draft Labeling

Synopsis

TITLE OF TRIAL	
A Randomised, Double-blind, Six-period, Cross-over, Dose-Response Trial Investigating the Pharmacodynamics and Pharmacokinetics of Single Doses of Insulin Detemir and NPH Insulin in Subjects of Blacks or African American, Whites of Hispanic or Latino origin and Whites not of Hispanic or Latino origin with Type 2 Diabetes	
INVESTIGATOR	
/	
TRIAL SITE	
—	
PUBLICATIONS	
None	
TRIAL PERIOD	DEVELOPMENT PHASE
26 February to 29 August 2004	Phase I
OBJECTIVES	
Primary objective	
<ul style="list-style-type: none"> To compare the dose-response of insulin detemir and NPH insulin in Blacks or African Americans, Whites of Hispanic or Latino origin and Whites not of Hispanic or Latino origin with type 2 diabetes over a range of clinically relevant doses based on the area under the glucose infusion rate curve from 0 to 16 hours 	
Secondary objectives	
<ul style="list-style-type: none"> To compare the dose-response of insulin detemir and NPH insulin in Blacks or African Americans, Whites of Hispanic or Latino origin and Whites not of Hispanic or Latino origin with type 2 diabetes over a range of clinically relevant doses based on the area under the insulin concentration curve from 0 to 16 hours To evaluate the acute safety profile of insulin detemir in Blacks or African Americans, Whites of Hispanic or Latino origin and Whites not of Hispanic or Latino origin with type 2 diabetes over a range of clinically relevant doses 	
METHODOLOGY	
<p>This trial was a randomised single-centre, double-blind, single-dose, six-period, cross-over, iso-glycaemic clamp trial investigating the dose-response relationship of insulin detemir and NPH insulin in Blacks, Hispanics and Whites with type 2 diabetes. The trial included eight (or nine) visits: a Screening Visit (Visit 1) was performed to assess subject eligibility. Subjects receiving combination treatment with insulin and OAD(s) discontinued all OAD(s) and attended the clinic for an additional Screening Visit (Visit 1B) after the washout period. Visit 1 (or Visit 1B) took place 5 to 28 days before the first dosing visit. Six dosing visits (Visits 2 to 7) were carried out 4 to 14 days apart, and a Follow-up Visit (Visit 8) was conducted within 14 days after the last dosing visit. Randomisation took place at the first dosing visit (Visit 2). On each dosing day human insulin infusion was initiated at least two hours before trial product administration to achieve an iso-glycaemic clamp level at 7.2 ± 1 mmol/L – 129.6 ± 18 mg/dL. No i.v. bolus injection was allowed within three hours before administration of the trial product. One hour prior to trial product administration, the insulin infusion rate was fixed at a rate of 0.2 mU/kg/min. Six different treatments were chosen for this trial; 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). Trial product was administered s.c. in the thigh and iso-glycaemia was maintained by the — which automatically calculated the appropriate adjustments of the intravenous glucose infusion rate (GIR). Blood samples were drawn during the entire clamp for analysis of serum concentration of insulin detemir, human insulin and C-peptide. The clamp was stopped after 16 hours.</p>	

NUMBER OF SUBJECTS PLANNED AND ANALYSED				
	All	Blacks	Hispanics	Whites
Screened	122	41	45	36
Randomised	50	17	16	17
Exposed	48	16	16	16
Completed	43	14	15	14

- 'Blacks' in this trial included people who considered themselves 'Black' or 'African American'
- 'Hispanics' in this trial included people who considered themselves 'White of Hispanic or Latino origin'
- 'Whites' in this trial included people who considered themselves 'White not of Hispanic or Latino origin'.

All exposed subjects were included in the evaluation of pharmacodynamics, pharmacokinetics and safety.

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION
 Men or women ≥ 18 years of age with type 2 diabetes belonging to one of the three ethnic groups Blacks, Hispanics or Whites. Body mass index (BMI) $< 35 \text{ kg/m}^2$, $\text{HbA}_{1c} \leq 10\%$ based on analysis from central laboratory with no clinical significant diseases. Subjects should have a history of diabetes of at least one year and should have been treated with insulin for at least three months with or without combination with ≤ 2 oral antidiabetic agents prior to inclusion.

TEST PRODUCT, DOSE AND MODE OF ADMINISTRATION, BATCH NUMBER
 Insulin detemir 100 U/mL (2400 nmol/mL) delivered in 3.0 mL Penfill[®] cartridges was administered s.c. in the thigh at three different doses: 0.3, 0.6 and 1.2 U/kg. Batch number NQ50409.

DURATION OF TREATMENT
 Six single doses (three different doses of insulin detemir and three different doses of NPH insulin) were administered to each subject during a 16-hour iso-glycaemic clamp at six different dosing visits (Visits 2 to 7) with 4 to 14 days in between.

REFERENCE THERAPY, DOSE AND MODE OF ADMINISTRATION, BATCH NUMBER
Reference Therapy
 NPH insulin (Human isophane insulin) 100 U/mL (600 nmol/mL) delivered in _____ was administered s.c. in the thigh at three different doses: 0.3, 0.6 and 1.2 IU/kg. Batch number NQ50438.

Insulin used to facilitate iso-glycaemia before trial product administration
 Human soluble insulin (_____) 100 IU/mL (600 nmol/mL) delivered in _____ was administered as i.v. bolus injection and as a fixed continuous i.v. infusion before trial product administration to facilitate iso-glycaemia. Batch number NQ50703.

CRITERIA FOR EVALUATION – PHARMACODYNAMICS AND PHARMACOKINETICS

- Glucose infusion rate (GIR)
- Insulin detemir serum concentration
- Human insulin serum concentration
- C-peptide serum concentration

CRITERIA FOR EVALUATION – SAFETY

- Physical examination (head-eyes-ear-nose-throat (HEENT), cardiovascular system, respiratory system, nervous system, gastro-intestinal system and musculoskeletal system)
- Vital signs (pulse and blood pressure)
- Standard 12-lead ECG
- Clinical laboratory tests (haematology, biochemistry, urinalysis)
- Adverse events (AEs)

STATISTICAL METHODS

Primary Endpoint

- $AUC_{GIR,0-16h}$, area under the glucose infusion rate curve from 0 to 16 hours

Secondary Endpoints

- GIR_{max} , maximum glucose infusion rate
- t_{GIRmax} , time to maximum glucose infusion rate
- AUC_{0-16h} , area under the insulin serum concentration curve from zero to 16 hours
- C_{max} , maximum insulin serum concentration
- t_{max} , time to maximum insulin serum concentration

Statistical Analysis

The overall significance level was set to 5%, and accordingly 95% confidence intervals ($CI_{95\%}$) were calculated for the relevant parameter estimates. For model reduction tests, solely used as a model check, a significance level of 1% was used.

Primary Analysis

The primary endpoint, $AUC_{GIR,0-16h}$, was calculated as the area under the smoothed GIR curve using the trapezoidal technique on interpolated points. The GIR curves were baseline-adjusted to account for the constant insulin infusion. The primary analysis addressed the primary objective of the trial, i.e., to compare the dose-response relationship for insulin detemir and for NPH insulin in Blacks, Hispanics and Whites with type 2 diabetes. The dose-response relationship within the three ethnic groups was evaluated in an ANOVA approach using log-transformed $AUC_{GIR,0-16h}$ as the dependent variable, and ethnic group, insulin dose/preparation and interaction effects as fixed effects and subject as a random effect to account for correlation within subjects. Due to the long washout period between clamps no carry-over effect was expected, and was hence not accounted for in the model.

Secondary Analysis

GIR_{max} and t_{GIRmax} were derived as the maximum of the smoothed GIR curve for each iso-glycaemic clamp and the corresponding time (measured from insulin injection). AUC_{0-16h} was approximated using the trapezoidal technique. C_{max} was determined as the maximum of all valid concentration measurements for each measurement series and t_{max} was determined as the corresponding time-point. GIR_{max} , AUC_{0-16h} and C_{max} were log-transformed and analysed using an ANOVA setup with ethnic group, insulin dose/preparation and interactions as fixed effects and subject as a random effect using an approach similar to the one used for $AUC_{GIR,0-16h}$. The time to maximum endpoints (t_{max} and t_{GIRmax}) were evaluated by summary statistics.

Safety Endpoints

Adverse events (AEs) and abnormal outcomes or changes in physical examination, vital signs (pulse and blood pressure), standard 12-lead ECG and clinical laboratory tests (haematology, biochemistry and urinalysis) were summarised.

DEMOGRAPHY OF TRIAL POPULATION

A total of 50 subjects (17 Blacks, 16 Hispanics and 17 Whites) were randomised into this trial. The subjects comprised 16 women and 34 men, and 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/m^2 . Mean age and mean BMI 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 HbA_{1c} varied between 4.6% and 10.2% with a mean HbA_{1c} of 8.0% (7.5% for Blacks, 8.3% for Hispanics and 8.1% for Whites). Fasting C-peptide was between 0.17 and 2.42 nmol/L.

Synopsis

TITLE OF TRIAL	
A randomised, double-blind, four-period, cross-over, dose-response trial investigating the pharmacodynamics and pharmacokinetics of single s.c. doses of insulin detemir and NPH insulin in subjects with type 1 diabetes mellitus	
INVESTIGATOR	
TRIAL SITE	
PUBLICATIONS	
None	
TRIAL PERIOD	DEVELOPMENT PHASE
02 April to 16 May 2002	Phase I
OBJECTIVES	
Primary objective:	
<ul style="list-style-type: none"> To describe the dose ratio of insulin detemir and NPH insulin over a range of clinically relevant doses based on area under the glucose infusion rate curve ($AUC_{GIR,0-24h}$) 	
Secondary objectives:	
<ul style="list-style-type: none"> To evaluate the dose-response relationship of insulin detemir and NPH insulin on endogenous glucose production (EGP) and peripheral glucose uptake (PGU) To characterise the pharmacodynamic and pharmacokinetic profiles of insulin detemir and NPH insulin including the duration of action To characterise the between-subject pharmacodynamic and pharmacokinetic variability of insulin detemir and NPH insulin 	
METHODOLOGY	
<p>This trial was a randomised, single-centre, double-blind, four-period, cross-over, dose-response trial in subjects with type 1 diabetes. The trial included six visits: a Screening Visit (5 to 21 days before the first dosing day), four dosing visits (7 to 21 days apart) and a Follow-up Visit (within 21 days after the last dosing visit). Randomisation took place at the first dosing visit. On each dosing day, infusion of human insulin was initiated approximately four hours before trial product administration to achieve iso-glycaemic clamp level (7.2 mmol/L), and primed continuous infusion of $[6,6-^3H_2]$glucose was initiated approximately three hours before trial product administration to achieve steady state. Up to one hour prior to trial product administration, glucose could be infused in order to facilitate the clamp. Six different treatments were chosen for this trial; three doses of insulin detemir (0.15, 0.3 and 0.6 U/kg) and three doses of NPH insulin (0.15, 0.3 and 0.6 IU/kg). However, for practical reasons, only four glucose clamps could be employed, and thus each subject received two of the three possible doses of insulin detemir and two of the three possible doses of NPH insulin. The trial products were administered s.c. in the abdomen. After trial product administration, the human insulin infusion was decreased gradually in steps of approximately 25% and was ultimately completely withdrawn when plasma glucose had dropped 0.3 mmol/L compared to the pretrial level. At this time, intravenous (i.v.) infusion of glucose (enriched with $[6,6-^3H_2]$glucose) was initiated to maintain plasma glucose levels of 7.2 mmol/L. Glucose infusion was continued until plasma glucose concentrations consistently exceeded 7.8 mmol/L. The clamp was stopped when plasma glucose concentration exceeded 11.1 mmol/L or after 24 hours, whichever came first. Blood samples were drawn during the entire clamp.</p>	

<p>NUMBER OF SUBJECTS PLANNED AND ANALYSED</p> <p>A total of 14 subjects were screened and 12 subjects were randomised and completed the trial. All 12 subjects were included in the pharmacodynamic, pharmacokinetic and safety analyses.</p>
<p>DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION</p> <p>Subjects with type 1 diabetes (men or women) ≥ 18 years of age. C-peptide negative (≤ 0.03 nmol/L), fasting HbA_{1c} ≤ 12 % and body mass index (BMI) < 30 kg/m². Subjects should have a history of diabetes of at least one year.</p>
<p>TEST PRODUCT, DOSE AND MODE OF ADMINISTRATION, BATCH NUMBER</p> <p>Insulin detemir 100 U/mL (2400 nmol/mL) delivered in 3.0 mL Penfill® cartridges was administered subcutaneously (s.c.) in the abdomen at three different doses: 0.15, 0.3 and 0.6 U/kg. Batch number KQ50522</p>
<p>DURATION OF TREATMENT</p> <p>Four single doses (two different doses of insulin detemir and two different doses of NPH insulin) were administered at four different dosing visits (Visits 2 to 5) with 7 to 28 days in between.</p>
<p>REFERENCE THERAPY, DOSE AND MODE OF ADMINISTRATION, BATCH NUMBER</p> <ul style="list-style-type: none"> • NPH insulin (—) 100 IU/mL (600 nmol/mL) delivered in — was administered s.c. in the abdomen at three different doses: 0.15, 0.3 and 0.6 IU/kg. Batch number LQ50039. • Human soluble insulin (—) 100 IU/mL (600 nmol/mL) delivered in — was administered as continuous i.v. infusion before s.c. injection of trial product. Batch number LQ50666.
<p>CRITERIA FOR EVALUATION - PHARMACODYNAMICS AND PHARMACOKINETICS</p> <p>Pharmacodynamic variables:</p> <ul style="list-style-type: none"> • Glucose infusion rate (GIR) • Unlabelled glucose and [6,6-²H₂]glucose plasma concentration to determine endogenous glucose production (EGP) and peripheral glucose uptake (PGU) • Human insulin infusion rate (initiated before dosing of trial products) to determine onset of action for insulin detemir/NPH insulin • Glucose plasma concentration to determine end of action for insulin detemir/NPH insulin • FFA plasma concentration <p>Pharmacokinetic variables:</p> <ul style="list-style-type: none"> • Insulin detemir serum concentration • Human insulin serum concentration
<p>CRITERIA FOR EVALUATION - SAFETY</p> <ul style="list-style-type: none"> • Physical examination (HEENT, cardiovascular system, respiratory system, nervous system, gastrointestinal system, and musculoskeletal system) • Vital signs (pulse and blood pressure) • Electrocardiogram (ECG) • Clinical laboratory tests (haematology, biochemistry and urinalysis) • Adverse events (AEs)

STATISTICAL METHODS

Primary endpoint:

$AUC_{GIR,0-24h}$ (area under the GIR curve from 0 to 24 hours) was determined from the individual smoothed GIR curves

Secondary endpoints:

Pharmacodynamic endpoints: Duration of action was defined as the time interval from 50% reduction in i.v. human insulin infusion following trial product administration until the glucose concentration consistently exceeded 18.3 mmol/L (150 mg/dL) after the last glucose infusion. GIR_{max} (maximum glucose infusion rate) and $tGIR_{max}$ (time to GIR_{max}) were determined from the individual smoothed GIR curves. $AOC_{EGP,0-24h}$ (area over the EGP curve from 0 to 24 hours), EGP_{min} (minimum EGP) and $tEGP_{min}$ (time to EGP_{min}) were determined from the individual smoothed EGP curves, and $AUC_{PGU,0-24h}$ (area under the PGU curve from 0 to 24 hours), PGU_{max} (maximum PGU) and $tPGU_{max}$ (time to PGU_{max}) were determined from the individual smoothed PGU curves. $AOC_{FFA,0-24h}$ (area over the free fatty acid concentration-time curve from 0 to 24 hours) was determined from the individual smoothed FFA curves.

Pharmacokinetic endpoints: $AUC_{0-\infty}$, AUC_{0-5h} , AUC_{0-24h} , C_{max} , t_{max} , MRT, λ and $t_{1/2}$ were determined from the individual serum concentration-time curves of insulin detemir and NPH insulin.

Statistical analysis:

The overall significance level was set to 5%, and accordingly 95% confidence intervals (95% CI) were calculated for the relevant parameter estimates, unless otherwise stated.

Primary analysis:

The primary endpoint, $AUC_{GIR,0-24h}$, was analysed using an ANOVA model with treatment period, insulin dose and type, and the interaction between insulin dose and type as fixed effects. The log-transformed baseline-GIR was included as a continuous effect and subject as a random effect.

Secondary analysis:

Pharmacodynamic endpoints: Statistical analyses for duration of action, GIR_{max} , $AOC_{EGP,0-24h}$, $AUC_{PGU,0-24h}$, EGP_{min} , PGU_{max} and $AOC_{FFA,0-24h}$ were carried out similarly to the primary analysis. $tGIR_{max}$, $tEGP_{min}$ and $tPGU_{max}$ were summarised.

Pharmacokinetic endpoints: $AUC_{0-\infty}$ and C_{max} were analysed similarly to the primary endpoint. t_{max} , MRT, λ , $t_{1/2}$, AUC_{0-24h} and AUC_{0-5h} were summarised.

Safety endpoints:

Adverse events and changes from baseline in physical examination, vital signs, ECG, haematology, biochemistry and urinalysis were listed.

DEMOGRAPHY OF TRIAL POPULATION

Twelve white subjects with type 1 diabetes (eight men and four women) between 25 and 62 years of age and BMI between 19 and 27 kg/m². Duration of diabetes varied from 12 to 36 years. C-peptide was between 0.002 and 0.015 nmol/L, and HbA_{1c} was between 5.4% and 8.8%.

PHARMACODYNAMIC AND PHARMACOKINETIC RESULTS

Glucose Infusion Rate

- $AUC_{GIR,0-24h}$ and GIR_{max} tended to be higher for insulin detemir than for NPH insulin when equal unit doses were compared; however there was no statistically significant difference.
- There was a tendency towards lower ratio of $AUC_{GIR,0-24h}$ between insulin detemir and NPH insulin with increasing dose.
- Dose proportionality was accepted for insulin detemir and NPH insulin in the dose range from 0.15 to 0.6 (I)U/kg with regard to $AUC_{GIR,0-24h}$ and GIR_{max} .

Molar Dose Ratio

- The molar dose ratio between insulin detemir and NPH insulin was estimated to 2.7 (95% CI [1.4; 5.1]) when equal unit doses were compared (four times higher molar doses of insulin detemir compared to NPH insulin).

PHARMACODYNAMIC AND PHARMACOKINETIC RESULTS continued

Duration of Action

- Duration of action was 17 hours for 0.3 U/kg insulin detemir and 13 hours for 0.3 IU/kg NPH; however, the difference was not statistically significant.

Endogenous Glucose Production and Peripheral Glucose Uptake

- There was a greater reduction of EGP for insulin detemir than for NPH insulin with regard to $AOC_{EGP,0-24h}$ ($p = 0.07$) and EGP_{min} ($p = 0.02$).
- There was a tendency towards a more steep increase in PGU with dose for insulin detemir than for NPH insulin ($p = 0.06$ with regard to PGU_{max}).
- Dose proportionality was accepted for insulin detemir and NPH insulin in the dose range from 0.15 to 0.6 (1)U/kg with regard to $AOC_{EGP,0-24h}$, EGP_{min} , $AUC_{PGU,0-24h}$ and PGU_{max} .
- The molar dose ratios based on $AOC_{EGP,0-24h}$ and $AUC_{PGU,0-24h}$ were estimated to 2.6 (90% CI [1.6; 4.0]) and 3.3 (90% CI [1.9; 5.6]), respectively.

Lipid Metabolism

- There was no statistically significant difference between insulin detemir and NPH insulin with regard to $AOC_{FFA,0-24h}$ or FFA_{min} .

Pharmacokinetic Dose Proportionality

- Dose proportionally was observed for insulin detemir with regard to AUC_{0-24h} and C_{max} .
- Dose proportionally was observed for NPH insulin with regard to AUC_{0-24h} .
- C_{max} increased less than proportionally with NPH insulin dose.

Pharmacodynamic and Pharmacokinetic Variability

- Pharmacodynamic within-subject variability was lower with insulin detemir than with NPH insulin with regard to $AUC_{GIR,0-24h}$, GIR_{max} and duration of action, and the differences were statistically significant ($p < 0.05$).
- There was no statistical significant difference in pharmacodynamic between-subject variability for insulin detemir or NPH insulin.
- Pharmacokinetic variability within subjects and between subjects was lower for insulin detemir than for NPH insulin.

SAFETY RESULTS

- One TEAE (unlikely related to the trial products) was reported during the trial.
- No SAEs were reported, and no subjects were withdrawn due to AEs.
- There were no clinical relevant findings in other safety parameters including clinical laboratory tests.
- Insulin detemir was safe and well tolerated.

CONCLUSIONS

- The molar dose ratio based on $AUC_{GIR,0-24h}$ between insulin detemir and NPH insulin was estimated to 2.7 (95% CI [1.4; 5.1]) within the investigated dose range (0.15 to 0.6 (1)U/kg).
- Duration of action was longer for 0.3 U/kg insulin detemir (17 hours) than for 0.3 IU/kg NPH insulin (13 hours); however, the difference was not statistically significant.
- Reduction of endogenous glucose production was greater for insulin detemir than for NPH insulin.
- The increase in peripheral glucose uptake with dose was steeper for insulin detemir than for NPH insulin.
- Pharmacokinetic dose proportionally was observed for insulin detemir within the investigated dose range (0.15 to 0.6 (1)U/kg).
- Pharmacodynamic and pharmacokinetic variability within subjects and between subjects was lower for insulin detemir than for NPH insulin.
- No safety concerns were raised during the trial.

The trial was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice.

Synopsis

TITLE OF TRIAL A randomised, double-blind, four-period, cross-over, dose-response trial investigating the pharmacodynamics and pharmacokinetics of single doses of insulin detemir and NPH insulin in subjects with type 2 diabetes	
INVESTIGATOR /	
TRIAL SITE /	
PUBLICATIONS None	
TRIAL PERIOD 31 March to 02 June 2003	DEVELOPMENT PHASE Phase 1
OBJECTIVES Primary objective <ul style="list-style-type: none">To compare the dose-response of insulin detemir and NPH insulin in subjects with type 2 diabetes over a range of clinically relevant doses based on area under the glucose infusion rate curve from 0 to 24 hours and if possible to estimate the molar dose ratio. Secondary objectives <ul style="list-style-type: none">To compare the pharmacodynamic and pharmacokinetic profiles of insulin detemir and NPH insulin including the duration of action.To compare the pharmacodynamic and pharmacokinetic variability of insulin detemir and NPH insulin.To evaluate the dose-response relationship of insulin detemir and NPH insulin on endogenous glucose production (EGP) and peripheral glucose uptake (PGU) and C-peptide secretion.	
METHODOLOGY <p>This trial was a randomised, single-centre, double-blind, four-period, cross-over, dose-response trial in subjects with type 2 diabetes. The trial included six visits; a Screening Visit (5 to 28 days before the first dosing day), four dosing visits (7 to 28 days apart) and a Follow-up Visit (within 21 days after the last dosing visit). Randomisation took place at the first dosing visit. On each dosing day, infusion of human insulin was initiated approximately four hours before trial product administration to achieve iso-glycaemic clamp level (7.2 mmol/L), and primed continuous infusion of [$6,6\text{-}^2\text{H}_2$]glucose was initiated approximately three hours before trial product administration to achieve steady state. Up to one hour before trial product administration, glucose could be infused in order to facilitate the clamp. Eight different treatments were chosen for this trial: four doses of insulin detemir (0.2, 0.4, 0.8 and 1.6 U/kg) and four doses of NPH insulin (0.2, 0.4, 0.8 and 1.6 IU/kg). However, for practical reasons, only four glucose clamps could be employed for each subject, thus each subject was randomised to a sequence comprising two out of the four doses of insulin detemir and two out of the four doses of NPH insulin. Trial product was administered s.c. in the thigh, and glucose was infused to maintain the clamp level. The clamp was stopped when plasma glucose concentration exceeded 11.1 mmol/L or after 24 hours, whichever came first. Blood samples were drawn during the entire clamp.</p>	
NUMBER OF SUBJECTS PLANNED AND ANALYSED Nineteen subjects were screened, and 15 subjects were randomised. All 15 subjects completed the trial and were included in the pharmacodynamic, pharmacokinetic and safety analysis.	
DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION Subjects with type 2 diabetes (men or women), ≥ 18 years of age, body mass index (BMI) $< 30 \text{ kg/m}^2$, $\text{HbA}_{1c} \leq 10\%$ based on analysis from central laboratory. Subjects should have a history of diabetes of at least one year and treatment with insulin for a minimum of three months.	

<p>TEST PRODUCT, DOSE AND MODE OF ADMINISTRATION, BATCH NUMBER</p> <p>Insulin detemir 100 U/mL (2400 nmol/mL) delivered in 3.0 mL Penfill® cartridges was administered subcutaneously (s.c.) in the thigh at four different doses: 0.2, 0.4, 0.8 and 1.6 U/kg. Batch number MQ50301.</p>
<p>DURATION OF TREATMENT</p> <p>Four single doses (two different doses of insulin detemir and two different doses of NPH insulin) were administered to each subject at four different dosing visits (Visits 2 to 5) with 7 to 28 days in between.</p>
<p>REFERENCE THERAPY, DOSE AND MODE OF ADMINISTRATION, BATCH NUMBER</p> <p>Reference therapy: NPH insulin () 100 IU/mL (600 nmol/mL) delivered in () was administered subcutaneously (s.c.) in the thigh at four different doses: 0.2, 0.4, 0.8 and 1.6 IU/kg. Batch number LQ50601.</p> <p>Insulin used to achieve the clamp level before trial drug administration: Human soluble insulin () 100 IU/mL (600 nmol/mL) delivered in () was administered as continuous intravenous (i.v.) infusion before trial product administration to facilitate iso-glycaemia. Batch number LQ50666.</p>
<p>CRITERIA FOR EVALUATION – PHARMACODYNAMICS AND PHARMACOKINETICS</p> <p>Pharmacodynamic variables:</p> <ul style="list-style-type: none"> • Glucose infusion rate (GIR) • Unlabelled glucose and [6,6-²H₂]glucose plasma concentration to determine endogenous glucose production (EGP) and peripheral glucose uptake (PGU) • Human insulin infusion rate (initiated before dosing of trial product) to determine onset of action for insulin detemir/NPH insulin • C-peptide serum concentration • Glucose plasma concentration to determine end of action for insulin detemir/NPH insulin • Free fatty acid (FFA) plasma concentration <p>Pharmacokinetic variables:</p> <ul style="list-style-type: none"> • Insulin detemir serum concentration • Human insulin serum concentration
<p>CRITERIA FOR EVALUATION – SAFETY</p> <ul style="list-style-type: none"> • Physical examination (HEENT, cardiovascular system, respiratory system, nervous system, gastro-intestinal system and musculoskeletal system) • Vital signs (diastolic and systolic blood pressure and pulse) • Standard 12-lead ECG • Clinical laboratory tests (haematology, biochemistry and urinalysis) • Adverse events (AEs)
<p>STATISTICAL METHODS</p> <p>Primary endpoint</p> <ul style="list-style-type: none"> • $AUC_{GIR,0-24h}$: area under the glucose infusion rate curve from 0 to 24 hours <p>Secondary Endpoints</p> <p>Pharmacodynamic Endpoints</p> <ul style="list-style-type: none"> • Duration of action • GIR_{max}: maximum of the smoothed glucose infusion rate curve • $tGIR_{max}$: time to maximum of the smoothed glucose infusion rate curve • $AOC_{EGP,0-24h}$: area over the endogenous glucose production (EGP) curve from 0 to 24 hours compared to baseline • $AUC_{PGU,0-24h}$: area under the peripheral glucose uptake (PGU) curve from 0 to 24 hours compared to baseline • EGP_{min}: minimum EGP • PGU_{max}: maximum PGU • $tEGP_{min}$: time to minimum EGP • $tPGU_{max}$: time to maximum PGU • $AOC_{FFA,0-24h}$: area over the free fatty acid (FFA) curve from 0 to 24 hours compared to baseline • FFA_{min}: minimum FFA plasma concentration

<ul style="list-style-type: none"> • $AOC_{C_{pep},0-24h}$: area over the C-peptide serum concentration curve from 0 to 24 hours compared to baseline • $C_{pep_{min}}$: minimum C-peptide serum concentration <p>Pharmacokinetic Endpoints:</p> <ul style="list-style-type: none"> • $AUC_{0-\infty}$: area under the insulin serum concentration-time curve from 0 to infinity • AUC_{0-5h}: area under the insulin serum concentration-time curve from 0 to 5 hours • AUC_{0-24h}: area under the insulin serum concentration-time curve from 0 to 24 hours • C_{max}: maximum insulin serum concentration • t_{max}: time to maximum insulin serum concentration • MRT: mean residence time of insulin • λ_z: terminal elimination rate constant of insulin • $t_{1/2}$: terminal half-life of insulin • CL: insulin clearance <p>Statistical Analysis The overall significance level was set to 5%, and accordingly 95% confidence intervals ($CI_{95\%}$) were calculated for the relevant parameter estimates.</p> <p>Primary Analysis The primary analysis addressed the primary objective of the trial, i.e., to compare the dose-response of insulin detemir and NPH insulin and if possible estimate the molar dose ratio in subjects with type 2 diabetes. The primary endpoint, AUC_{GIR}, was analysed using an analysis of variance model with treatment period and insulin dose and type and the interaction between insulin dose and type as fixed effects, subject as a random effect with a variance depending on insulin preparation and an error term with a covariance depending on insulin preparation. Due to the long washout period between the dosing visits, no carry-over effect was expected and was therefore not accounted for in the model.</p> <p>Secondary Analysis Pharmacodynamic Endpoints The secondary pharmacodynamic endpoints were analysed similarly to the primary endpoint. The endpoints were log-transformed before entering the analysis.</p> <p>Pharmacokinetic Endpoints The secondary pharmacokinetic endpoints, AUC_{0-24h} and C_{max}, were evaluated for dose linearity. The endpoints, $AUC_{0-\infty}$, AUC_{0-5h}, t_{max}, MRT, λ_z, $t_{1/2}$, and CL were summarised.</p> <p>Safety Endpoints Adverse events and changes from baseline in physical examination, vital signs, ECG, haematology, biochemistry and urinalysis were listed.</p>
<p>DEMOGRAPHY OF TRIAL POPULATION</p> <p>The trial included 15 white subjects with type 2 diabetes (12 men and 3 women) between 40 and 73 years of age and a BMI between 22.3 and 29.6 kg/m². Duration of diabetes varied from 3 to 28 years, and HbA_{1c} was between 6.4% and 8.4%.</p>
<p>PHARMACODYNAMIC AND PHARMACOKINETIC RESULTS</p> <ul style="list-style-type: none"> • The dose-response profiles for insulin detemir and NPH insulin with regard to $AUC_{GIR,0-24h}$ were parallel on logarithmic scales within the investigated dose range (0.2 to 1.6 (I)U/kg). • The glucose-lowering effect, as measured by $AUC_{GIR,0-24h}$, of 1 U of insulin detemir was not statistically significantly different from 1 IU of NPH insulin. • Duration of action could not be estimated according to the method described in the statistical analysis plan. • There was no statistically significant difference between insulin detemir and NPH insulin with regard to $AOC_{EGP,0-24h}$, $AUC_{PGU,0-24h}$, $AOC_{FA,0-24h}$ or $AOC_{C_{pep},0-24h}$. • Less within-subject variability was observed for insulin detemir compared to NPH insulin based on $AUC_{GIR,0-24h}$ and GIR_{max}. • Dose linearity was shown for insulin detemir with regard to AUC_{0-24h} and C_{max}. • Dose linearity was not shown for NPH insulin with regard to AUC_{0-24h} and C_{max}.

SAFETY RESULTS

- Four TEAEs were reported during the trial.
- One TEAE (injection site reaction) was evaluated as probably related to the trial product (0.4 U/kg insulin detemir).
- No SAEs were reported after trial product administration, and no subjects were withdrawn due to AEs.
- No clinically relevant findings in other safety parameters including clinical laboratory tests were reported.

CONCLUSIONS

- Parallel dose-response profiles were obtained for insulin detemir and NPH insulin with regard to $AUC_{GIR,0-24h}$ on logarithmic scales.
- The potency estimate between insulin detemir and NPH insulin on a unit scale was not statistically significantly different from 1, i.e., one unit of insulin detemir was equal to one unit of NPH insulin in subjects with type 2 diabetes.
- Less within-subject variability was observed for insulin detemir compared to NPH insulin with regard to $AUC_{GIR,0-24h}$ and GIR_{max} .
- There was no statistically significant difference between insulin detemir and NPH insulin with regard to glucose metabolism assessed by reduction of endogenous glucose production and stimulation of peripheral glucose uptake.
- There was no statistically significant difference between insulin detemir and NPH insulin with regard to suppression of FFA and C-peptide.
- Duration of action could not be estimated in subjects with type 2 diabetes by this clamp technique.
- Dose linearity was shown for insulin detemir with regard to the pharmacokinetic endpoints AUC_{0-24h} and C_{max} .
- Dose linearity could not be shown for NPH insulin with regard to the pharmacokinetic endpoints, AUC_{0-24h} and C_{max} .
- No safety concerns were raised during the trial.

The trial was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice.

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OFFICE OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA: 21-536	Submission Date(s): 12/05/02, 03/03/03, 03/07/03, 05/01/03
Brand Name	Levemir™
Generic Name	Insulin Detemir (rDNA origin) injection
Reviewer	Xiaoxiong (Jim) Wei, M.D., Ph.D.
Team Leader	Hae-Young Ahn, Ph.D.
OCPB Division	Division of Pharmaceutical Evaluation II
ORM division	Division of Endocrine and Metabolic Drug Products (HFD-510)
Sponsor	Novo Nordisk
Relevant IND(s)	50,283
Submission Type; Code	NME, 1S
Formulation; Strength(s)	100 U/ml (2400 nmol/ml)
Dosing regimen	Basal insulin, once or twice a day, subcutaneously injection. Dosing is dependent on individual patients' glucose levels.
Indication	Type 1 or insulin-dependent diabetes mellitus (IDDM) Type 2 or non-insulin-dependent diabetes mellitus (INDDM)

1 Executive Summary

On December 5, 2002, Novo Nordisk submitted NDA 21-536 for Levemir™ (insulin detemir) 100 U/ml for injection. Insulin detemir is a long-acting insulin analog produced by recombinant DNA in Yeast followed by chemical synthesis. Insulin detemir differs from human insulin in that the amino acid molecule in position B30 has been omitted, and a 14-C fatty acid chain has been attached to position B29. Insulin detemir is designed to provide diabetic patients with basal insulin, once or twice a day. Dosing is dependent on individual patients' levels of hyperglycemia. The sponsor provided 35 studies to support "Human Pharmacokinetics and Biopharmaceutics".

The absolute bioavailability of insulin detemir is ranging from 59% to 72% in different studies. A linear pharmacokinetics has been observed from the doses investigated from 0.1U/kg to 1.6 U/kg. There is a slight accumulation after multiple doses (ratio =1.2). The injection sites may affect its bioavailability. AUC (0-5h) was 30-40% larger and Cmax approximately 20% higher following subcutaneous administration in the deltoid and the abdomen than in the thigh. Insulin detemir was absorbed at a slightly slower rate in patients with Type 2 diabetes than in patients with Type 1 diabetes. Serum insulin detemir concentrations, as measured by AUC_{0-16h} and Cmax, tended to be lower for patients with Type 2 diabetes than for patients with Type 1 diabetes.

More than 98% insulin detemir in bloodstream is bound to albumin. Volume of distribution for Insulin detemir is small. It is estimated that the Volume of Distribution at steady state is ranging from 0.065 – 0.1 L/kg.

Based on in vitro metabolism studies with cytosol, insulin detemir has a similar metabolic pathway to human soluble insulin for breakup of disulfide bond and chain A. For chain B, human soluble insulin has multiple fragments, but not for insulin detemir. However, these study results differ from what have been reported in literature regarding human insulin metabolism. From rat liver microsomal studies, insulin detemir induces CYP1A family and CYP2E1 up to 30% as well as total cytochrome P450 activity up to 21%.

Insulin detemir has a terminal half-life of 4-7 hours depending on doses after subcutaneous administration in Type 1 diabetic patients. Clearance of insulin detemir is independent of dose. Clearance of insulin detemir (0.0018 to 0.0027 L/min/kg) is approximately 6-9 times lower than that of human insulin (0.0158 to 0.0196 L/min/kg). Clearance tends to be higher in patients with Type 2 diabetes than in patients with Type 1 diabetes for both insulin detemir and human insulin.

There are no pharmacokinetic differences between gender and race (Japanese versus Caucasians). No correlation could be established between creatinine clearance and the pharmacokinetics of insulin detemir. The extent of bioavailability of insulin detemir as estimated by AUC (0-∞) appears to decrease with increasing degree of hepatic insufficiency. Elderly subjects tend to have higher exposure than young adults. No overall differences were found in the pharmacokinetic profiles between children, adolescents, and adults for insulin detemir.

The time interval during which the effects were above 50% of GIR_{max} (maximal glucose infusion rate) occurred from 3 to 4 hours and up to approximately 19 hours depending on doses after subcutaneous administration. Dose response was investigated in terms of pharmacodynamic parameters, AUC_{GIR} and GIR_{max}. Both pharmacokinetic and pharmacodynamic endpoints were linear for the dose range studied (0.1U/kg to 1.6 U/kg).

There was a marked effect of premixed treatment (mixture of insulin detemir with insulin aspart) on early insulin aspart profiles. The AUC_{(Aps (0-2h))} of insulin aspart following premixed treatment was approximately 60% of the value following separate administration. Insulin detemir following premixed treatment, with C_{max} observed to increase by approximately 10% over that of the value following separate injections. Therefore, pre-mixture of insulin detemir with insulin aspart should be avoided.

1.1 Recommendation

The Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation II (OCPB/DPE-2) has reviewed the information provided in the original NDA21-536 for insulin detemir to support the section of human pharmacokinetics and biopharmaceutics. OCPB has found that the clinical pharmacology information is adequate and acceptable from standpoint of clinical pharmacology and biopharmaceutics. This recommendation and the reviewer's comments should be sent to the sponsor as appropriate.

Reviewer's Comments:

- 1) From rat liver microsomal studies, insulin detemir induced CYP1A family and CYP2E1 up to 30% as well as total cytochrome P450 activity up to 21%. It has been known that the diabetic status induces CYP2E1 activity as well. The firm should further investigate this phenomenon in humans. An in vitro induction study using human hepatocytes should be conducted.
- 2) In vitro insulin degradation profiles have been well established and the information is readily available from literature. The initial degraded product is an intact A chain with one or more cleavages in the B chain and intact disulfide bond, which is remarkably consistent from cell type to cell type (*Duckworth et al., Endocrine Review 19(5):608-624, 1998*). However, the metabolic pathways the sponsor provided even for human insulin are very different regarding the sequence

and products. Since insulin detemir has many unique characteristics that other insulin analogues do not have, a valid in vitro metabolic profile of insulin detemir needs to be established. The firm is encouraged to submit the protocol for review before the study is initiated.

1.2 Phase IV Commitments

None.

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3 Summary of CPB Findings

Pharmacokinetics

- **Absolute and relative bioavailability:**

The absolute bioavailability of insulin detemir is ranging from 59 % - 65% for thigh injection to 64-72% for abdomen injection in different studies. Table 1 summarizes the outcomes from different trials.

Table 1. Bioavailability of s.c. administered Insulin detemir in healthy subjects

Injection Site	Trial ID	Insulin detemir formulation (nmol/mL)	Dose (U/kg)	N	Bioavailability Mean [95% CI]
Thigh	1451	2400	0.50	25	59% [55%; 63%]
	1320	2400	0.38	12	64% [55%; 75%]
Abdomen	1451	2400	0.50	25	64% [60%; 69%]
	1028	600	0.05	14	72% [60%; 85%]
Deltoid	1451	2400	0.50	25	65% [61%; 69%]

AUC over the first 5 hours after administration was estimated to be 2.49 times greater with i.m. injection than with s.c. injection. AUC from 0 to 24 hours after administration was estimated to be 1.26 times greater with i.m. injection than with s.c. injection. Cmax was 1.72 times higher with i.m. than with s.c. administration and occurred 210 minutes earlier.

- **Single dose and steady state pharmacokinetics:**

Single dose:

The single dose pharmacokinetics of s.c. insulin detemir was investigated in healthy subjects and diabetic patients in Trials 1309, 1320, 1340, 1410, and 1451. The serum insulin detemir concentration-time curves (AUC) increased proportionally with increasing doses. The dose adjusted AUC in healthy subjects tend to be slightly smaller (Table 2).

Table 2. Across-trial Comparison of Dose-Adjusted AUC and C_{max} in Healthy Subjects and Patients with Type 1 Diabetes

Subjects	Trial ID	N	Sex	Age	Serum Albumin	BMI	Dose-Adjusted AUC	Dose-Adjusted C _{max}
			(M/F)	Mean (years)	Mean (g/L)	Mean (kg/m ²)	Mean (kg-min/L)	Mean (kg/L)
Type 1	1222	9	6/3	22	50	24	282	0.39
	1338	12	7/5	36	46	23	307	0.49
	1450	18	13/5	38	46	24	209	0.30
Healthy	1309	24	12/12	33	43	23	278 ^b	0.39
	1320	15	11/4	31	43	23	209	0.27
	1340 ^a	36	23/13	28	45	23	240	0.42
	1410 ^a	28	14/14	32	-	22	247 ^c	0.36
	1451	27	14/13	33	43	24	220 ^d	0.30

^a Data for White and Japanese subjects have been included in dose adjusted estimates.

^b AUC for Trial 1309 is based on 0-56 hours.

^c AUC for Trial 1410 is based on 0-32 hours.

^d AUC for Trial 1451 is based on 0-24 hours.

Steady-state:

Insulin detemir is intended for use in a once or twice-daily basal regimen. Concentration-time curves over 24 hours after two consecutive single doses (12 hour injection interval) and at steady state were investigated in an open label euglycaemic clamp transfer trial in patients with Type 1 diabetes (Trial 1446). Table 3 summarizes pharmacokinetics of single and steady state and their ratio is about 1.2.

Table 3. Comparison of Pharmacokinetic Endpoints after Single Dose and Steady State Administration of Insulin Detemir Twice-daily in Subjects with Type 1 Diabetes

Endpoint	N	Steady State Mean (SD)	N	Single Dose Mean (SD)	Steady State/Single Dose Ratio [95% CI]
AUC (pmol·10³·min/L)					
0-24 hours	24	2418 (1289)	23	1998 (888)	1.20 [1.11; 1.29]
0-12 hours (1 st dose)	24	1214 (621)	23	789 (307)	-
12-24 hours (2 nd dose)	24	1204 (695)	23	1209 (611)	-
C_{0-24h} (pmol/L)					
12 hours (1 st dose)	24	1166 (952)	23	918 (537)	1.22 [1.06; 1.41]
24 hours (2 nd dose)	24	1318 (942)	23	1262 (776)	1.03 [0.93; 1.13]
C_{max} (pmol/L)					
0-12 hours (1 st dose)	24	2228 (943)	23	1755 (624)	-
12-24 hours (2 nd dose)	24	2136 (1032)	23	2217 (960)	-
Delta_{0-24h}^a	24	0.96 (0.41)	23	1.73 (0.38)	-

^a Delta_{0-24h}: Peak to trough fluctuation during the time interval from 0 to 24 hours.

- **Protein binding:**

From an in vitro study, the association constant for binding of insulin detemir to human serum albumin (HSA) is determined to be $1.0 \pm 0.3 \times 10^5 \text{ M}^{-1}$ at 37°C indicating that insulin

detemir will be 98.4% albumin bound in the bloodstream (0.6 mM albumin). The effect of selected albumin bound drugs on the binding of insulin detemir was investigated in competition binding experiments. It was shown that warfarin, phenylbutazone, diazepam and valproate cannot displace insulin detemir from HSA.

The results of the in vitro investigation of plasma protein binding of insulin detemir in blood samples drawn from 7 subjects with Type 2 diabetes (Trial 1220) indicate that 98.1% to 99.8% protein binding is in accordance with the results from the non-clinical in vitro studies.

The results of the in vitro investigation of plasma protein binding of insulin detemir in blood samples drawn from subjects with varying degree of renal impairment indicate that protein binding may be slightly reduced with severe renal impairment and hemodialysis (Trial 1135, Table 4). The results of the in vitro investigation of plasma protein binding of insulin detemir in blood samples drawn from subjects with varying degrees of hepatic impairment indicate that absolute differences in plasma protein binding between the groups were small (Trial 1136). There was no evident trend for differences in protein binding in subjects with severely impaired hepatic function (Table 4).

Table 4. Protein Binding of Insulin Detemir in Subjects with Renal Impairment or Hepatic Impairment

Degree of impairment	N	Renal Impairment (Trial 1135)		N	Hepatic impairment	
		Mean (SD) (%)	Range (min-max) (%)		Mean (SD) (%)	Range (min-max) (%)
Healthy	6	99.3 (0.15)		6	99.2 (0.19)	
Mild	6	99.1 (0.16)		4	98.9 (0.21)	
Moderate	5	99.1 (0.19)	/	6	99.4 (0.16)	/
Severe	4	98.8 (0.29)		6	98.9 (0.21)	
Hemodialysis	6	98.8 (0.36)		-	-	-

No obvious trends were observed towards a relationship between total cholesterol plasma concentration and extent of plasma protein binding of insulin detemir, nor between plasma triglyceride concentrations and plasma protein binding.

• **Metabolism:**

From an in vitro metabolism study using cytosol, insulin detemir has a similar metabolic pathway to human soluble insulin for breakup of disulfide bond and chain A. For chain B, insulin detemir does not have further fragmentation as human soluble insulin does. Therefore, the metabolism pathways of insulin detemir and human insulin were found to be not identical. No species or tissue specific metabolism was observed. From rat liver microsomal studies, insulin detemir induced CYP1A family and CYP2E1 up to 30% as well as total cytochrome P450 activity up to 21%, which is a novel finding for an insulin product to induce CYP2E1. There are no drug interaction studies in the submission.

• **Distribution:**

The distribution of insulin is dependent on the diffusion of unbound insulin across the capillary wall into the various tissue compartments. Unlike human insulin, more than 98% of insulin detemir in the bloodstream is bound to albumin. Thus, the distribution of insulin detemir to the interstitial compartment is limited by the low concentration of unbound insulin detemir.

The distribution of insulin detemir and human insulin to muscle tissue, adipose tissue, and the splanchnic bed was compared between healthy subjects and patients with type 1 or type 2 diabetes at steady state during continuous i.v. insulin infusion (Trials 1173, 1196, 1220, and 1221). Volume of distribution (Vd) was estimated in Trials 1173, 1320, and 1451. Vd is very small ranging from 0.065 to 0.1 L/kg (Table 5).

Table 5. Volume of Distribution of Insulin Detemir in Healthy Subjects

Trial ID	i.v. Dose	N	V _d (L/kg)	
			Mean	(SD)
1173	0.45 mU/kg/min	10	0.087	(0.019)
1173	1.35 mU/kg/min	10	0.092	(0.020)
1320	0.38 U/kg	16	0.098	(0.058)
1451	0.03 U/kg	26	0.065	(0.010)

• **Elimination:**

Elimination of insulin detemir after a single i.v. injection was investigated in healthy subjects (Trials 1320 and 1451). Elimination of insulin detemir and human insulin after continuous i.v. infusion was investigated in healthy subjects (Trials 1173, 1196, and 1323) and in patients with diabetes (Trial 1221). Clearance (CL) and elimination half-life ($t_{1/2}$) were estimated.

Table 6. Elimination of Insulin Detemir and Human Insulin after i.v. Administration in Healthy Subjects and Subjects with Type 1 or Type 2 Diabetes

Subjects	Insulin	Trial ID	i.v. Dose (mIU/kg/min)	N	CL (L/min/kg) mean (SD)	t _{1/2} (min) harmonic mean	
						Initial ^a	Terminal ^b
Healthy	Insulin detemir	1451	0.025 ^c	26	0.0024 (0.0004)	19	195
		1320	0.025 ^d	12	0.0027 (0.0007)	21 ^c	
		1323	0.13	6	0.0020 (0.0003)		
		1323	0.45	5	0.0022 (0.0001)		
		1173	0.45	10	0.0026 (0.0006) ^f	23 ^f	
		1173	1.0	10	0.0024 (0.0003) ^f	25 ^f	
		1196	2.5	10	0.0020 (0.0003)		
	1196	5.0	10	0.0019 (0.0004)			
	Human insulin	1323	0.5	6	0.0163 (0.0038)		
		1173	0.6	11	0.0179 (0.0047)		
		1196	1.0	11	0.0177 (0.0034)		
1173		1.8	12	0.0158 (0.0035)			
Type 1	Insulin detemir	1221	0.75	10	0.0018 (0.0006)		
		1221	1.25	10	0.0018 (0.0004)		
	Human insulin	1221	1.0	10	0.0158 (0.0033)		
Type 2	Insulin detemir	1221	0.75	10	0.0027 (0.0022)		
		1221	1.25	10	0.0026 (0.0010)		
	Human insulin	1221	1.0	10	0.0196 (0.0058)		

^a The initial (alpha-phase) t_{1/2} was estimated for the slope in the interval from 0 to 60 minutes (see Appendix D).

^b The terminal (beta-phase) t_{1/2} was estimated for the slope in the interval from 240 to 480 minutes.

^c i.v. dose in Trial 1451 was given as a single dose (0.025 U/kg).

^d i.v. dose in Trial 1320 was given as a single dose over 30 min (0.025 U/kg)

^e t_{1/2} was recalculated for the purpose of this summary. The value in the clinical trial report (38 min) includes both alpha- and beta-phase elimination.

^f CL and t_{1/2} were calculated for the purpose of this summary and are therefore not presented in the clinical trial report.

Clearance of insulin detemir was independent of dose. Clearance of insulin detemir (0.0018 to 0.0027 L/min/kg) was approximately 6-9 folds lower than that of human insulin (0.0158 to 0.0196 L/min/kg). This could be expected considering the high plasma-protein binding of insulin detemir, which delays distribution into the tissues, thereby making it less susceptible to elimination.

Clearance tended to be higher in patients with Type 2 diabetes than in patients with Type 1 diabetes for both insulin detemir and human insulin.

Elimination half-life ($t_{1/2}$) after i.v. administration was longer for insulin detemir than for human insulin; the initial (dominant) $t_{1/2}$ for insulin detemir was 19 to 25 min, and the terminal $t_{1/2}$ for insulin detemir was 195 min (Table 6).

Elimination after s.c. administration is influenced by both the rate of absorption from the injection site and the rate of elimination. Consequently, estimates of $t_{1/2}$ are longer after s.c. administration than after i.v. administration. Terminal half life of insulin detemir after s.c. administration was estimated in healthy subjects and in patients with Type 1 diabetes (Table 7). In the therapeutic dose range (0.2 to 0.8 U/kg), $t_{1/2}$ was found to be between 155 and 372 min (approximately 2.5 to 6 hours) in healthy subjects and between 288 and 414 min (about 5 to 7 hours) in patients with Type 1 diabetes.

Table 7. Elimination of Insulin Detemir after s.c. Administration in Healthy Subjects and Patients with Type I Diabetes

Subjects	s.c. Dose (U/kg)	Trial ID	N	CL/F (L/min/kg) mean (SD)	$t_{1/2}$ (min) harmonic mean	MRT (min) mean (SD)
Healthy	0.19	1340	16	0.0046 (0.0014)	194	573 (133)
	0.38	1340	15	0.0038 (0.0016)	185	577 (138)
	0.38	1309	24	0.0036 (0.0007)	371	786 (185)
	0.38	1320	12	0.0043 (0.0009)	332	781 (90)
	0.38	1410	14	-	372	-
	0.50 ^a	1451	26	-	352	786 (156)
	0.75	1309	24	0.0037 (0.0006)	322	724 (165)
	0.75	1340	15	0.0038 (0.0009)	155	640 (80)
Type 1	0.10	1338	9	-	238	843 (722)
	0.20	1338	11	-	288	659 (246)
	0.40	1338	12	-	339	747 (174)
	0.40	1450	18 ^b	-	381	819 (127)
	0.50	1222	9	0.0034 (0.001)	414	827 (140)
	0.80	1338	11	-	375	837 (181)
	1.60	1338	11	-	394	1017 (543)

^a administration in the thigh.

^b N is number of subjects with four glucose clamps.

Clearance of Insulin detemir was independent of dose, which was consistent with the linear concentration relationship observed in the dose range from 0.2 to 1.6 U/kg. Mean residence time (MRT) for insulin detemir was estimated to be 53 min after i.v. administration (Trial 1451) and 573 to 1017 min (10 to 17 hours) after s.c. administration.

- **Special populations:**

In terms of pharmacokinetics, there were no differences between gender and race (Japanese versus Caucasians). No correlation could be established between creatinine clearance and the pharmacokinetics of insulin detemir. The extent of bioavailability of insulin detemir as estimated by AUC (0- ∞) appeared to decrease with increasing degree of hepatic insufficiency. Elderly subjects tend to have higher exposure than young adults. No overall differences were found between the pharmacokinetic profiles in children, adolescents, and adults for insulin detemir.

- **Mixing insulin detemir with insulin aspart:**

A clinical pharmacokinetic study has shown that — (a fixed mixture of insulin detemir with insulin aspart) affected significantly the pharmacokinetic parameters of both individual insulin products. The pharmacokinetic results showed that there was a marked effect of premixed treatment on early insulin aspart profiles. The $AUC_{IAsp(0-2h)}$, the extent of exposure to insulin aspart following — was approximately 60% of the value following separate administration. A similar reduction was observed for insulin aspart C_{max} . The converse was observed for insulin detemir following —, with C_{max} observed to increase by approximately 10% over that of the value following separate injections. Therefore, any pre-mixture between insulin detemir and insulin aspart should be avoided.

- **Pharmacodynamics:**

The pharmacodynamic properties of insulin detemir in patients with type I diabetes were investigated by evaluation of the time action profile, dose response, and duration of action in Trial 1338. **Time action profile:** The time interval during which the effects were above 50% of GIR_{MAX} occurred from 3 to 4 hours and up to approximately 19 hours after dose administration. **Dose Response:** Both PD endpoints AUC_{GIR} and GIR_{max} at five dose levels were shown to be linear in the dose range investigated (0.1 to 1.6 U/kg). **Duration of Action:** The duration of action of insulin detemir ranged from 5.7 hours at the lowest dose to 23.2 hours at the highest dose. GIR_{max} occurred later with increasing insulin detemir dose up to a maximum of 9 hours, while time to 50% of GIR_{max} occurred 3 to 4 hours after administration at therapeutically relevant doses.

- **Analytical assay:**

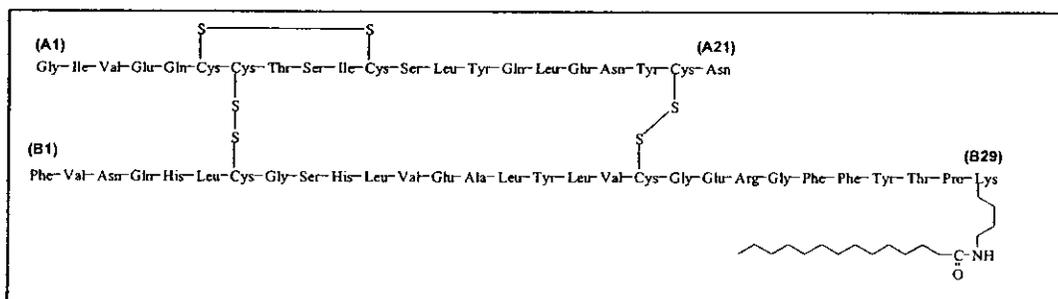
The method of analysis is a — ELISA. An antigen specific ELISA (NN304-ELISA) has been set up to measure insulin detemir in plasma or serum during preclinical studies and clinical trials. Albumin, hemolysis, freeze/thaw cycles may affect the measurement of insulin detemir. The ELISA assay has no cross reactivity with human insulin antibodies, regular human insulin and insulin aspart.

4 QUESTION BASED REVIEW

4.1 GENERAL ATTRIBUTES

- **What are the highlights of the chemistry and physical-chemical properties of the drug substance?**

Insulin detemir is a long-acting insulin analog produced by a process that includes expression of recombinant DNA in Yeast (*Saccharomyces cerevisiae*) followed by chemical synthesis. Insulin detemir differs from human insulin in that the amino acid molecule in position B30 has been omitted, and a 14-C fatty acid chain has been attached to position B29. Insulin detemir has a molecular formula of $C_{267}H_{402}O_{76}N_{64}S_6$ and a molecular weight of 5916.9. It has the following structure:



- **What are the highlights of the formulation of drug product?**

The sponsor has developed 3 formulations during development. The to-be-market formulation is 2400 nmol/ml, which has been used in pivotal clinical trials.

Table 8. Formulations of Insulin Detemir Used in Clinical Trials

	600 nmol/mL Formulation	1200 nmol/mL Formulation	2400 nmol/mL Formulation
Insulin detemir	600 nmol/mL	1200 nmol/mL	2400 nmol/mL
Mannitol	—	30 mg/mL	30 mg/mL
Phenol	—	—	1.80 mg/mL ^a
m-Cresol	—	—	2.06 mg/mL
Zinc	—	—	65.4 µg/mL ^a
Sodium chloride	1.17 mg/mL	—	1.17 mg/mL
Disodium phosphate, dihydrate	—	0.89 mg/mL	0.89 mg/mL
Water for Injection	—	—	—
Sodium hydroxide	q.s.	q.s.	q.s.
Hydrochloric acid	q.s.	q.s.	q.s.
pH	—	7.4	7.4

- **What is the proposed mechanism of drug action and the therapeutic indications?**

The primary activity of insulin detemir is the regulation of glucose metabolism. Insulin detemir like other insulins, exerts its specific action through the binding to insulin receptors. Receptor-bound insulin lowers blood glucose by facilitating cellular uptake of glucose into skeletal muscle and fat, and by inhibiting the output of glucose from the liver.

- **What is the potency of insulin detemir to lower blood glucose relative to human regular insulin and insulin NPH?**

The early stage preclinical studies showed that receptor binding affinity and the metabolic potency of insulin detemir in mouse primary adipocytes were 4-5 folds lower than those of human insulin. The potency of insulin detemir relative to human insulin in the mouse and rat was 6% and 15%, respectively.

Clinical trials have demonstrated that the potency of insulin detemir to control blood glucose is lower than that of human soluble insulin or insulin NPH.

An equivalent dose of insulin detemir to insulin NPH was studied in Trial 1338 (a randomized, single-dose, six-period cross-over, dose-response trial in patients with Type 1 diabetes). In order to compare duration of action for insulin detemir and NPH insulin, AUC_{GIR} was considered to be the most relevant pharmacodynamic parameter when comparing insulin potencies because it reflects the total metabolic activity. By interpolating from a linear regression model, it was found that 0.29 U/kg insulin detemir (7.0 nmol/kg) would give the same effect in terms of AUC_{GIR} as 0.3 IU/kg NPH. Taking into account that the insulin detemir formulation was 2400 nmol/mL, and the NPH insulin formulation was 600 nmol/mL, the molar dose factor for AUC_{GIR} is listed in the following Table:

Table 9. Equivalent Doses of Insulin Detemir and NPH Insulin

	Insulin detemir	NPH insulin	Molar dose factor
Equal AUC _{GIR}	0.29 U/kg [0.12; 0.42] ^a (~ 7.0 nmol/kg)	0.3 IU/kg (~ 1.8 nmol/kg)	3.9 [1.67;5.93] ^a

^a The estimated range of insulin detemir doses corresponding to NPH insulin was calculated by ad hoc interpolation of the lower and upper confidence limits.

Results from the confirmatory therapeutic (phase III) trials comparing the long term efficacy of treatment with insulin detemir showed that similar metabolic control was achieved with approximately 4 times higher molar doses of insulin detemir than NPH insulin in patients with diabetes.

- **What is the proposed dosage and route of administration?**

Insulin detemir is indicated for once or twice-daily subcutaneous administration in the treatment of patients with diabetes mellitus who require basal insulin for the control of hyperglycemia depending on patients' needs. For patients who require twice daily dosing for effective blood glucose control, the evening dose can be administered either with the evening meal, at bedtime, or 12 hours after the morning dose. Insulin detemir should be administered by subcutaneous injection in the thigh, abdominal wall, or upper arm. Injection sites should be rotated within the same region. As with all insulins, the duration of action will vary according to the dose, injection site, blood flow, temperature, and level of physical activity.

4.2 GENERAL CLINICAL PHARMACOLOGY

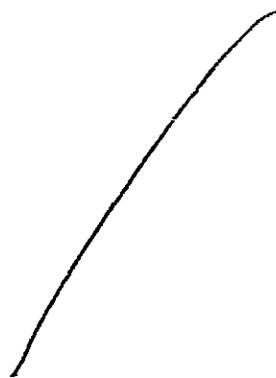
- **What is absolute and relative bioavailability of insulin detemir?**

A three period randomized, crossover trial was conducted in healthy subjects investigating the bioavailability of insulin detemir and comparing the pharmacokinetics between subcutaneous, intramuscular and intravenous administration of insulin detemir (formulation 2400 nmol/mL) using a euglycaemic clamp. Subjects were given a single subcutaneous dose of 9 nmol/kg body weight administered into a skin of the thigh, a single intramuscular dose of 9 nmol/kg body weight in the thigh and a single intravenous infusion of 60 nmol/mL over 30 min. Results indicated that absolute bioavailability (s.c. /i.v.) was 64% and the bioavailability of intramuscular administration is much greater than subcutaneous administration (Table 10 and Figure 1).

Table 10. Comparison of Pharmacokinetic endpoints following i.m. vs. s.c. injection (N=12)

Parameter	AUC (0-5h)	AUC (0-24h)	Cmax	Tmax	T1/2
Ratio (i.m./s.c.)	2.49	1.26	1.72	-210 min	0.67
90% CI	2.05, 3.01	1.15, 1.37	1.48, 2.01	-270, -150	0.61, 0.73

Figure 1. Plasma concentration profiles of insulin detemir after I.M., S.C. and I.V. administration.



An early phase 1 study using 600 nmol/mL showed that the absolute bioavailability of insulin detemir was 72% based on the ratio of subcutaneous administration to intravenous administration in 14 healthy subjects in a cross-over, randomized trial. The absolute bioavailability of NPH was 49% based on 12 subjects in the same trial.

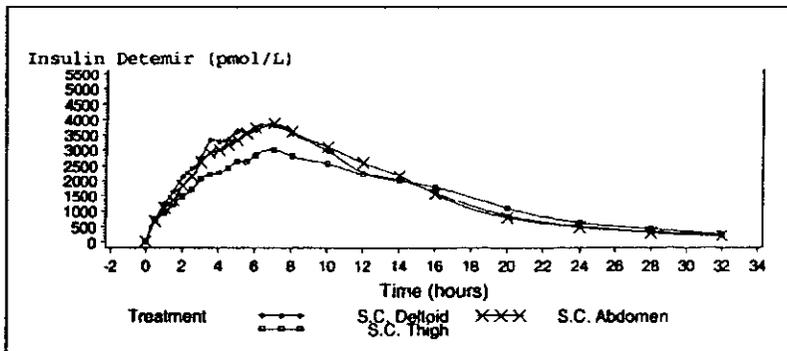
- **What is the effect of injection sites on the bioavailability of insulin detemir?**

An open, randomized, cross-over trial in healthy subjects was conducted to compare the pharmacokinetics of insulin detemir when administered subcutaneously at abdomen, thigh and deltoid using 1200 nmol/mL formulation. The results showed that the primary endpoint, AUC (0-∞), was approximately 10% larger following s.c. administration in the deltoid and the abdomen than in the thigh. These differences were statistically significant. AUC (0-5h) was 30-40% larger and Cmax approximately 20% higher following s.c. administration in the deltoid and the abdomen than following s.c. administration in the thigh. These differences were statistically significant. There was no statistically significant difference between s.c. administration in the deltoid and the abdomen with regard to any of the pharmacokinetic endpoints.

Table 11. Comparison of AUC (0-∞) between subcutaneous injection sites.

	Ratio of AUC(0-∞)		
	Abdomen vs. Deltoid	Abdomen vs. thigh	Deltoid vs. Thigh
N	26	25	25
Ratio	0.991	1.085	1.095
P-value	0.785	0.022	0.011
Lower 95% CI	0.925	1.013	1.022
Upper 95% CI	1.061	1.161	1.173

Figure 2. Mean profile of insulin detemir by subcutaneous injection site.



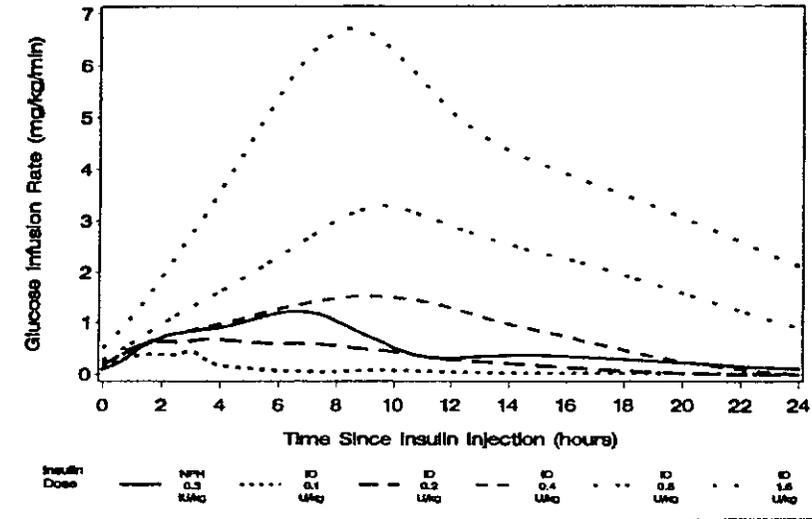
- **What are pharmacodynamic properties of insulin detemir in Type 1 diabetes?**

The pharmacodynamic properties of insulin detemir in patients with Type I diabetes was investigated by evaluation of the time action profile, dose response, and duration of action in Trial 1338.

Time Action Profile

The glucose-lowering effects of insulin detemir and NPH insulin were compared during a 24-hour euglycaemic clamp in a cross-over design in 12 patients with Type 1 diabetes. The smoothed mean glucose infusion rate (GIR) curves following five s.c. doses of insulin detemir ranging from 0.1 to 1.6 U/kg and one s.c. dose of NPH insulin (0.3 IU/kg) are presented in Figure 3.

Figure 3. Smoothed Mean GIR Curves for Insulin Detemir and NPH Insulin in Subjects with Type 1 Diabetes



The time interval during which the effects were above 50% of GIR_{MAX} occurred from 3 to 4 hours and up to approximately 19 hours after dose administration (Table 12).

Table 12. Time Interval with GIR above 50% of GIR_{MAX} for Insulin detemir in Patients with Type 1 Diabetes.

s.c Dose (U/kg)	Time interval with GIR above 50% of GIR_{MAX} (hour)
0.2	4 – 9
0.4	3 – 14
0.8	4 - 19

Dose-Response

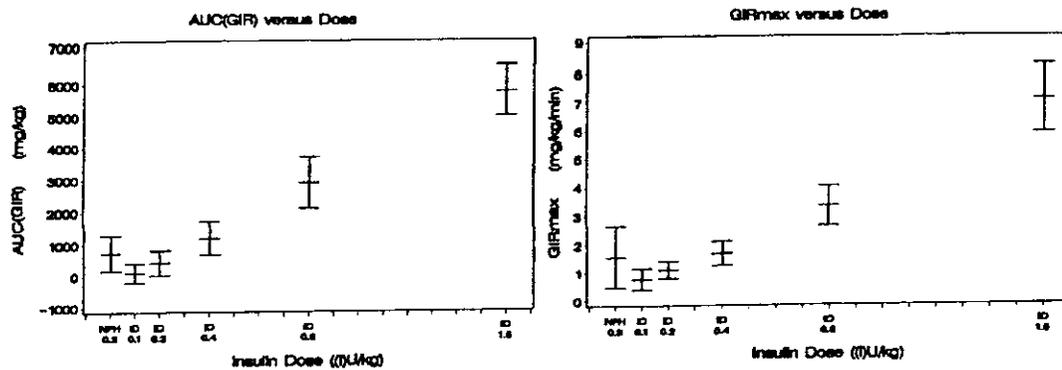
Dose response was investigated for AUC_{GIR} and GIR_{max} at five dose levels in Trial 1338 (Table 13 and Figure 4). Both endpoints were shown to be linear in the dose range investigated (0.1 to 1.6 U/kg). As indicated by the width of the 95% confidence intervals of the estimates, the between-subject variability of AUC_{GIR} and GIR_{max} was consistently less for insulin detemir (0.1 to 0.4 U/kg) than for NPH insulin (0.3 IU/kg).

Table 13. Pharmacodynamic Endpoints for Insulin Detemir and NPH Insulin in Patients with Type 1 Diabetes

Insulin	Trial ID	N	s.c. Dose (IU/kg)	AUC _{GIR, 0-24h} (mg/kg)	GIR _{max} (mg/kg/min)	tGIR _{max} (min)
				mean (SD)	mean (SD)	median (min;max)
Insulin detemir	1338	11	0.1	132 (118)	0.8 (0.5)	140 (
	1338	11	0.2	450 (432)	1.1 (0.5)	340 (
	1338	12	0.4	1184 (741)	1.7 (0.8)	535 (
	1450	18 ^a	0.4	1703 (490)	2.3 (0.5)	495 (
	1338	11	0.8	2911 (1220)	3.4 (1.2)	580
	1338	11	1.6	5734 (1162)	7.1 (1.9)	500 (
NPH insulin	1338	12	0.3	743 (835)	1.6 (1.9)	280 (
	1450	17 ^a	0.4	1923 (765)	2.7 (1.1)	450 (

^a. Number of subjects with four glucose clamps

Figure 4. AUC_{GIR, 0-24h} and GIR_{max} versus Insulin Detemir and NPH Insulin Dose in Patients with Type 1 Diabetes - including 95% Confidence Intervals



In order to compare the pharmacodynamic properties of insulin detemir and NPH insulin, the insulin detemir dose equivalent to 0.3 IU/kg NPH insulin was interpolated; i.e., the insulin detemir dose with the same glucose-lowering effect. AUC_{GIR, 0-24h} was considered to be the most relevant pharmacodynamic endpoint for comparing the pharmacodynamic effects because it reflects the total glucose-lowering activity. The interpolated insulin detemir dose was 0.3 U/kg (95% CI [0.12; 0.42]); thus, confirming that one unit of the to-be-marketed insulin detemir preparation is equivalent to one unit of NPH insulin. The corresponding interpolated GIR_{max} for 0.3 U/kg insulin detemir was estimated to be 1.4 mg/kg/min as compared with 1.6 mg/kg/min for 0.3 IU/kg NPH insulin.

Duration of Action

The duration of the glucose-lowering effect of the five s.c. doses of insulin detemir were compared with NPH insulin (Table 14).

Duration of action was defined as the time between onset of action and end of action. Onset of action was defined as the time point where rate of intravenous insulin was reduced by >50% compared with the pre-injection level. End of action was defined as the time point where plasma glucose consistently exceeded 8.3 mmol/L (150 mg/dL) and GIR remained at 0 until the end of the clamp period.

The mean time to onset of action was earlier, and the duration of action was longer for insulin detemir than for 0.3 IU/kg NPH insulin at doses greater than 0.4 U/kg. The duration of action of insulin detemir ranged from 5.7 hours at the lowest dose to 23.2 hours at the highest

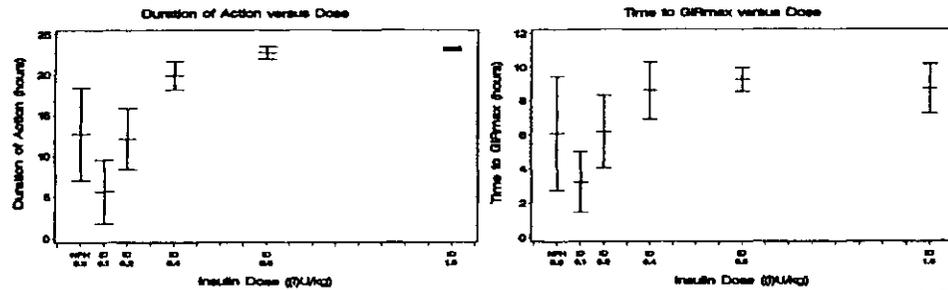
dose (Table 14 and Figure 5). End of action was not reached by 24 hours for 40% of subjects with 0.4 U/kg, and for approximately 90% of subjects at the two highest doses (0.8 U/kg and 1.6 U/kg). When end of action was not reached, the estimate for end of action was truncated to 24 hours. Thus, the duration of action is underestimated, especially at the high dose levels, and the width of the corresponding confidence intervals decreases with increasing dose.

Table 14. Duration of Action of Insulin Detemir and NPH Insulin in Patients with Type 1 Diabetes (Trial 1338)

Insulin	N	s.c. Dose (I)U/kg	Onset of Action (h)	End of Action (h)	Duration of Action (h)
			Mean (SD)	mean (SD)	mean (SD)
Insulin detemir	11	0.1	2.0 (1.8)	7.6 (6.1)	5.7 (6.6)
	11	0.2	2.0 (2.5)	14.0 (5.3)	12.1 (6.2)
	12	0.4	1.6 (1.1)	21.5 (3.3)	19.9 (3.2)
	11	0.8	1.0 (0.7)	23.7 (0.9)	22.7 (1.2)
	11	1.6	0.8 (0.3)	23.9 (0.2)	23.2 (0.3)
NPH insulin	12	0.3	2.6 (2.9)	15.3 (9.0)	12.7 (9.9)

Duration of action for the interpolated dose insulin detemir (0.3 U/kg) that is equivalent to 0.3 IU/kg NPH insulin was estimated to be 4 hours longer (17 hours versus 13 hours).

Figure 5. Duration of Action and Time to GIRmax for Insulin Detemir and NPH Insulin in Subjects with Type 1 Diabetes - Including 95% Confidence Intervals



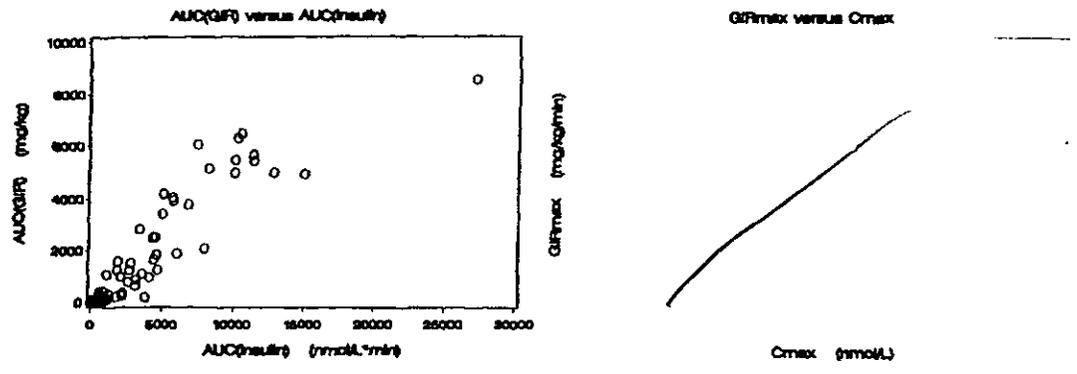
GIR_{max} occurred later with increasing insulin detemir dose up to a maximum of 9 hours, while time to 50% of GIR_{max} occurred 3 to 4 hours after administration at therapeutically relevant doses. Between-subject variability in time to GIR_{max}, as indicated by the width of the 95% confidence intervals in Figure 5, was consistently lower for insulin detemir than for NPH insulin.

- **What is the relationship between pharmacokinetics and pharmacodynamics?**

The pharmacokinetic and pharmacodynamic properties of insulin detemir were characterized in a therapeutically relevant dose range (0.1 to 1.6 U/kg), which was also used in the confirmatory therapeutic trials (phase III trials) in patients with type 1.

The relationships between AUC versus AUC_{GIR} and for C_{max} versus GIR_{max} in patients with Type I diabetes are shown in Figure 6. There is a linear relationship between the pharmacokinetic endpoints and corresponding pharmacodynamic endpoints within the dose range investigated.

Figure 6. Serum Insulin Detemir Concentration versus AUC_{GIR} and GIR_{max} Patients with Type 1 Diabetes (Trial 1338)



- **What is difference in pharmacokinetic and pharmacodynamic properties between patients with Type 1 and Type 2 Diabetes?**

A single dose study of pharmacokinetics and pharmacodynamics of s.c. insulin detemir and NPH insulin was conducted in six patients with Type 2 diabetes and six patients with Type 1 diabetes in a cross-over design (Trial 1223).

The mean serum insulin concentration-time curves with two doses of insulin detemir (0.38 U/kg and 0.75 U/kg; Figure 7) and one dose of NPH insulin (0.6 IU/kg; Figure 8) were assessed for both patient groups over 16 hours.

Insulin detemir was absorbed at a slower rate in patients with Type 2 diabetes than in patients with Type 1 diabetes (Figure 7). Serum insulin detemir concentrations, as measured by AUC_{0-16h} and C_{max} , tended to be lower for patients with Type 2 diabetes than for patients with Type 1 diabetes, particularly for low dose (0.375 U/kg). AUC and C_{max} were greater after administration of 0.75 U/kg than 0.38 U/kg for both groups and the difference between Type 1 and Type 2 diabetes tended to be smaller for the high dose (0.70 U/kg) (Table 15).

Figure 7. Mean Serum Insulin Detemir Concentration-time Curves in Subjects with Type 2 Diabetes or Type 1 Diabetes (Trial 1223)

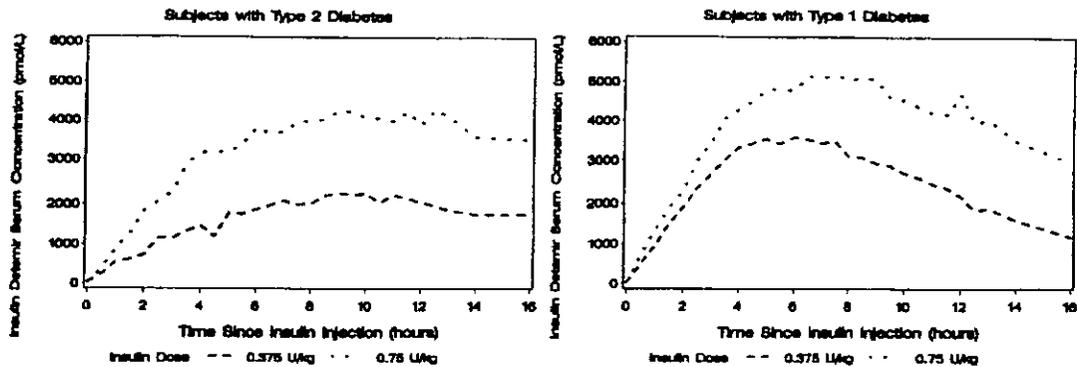


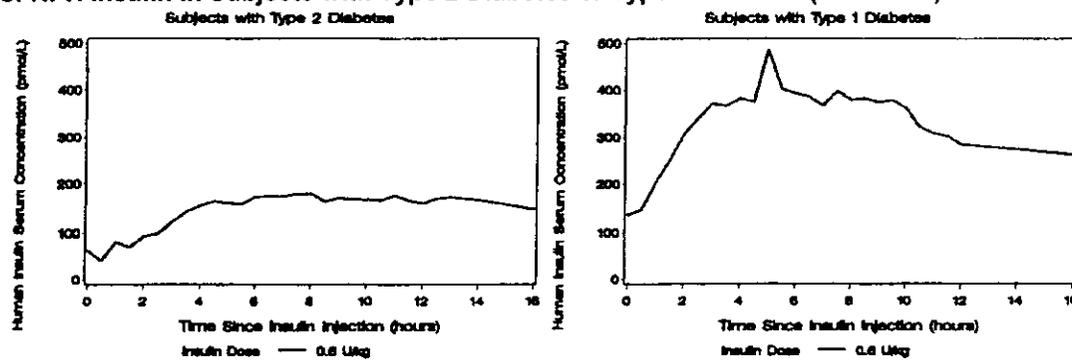
Table 15. Pharmacokinetic Endpoints for Insulin Detemir in Patients with Type 2 or Type 1 Diabetes (Trial 1223)

s.c. Dose (U/kg)	Subjects	N	AUC _{0-16h} (pmol·10 ³ ·min/L)	C _{max} (pmol/L)	t _{max} (min)
			mean (SD)	mean (SD)	median (min;max)
0.38	Type 2	6	1578 (538)	2660 (762)	585 (
	Type 1	5	2302 (1128)	4182 (2266)	390
0.75	Type 2	6	3132 (642)	4997 (465)	616
	Type 1	6	3703 (563)	6160 (567)	525

1200 nmol/mL insulin detemir formulation was used in Trial 1223.

Absorption of human insulin after administration of NPH insulin was also slower in patients with Type 2 diabetes than in patients with Type 1 diabetes (Figure 8)

Figure 8. Mean Serum Human Insulin Concentration-time Curves after s.c. Administration of NPH insulin in Subjects with Type 2 Diabetes or Type 1 Diabetes (Trial 1223)

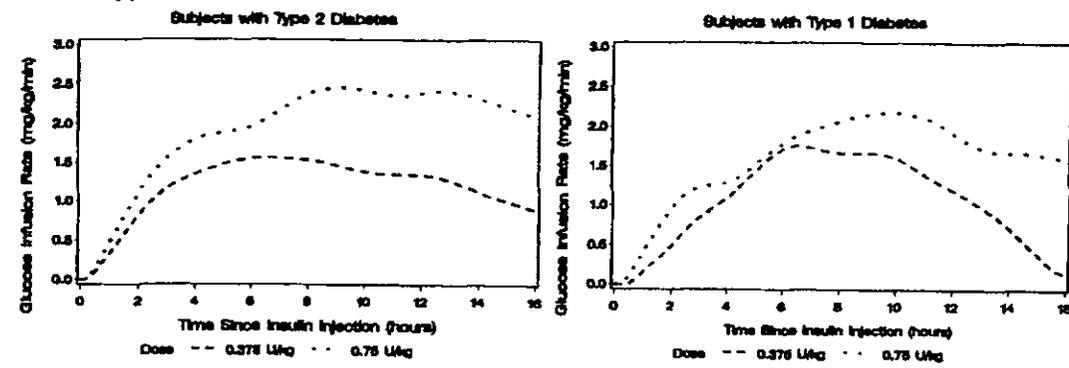


The smaller AUC observed for patients with Type 2 diabetes may be related to the relatively short evaluation period (16 hours). The apparent difference in total exposure may have been less pronounced if the entire concentration-time profile had been assessed.

The sponsor has indicated that their current study results are consistent with one published article (*Clayson and Linde, Diabetes Care, 18(7), 1995*) where the rate of absorption of human soluble insulin has been shown slower for patients with Type 2 diabetes compared with patients with Type 1 diabetes.

The glucose-lowering effect of insulin detemir was investigated simultaneously. The smoothed GIR curves over 16 hours after two s.c. doses of insulin detemir (0.38 U/kg or 0.75 U/kg) are presented for patients with type 1 and type 2 diabetes in Figure 9. The corresponding pharmacodynamic endpoints are summarized in Table 16.

Figure 9. Smoothed Mean GIR Curves for Insulin Detemir in Patients with Type 1 and Type 2 Diabetes



The GIR curve for patients with Type 2 was flatter than that for patients with Type 1. However, the pharmacodynamic endpoints, measured by $AUC_{GIR, 0-16h}$ and GIR_{MAX} were similar (Table 16).

Table 16. Pharmacodynamic Endpoints for Insulin Detemir in Patients with Type 1 and Type 2 Diabetes

s.c. Dose (U/kg)	Subjects	N	$AUC_{GIR, 0-16h}$ (mg/kg)	GIR_{max} (mg/kg/min)	$tGIR_{max}$ (min)
			mean (SD)	mean (SD)	median (min; max)
0.38	Type 2	5	1136 (368)	1.7 (0.6)	458
	Type 1	6	1026 (597)	2.0 (1.0)	390
0.75	Type 2	6	1854 (847)	2.7 (1.1)	720
	Type 1	6	1526 (674)	2.6 (1.1)	558

1200 nmol/mL formulation was used in Trial 1223.

Although the difference in pharmacokinetics parameters between Type 1 and Type 2 diabetes is obvious, the difference in pharmacodynamics tends to be less.

- **What is the intra-subject variability of pharmacodynamics and pharmacokinetics of insulin detemir in comparison with NPH insulin and insulin glargine in patients with type 1 diabetes?**

A single center, parallel group, randomized, double-blind trial comparing the intra-subject variability of insulin detemir, NPH insulin and insulin glargine was conducted in type 1 diabetic patients with respect to certain pharmacodynamic and pharmacokinetic parameters. Patients were randomized to one of three treatment arms and underwent the 24-hour euglycemic glucose clamp procedure on four separate treatment days at intervals of 5-21 days. The following doses were subcutaneously delivered: Insulin detemir (Formulation: 2400 nmol/mL) as a single dose of 0.4 U/kg corresponding to 9.6 nmol/kg, Human (NPH) insulin 0.4 IU/kg corresponding to 2.4 nmol/kg and insulin glargine 0.4 IU/kg corresponding to 2.4 nmol/kg. Human soluble insulin was dosed intravenously in a rate of at least 0.15 mU/kg/min and infused for 4-6 hours before administration of trial drug. The results are summarized in the following table:

Table 17. Intra-subject variability

Drug Product	Insulin detemir (CV %)	NPH (CV %)	Insulin glargine (CV %)
Pharmacodynamic Endpoints			
AUC _{GIR(0-12 hours)}	27	59	46
GIR _{max} (mg/min/kg)	23	46	36
T _(GIRmax) (min)	16	28	31
Pharmacokinetic Endpoints			
AUC _(0-12 hours) (pmol/L x min)	15	26	34
AUC _(0-infinity) (pmol/L x min)	14	28	33
C _{max} (pmol/L)	18	24	34

Therefore, insulin detemir has the smallest intra-subject variability in terms of pharmacokinetic and pharmacodynamic parameters.

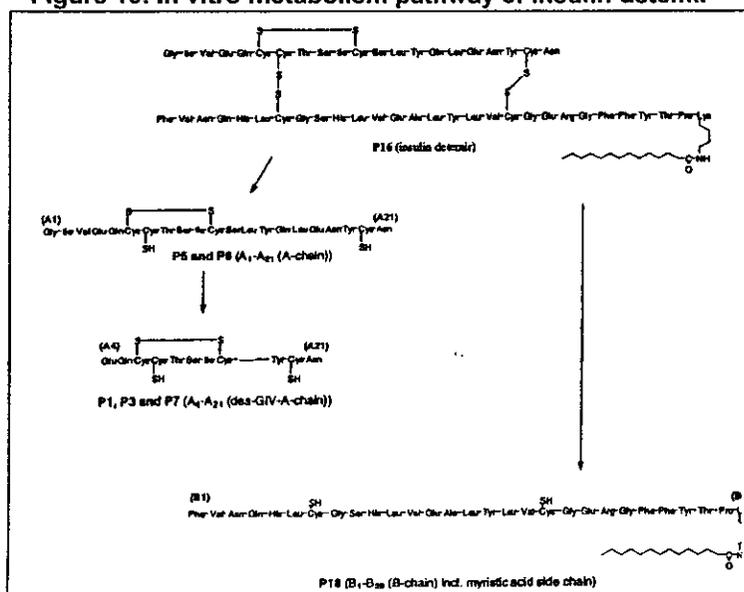
- **What is the metabolism profile of insulin detemir? Is there any difference in metabolic profiles between insulin detemir and regular insulin?**

The in vitro metabolism pathways of insulin detemir and human regular insulin were investigated using liver cytosol from four species (human, rat, dog and pig) and kidney S9 mixture from two species (rat and human). All major metabolites of human insulin were identified and found to be either A-chain or B-chain related metabolites. No metabolites containing both A- and B-chain fragments were found. All A-chain related metabolites could be found in both insulin detemir and human insulin related incubations. More B-chain related metabolites were identified in human regular insulin incubations than in insulin detemir incubations. These metabolite profiles are illustrated below (Figure 10 and Figure 11).

Based on these results, the metabolism pathways of insulin detemir and human insulin were found to be similar, but not identical. No species or tissue specific metabolism was observed. The first step of metabolism is supposed to be cleavage of the S-S bonds between the A-chain and the B-chain and hereafter the A- and B-chain are further metabolized.

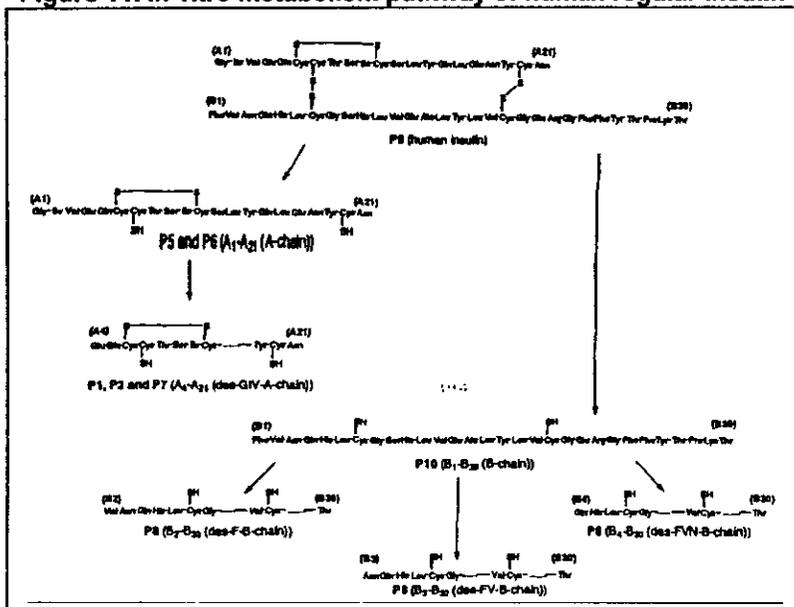
In vitro monolayer hepatocytes from human and animals were used to study the in vitro metabolite profile of insulin detemir. However, the yield was very low and variation was big. The study failed to draw any reliable conclusion (Study No: 990056).

Figure 10. In vitro metabolism pathway of insulin detemir



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Figure 11. In vitro metabolism pathway of human regular insulin



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As a result, insulin detemir has a similar metabolic pathway to human regular insulin for chain A. Chain B of insulin detemir did not go much further fragmented. The chain B in human regular insulin has much more fragments. The clinical relevance of the difference in chain B metabolic profile is unknown. It may be more concerned about immunogenicity with large or unfragmented chain B from insulin detemir. However, these metabolic pathways for human insulin are different from what has been established in literature. The sponsor should explain why their study results of insulin metabolic profiles are different. A valid in vitro metabolism study need to be conducted.

4.3 INTRINSIC FACTORS

4.3.1 Gender

Throughout drug development program, insulin detemir has been assessed for gender difference in terms of pharmacokinetic parameters. However, the results vary in individual trials. An across-trial assessment was performed to conclude that there is no gender difference in AUC and Cmax (Figure 12-13).

Figure 12. Across-trial assessment of AUC and Cmax ratios between healthy males and females.

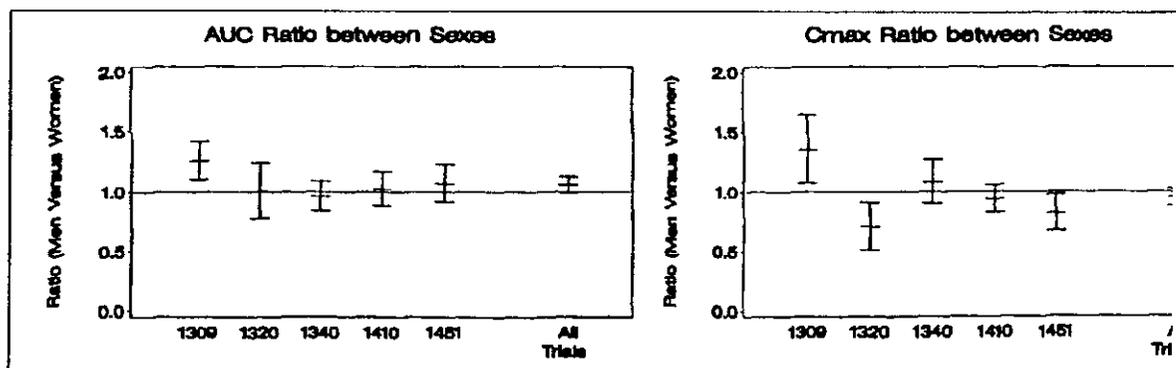
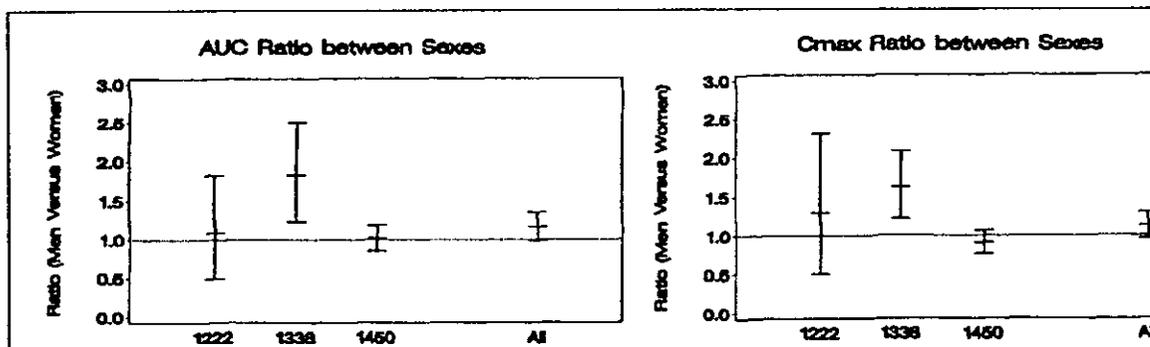


Figure 13. Across-trial assessment of AUC and Cmax ratios between males and females with type 1 diabetes.



Race:

A comparison of pharmacokinetics of ascending doses of insulin detemir in healthy Japanese-American and Caucasian subjects was conducted with three doses: 4.5 nmol/kg, 9.0 nmol/kg, or 18 nmol/kg. The results indicated that there was a clear dose-response relationship between the three ascending insulin detemir doses and serum insulin detemir AUC values for both Japanese and Caucasian subjects. There is no statistically significant difference in pharmacokinetic parameters between these two groups of subjects.

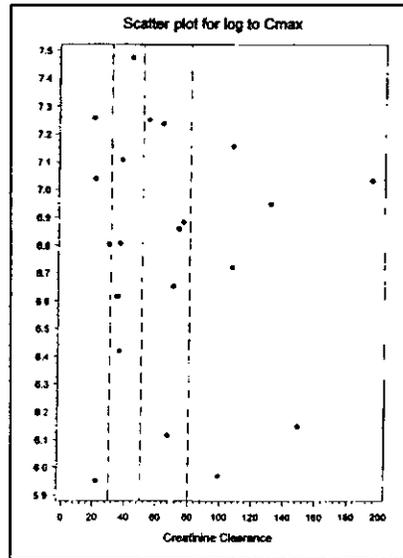
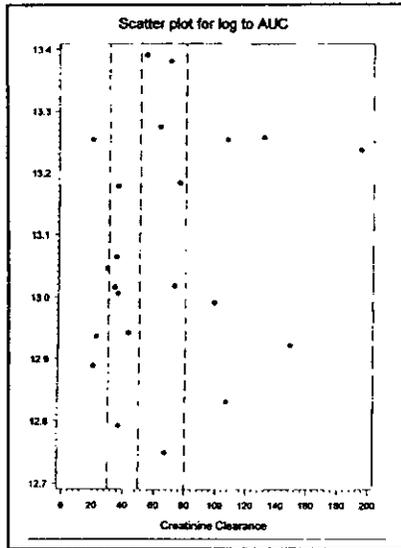
Table 18. Pharmacokinetic Parameters

PK Parameter	Insulin Dose (nmol/kg)	Japanese		Caucasian		p value
		N	Geometric Mean	N	Geometric Mean	
AUC (0-30h), (pM.min)	4.5	19	971643	16	992992	0.832
	9.0	17	2111226	15	2391683	0.284
	18.0	15	4290316	15	4652688	0.369
Cmax (pmol/L)	4.5	19	1736	16	1819	0.770
	9.0	17	3175	15	4138	0.614
	18.0	15	5796	15	6880	0.713
Tmax (hr)	4.5	19	4.53	16	5.38	0.198
	9.0	17	6.03	15	6.0	0.752
	18.0	15	6.93	15	6.23	0.487

No studies were conducted to compare PK/PD parameters between Caucasians and black or Hispanic subjects.

Renal impairment:

A single dose open label, parallel group study was conducted to investigate the pharmacokinetics of insulin detemir in subjects with various degrees of renal impairment in comparison to healthy volunteers. The results indicated that there were no statistically significant differences among the five groups (healthy, mild, moderate, severe renal insufficiency and hemodialysis group) regarding the pharmacokinetics of insulin detemir. No correlation could be established between creatinine clearance and the pharmacokinetics of insulin detemir. The following figures show scatter plots of log-transformed AUC and Cmax versus creatinine clearance.



Hepatic impairment:

The pharmacokinetics of the long-acting insulin analogue, insulin detemir in subjects with chronic liver diseases compared with healthy subjects was studied. Twenty-nine subjects were screened, 24 were included and assigned to four equal size groups of six subjects (one group with healthy subjects and three groups according to severity of hepatic insufficiency (Child-Pugh Classification grade A, B or C). All 24 subjects completed and were included in the pharmacokinetic and safety analyses. The extent of bioavailability of insulin detemir as estimated by AUC (0-∞) appeared to decrease with increasing degree of hepatic insufficiency (four groups: Healthy, mild, moderate and severe). In patients with severely impaired hepatic function, the AUC (0-∞) was decreased by 37%. No impact of hepatic insufficiency on other pharmacokinetic characteristics appeared. No safety issues were identified during the trial.

Table 19. The ratios of AUC (0-∞) between healthy and hepatic impairment and between various degrees of hepatic impairment

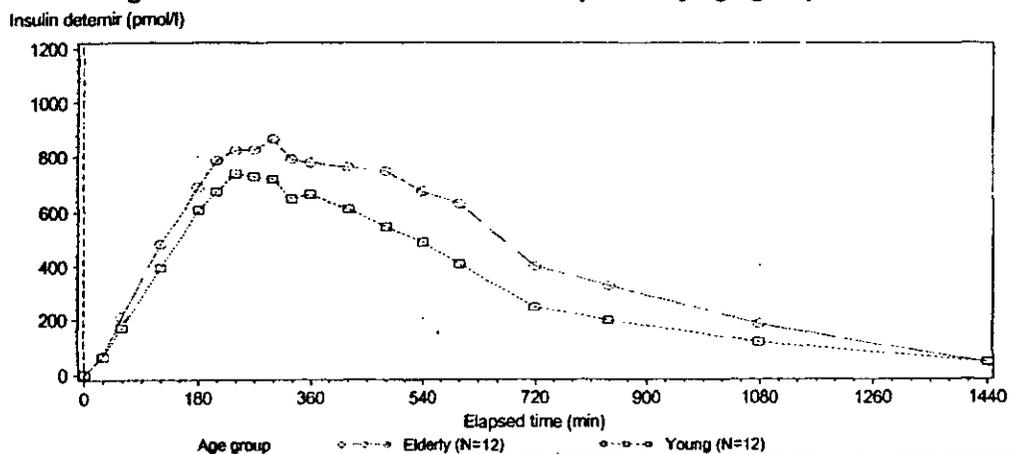
	Healthy over mild	Healthy over moderate	Healthy over severe	Mild over moderate	Mild over severe	Moderate over severe
Estimate (ratio of GMs)	1.22	1.39	1.58	1.14	1.30	1.14
p value	0.421	0.074	0.009	0.728	0.207	0.751

Elderly:

An open-label, parallel group trial comparing the pharmacokinetics of a single subcutaneous dose of insulin detemir was conducted in young and elderly healthy subjects. Twenty-four subjects completed the study (six young males (25-35 years old), six young females (20-32 years old), six elderly males (68-85 years old) and six elderly females (70-79 years old)). Insulin detemir was given as 1.2 nmol/kg body weight in the right thigh (formulation 600 nmol/ml). The results revealed that the young subjects group had lower serum concentrations than in the

elderly group. Young females had a 35% lower AUC (0-∞) compared to elderly females (P<0.05) (Figure 14). Young males had a 17% lower AUC (0-∞) compared to elderly males (P=0.0527).

Figure 14. Insulin detemir mean serum profile by age group



Pediatric:

The pharmacokinetics for insulin detemir and NPH insulin was investigated in children as compared with adolescents and adults with type I diabetes. 13 prepubertal children (6 to 12 years of age), 10 adolescents (13 to 17 years of age) and 11 adults (18 to 65 years of age) with type I diabetes were included in a cross-over trial. A single s.c. doses of 0.5 U/kg of insulin detemir or 0.5 IU/kg NPH insulin were administered. No overall differences were found between the pharmacokinetic profiles in children, adolescents, and adults for insulin detemir (Table 20).

Table 20. Comparison of Pharmacokinetic Endpoints for Insulin Detemir and NPH Insulin in Children, Adolescents and Adults with Type 1 Diabetes (Trial 1222)

Endpoints	Subjects	Insulin detemir ^a			NPH insulin ^b		
		Ratio	95% CI	p-value	Ratio	95% CI	p-value
AUC _{0-24h}	Children/adults	1.10	0.81, 1.50		2.92	1.14, 7.44	
	Adolescents/adults	0.95	0.70, 1.30		1.93	0.77, 4.83	
	Children/adolescents/adults			0.61			0.08
C _{max}	Children/adults	1.24	0.86; 1.79		3.24	1.06;9.95	
	Adolescents/adults	1.02	0.71; 1.47		2.07	0.69; 6.20	
	Children/adolescents/adults			0.41			0.12

^a. N for analyses with insulin detemir: Children = 10; Adolescents = 10, Adults = 9

^b. N for analyses with NPH insulin: Children = 9; Adolescents = 10, Adults = 7

4.4 Extrinsic Factors

- What is the effect of insulin detemir on cytochrome P450 enzymes?

The study of effect of insulin detemir is limited to rats only. The Sprague-Dawley rats were given with either pharmacological dose or toxicological dose for 7 days. The results show that the cytochrome P450 concentrations in female rats were about 20% higher than control, but not in male rats (Table 21).

Table 21. The effect of insulin detemir and phenobarbital on cytochrome P-450 concentration (nmol/mg protein) in rat liver microsomes

Sex	Control (Vehicle)	Insulin detemir (1 unit/kg/day)	Insulin detemir (50 unit/kg/day)	Phenobarbital (50 mg/kg)
Female	0.37 ± 0.04	0.41 ± 0.08	0.45 ± 0.04 (*)	0.86 ± 0.07 (***)
Male	0.50 ± 0.06	0.50 ± 0.03	0.53 ± 0.03	1.44 ± 0.21 (***)

Data are the means (± SD, n=5). (*), and (***) indicate significant different from the control using unpaired t-test where p<0.05 and p<0.001, respectively.

At toxicological dose (50 units/kg/day), insulin detemir increased dealkylase activity although the increase was not statistically significant (Table 22).

Table 22. The effect of insulin detemir and phenobarbital on methoxyresorufin and ethoxyresorufin-O-dealkylation in rat liver microsomes

Sex	Dealkylase activity	Control	Insulin detemir (1 Unit/kg/day)	Insulin detemir (50 Units/kg/day)	Phenobarbital (50 mg/kg)
Female	Methoxy-	64.1 ± 12.7	64.2 ± 14.4	68.7 ± 7.1	108.8 ± 15.4
	Ethoxy-	237 ± 18	219 ± 61	294 ± 59	829 ± 43 (***)
Male	Methoxy-	53.4 ± 6.9	60.6 ± 13.1	69.3 ± 18.4	191.3 ± 19.6 (***)
	Ethoxy-	194 ± 20	187 ± 37	231 ± 52	1424 ± 207 (***)

Note: Data are the means (± SD, n=5). (***) indicate significant different from the control using unpaired t-test with p<0.001.

However, the increase for CYP2E1 content is quite obvious (Table 23). Other CYP enzyme contents were not increased, such as CYP2C11 and CYP4A.

Table 23. The effect of Insulin detemir on CYP2E1 as measured by western blot analyses (N=5).

Sex	Control (Vehicle)	1 Unit/kg/day	50 Units/kg/day
Male	12400 ± 5304	15610 ± 4233	16210 ± 6052
Female	13920 ± 6521	13470 ± 7113	16300 ± 3747

As reported, hyperinsulinemia may lead to increase CYP1A activity in animal as well as in man (indicated by increased antipyrine clearance in man). CYP2E1 is induced in diabetic status. Insulin therapy may correct CYP2E1 induction. Therefore, it seems a novel finding that insulin detemir increases CYP2E1 contents. From these animal studies, insulin detemir tent to behave as a weak inducer of certain CYP enzymes. Since the sponsor has not conducted any human in vitro or in vivo studies, the clinical relevance is unknown.

4.5 General Biopharmaceutics

- **What is the outcome of bioequivalent studies between these formulations?**

The sponsor has developed total 3 formulations: 600 nmol/mL, 1200 nmol/mL and 2400 nmol/mL, of which 2400 nmol/mL is the to-be-marketed formulation. The formulation of 2400 nmol/mL was used in pivotal clinical trials. However, many early stage pharmacokinetic and

pharmacodynamic studies were completed with the formulations, 600 nmol/mL and 1200 nmol/mL. The sponsor conducted two bioequivalence studies: 600 nmol/mL versus 1200 nmol/mL and 1200 nmol/mL versus 2400 nmol/mL in healthy subjects.

Table 25. Summary of ratios

Parameter	Study NN304-1055		Study NN304-1309	
	Formulation 1200 nmol/mL vs. 600 nmol/mL		Formulation 2400 nmol/mL vs. 1200 nmol/mL	
AUC(0-∞)	0.96	0.81	0.96	0.81
Cmax	0.91, 1.01	0.68, 0.97	0.89, 1.03	0.71, 0.93

Apparently, the extent of absorption [AUC (0- ∞)] passes BE criteria, but not for Cmax (rate of absorption). The sponsor did not conduct a BE study between formulations 600 nmol/mL vs. 2400 nmol/mL. Although the BE criteria could be extrapolated from the BE studies above, the results may not be always reliable. Since pivotal clinical trials and key clinical pharmacology studies were conducted with the to-be-marketed formulation (2400 nmol/mL), bioequivalence between 600 nmol/mL and 2400 nmol/mL is not critical.

• **What is the consequence of mixing insulin detemir with rapid-acting insulin drug product (Insulin aspart)?**

A randomized, two-period crossover trial with _____, insulin aspart and insulin detemir was conducted to investigate the effect of mixing insulin detemir with insulin aspart on the pharmacokinetics of insulin aspart in healthy subjects. _____ is a fixed mixture of insulin detemir and insulin aspart. _____ 100 U/ml corresponds to 180 nmol/ml insulin aspart and 840 nmol/ml insulin detemir. A single dose of 0.5 U/kg _____ corresponding to 0.15 U/kg [0.9 nmol/kg] insulin aspart and 0.35 U/kg [4.2 nmol/kg] insulin detemir) was administered. The dose of insulin aspart and insulin detemir, when administered separately, was identical, 0.15 U/kg (0.9 nmol/kg) and 0.35 U/kg (4.2 nmol/kg), respectively.

The pharmacokinetic results showed that there was a marked effect of premixed treatment on early insulin aspart profiles. The AUC_{IAsp} (0-2h), the extent of exposure to insulin aspart following _____ was approximately 60% of the value following separate administration (Figure 15). A similar reduction was observed for insulin aspart Cmax. The effect of premixed treatment _____ on GIR (glucose infusion rate) was also distinguishable, with AUC_{GIR} (0-2h) lowered to approximately 60% of the value following separate administration. The converse was observed for insulin detemir following _____, with Cmax observed to increase by approximately 10% over that of the value following separate injections (Figure 16).

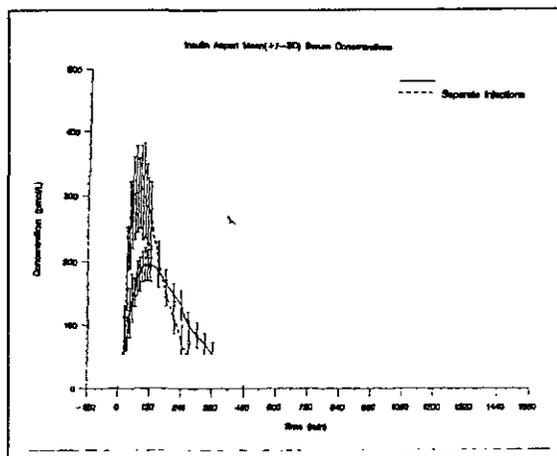
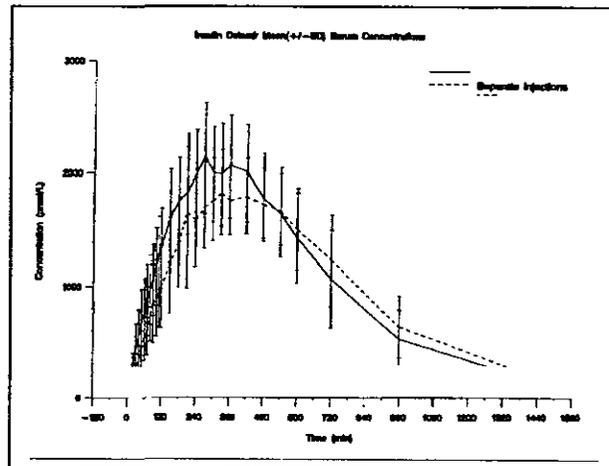


Figure 15. Insulin aspart mean serum concentrations

Figure 16. Insulin detemir mean serum concentrations



Therefore, mixing of insulin detemir with insulin aspart should be avoided.

4.6 Analytical

- What is the property of analytical method?

The method of analysis is a ELISA. An antigen specific ELISA has been set up to measure insulin detemir in plasma or serum during preclinical studies and clinical trials

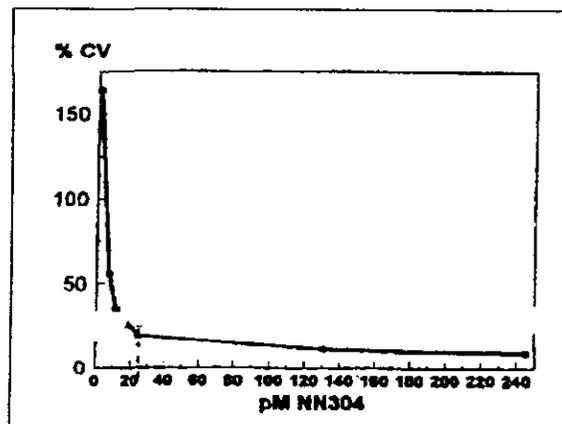
 Table 26 summarizes the analytical parameters for measurement.

Table 26. Analytical Features

Insulin detemir	Accuracy	Precision	Linearity	Limit of detection
<u> </u>				

The limit of detection is set up at of insulin detemir. The analytical results below were so variable that it was no longer reliable. Figure 20 illustrates the relationship between the concentrations of insulin detemir and CV.

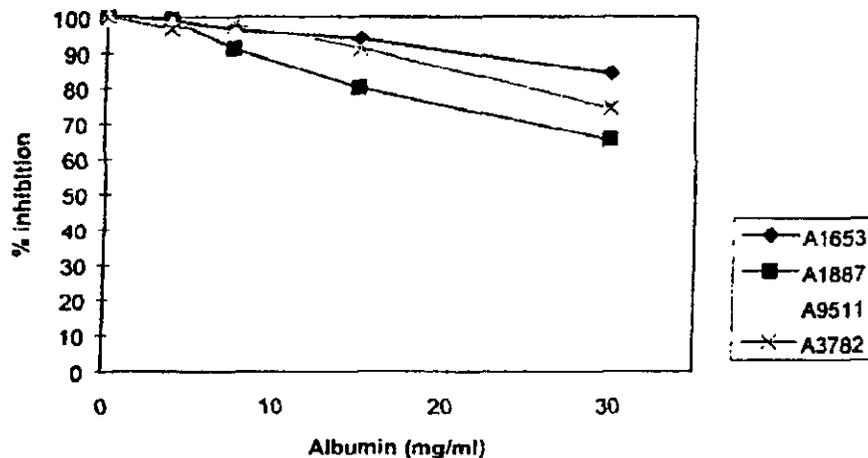
Figure 17. Inter assay variation given as % CV at different concentrations of insulin detemir



- **What may interfere with analytical measurement?**

Albumin: There was some interference of purified human albumin of any preparation. Insulin detemir detection decreased up to 35% in the presence of 30 mg/ml albumin. The different preparations of albumin differed in purity and free fatty acid. The sponsor speculated that the purified albumin adsorbs insulin detemir from plasma, binding it stronger than endogenous plasma to escape the capture of detemir by the antibody in the ELISA well.

Figure 18. Interference by purified albumin of different preparation (A1653: 96-99% pure; A1887, >96% pure and essential free acid free; A3782: 99% pure, essential fatty acid free). Results are expressed in percent of non-inhibited samples.



Hemolyzed blood samples and freeze/thaw cycles also significantly reduce recovery of insulin detemir (Table 27). Hemolysis should be avoided as erythrocytes release an insulin degrading enzyme leading to a decrease in the measured insulin detemir concentrations.

Table 27. Recovery of insulin detemir in hemolyzed samples

Frozen	Strong hemolysis	Weak hemolysis	No hemolysis
Once	7%	75%	100%
Twice	7%	32%	100%

As it is always concerned that human insulin antibodies may interfere with the measurement of insulin analogues, the sponsor has investigated and found that diabetic patients' sera with high human insulin antibody does not interfere with insulin detemir measurement with ELISA method (Table 28).

Table 28. Recovery of insulin detemir from normal subjects and diabetic patients with high insulin antibody titers.

	Sample ID	Insulin antibody titers (%)	Recovery (%)		Sample ID	Insulin antibody titers (%)	Recovery (%)
Diabetic patients' sera with high human insulin antibody	Ab1 + detemir	49	83	Normal donor plasma	NP1 + detemir	8	92
	Ab2 + detemir	47	88		NP2 + detemir	8	83
	Ab3 + detemir	41	82		NP3 + detemir	10	80
	Ab4 + detemir	38	81		NP4 + detemir	11	90
	Ab5 + detemir	59	94		NP1 + detemir	8	104
Mean +SD			86 ± 5				90 ± 9

• **What may cause cross reactivity in ELISA assay?**

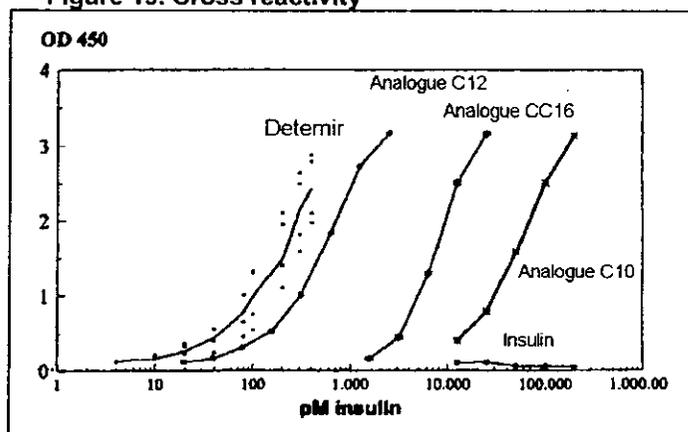
The sponsor has studied cross reactivity of insulin detemir with many other similar analogues. The study has indicated that there are no cross reactivity with regular human insulin or other insulin of animal sources and insulin aspart.

This study also showed that no cross reactivity was seen towards:

- 1) Insulin fatty acid analogues in which amino acid B30 is present
- 2) Human insulin lacking amino acid B30 (equals insulin detemir without the fatty acid side chain)
- 3) Insulin fatty acid analogue in which the fatty acid is coupled to amino acid B 1
- 4) Insulin analogue where glutamic acid is induced as a linker between human insulin des B30 and tetradecanoic acid through lysine in position B29

However, insulin fatty acid analogues with C12, C16, and C10 in position B29 showed to some extent cross reactivity with the antibody (Figure 19).

Figure 19. Cross reactivity



5 LABELING RECOMMENDATIONS

Because the NDA is recommended for "approvable" pending further efficacy data from type 2 diabetic patients at the current stage, the proposed package insert will be not reviewed.

6 Appendix

6.1 Proposed package insert for reference

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13 Page(s) Withheld

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

 § 552(b)(5) Deliberative Process

✓ § 552(b)(5) Draft Labeling

References:

Ref. 1:

Insulin Administration. Diabetes Care. American Diabetes Association: Clinical Practice Recommendations 1998. 21: 572-575.

Ref. 2:

Edited by Pickup, J., Williams, G. Textbook of Diabetes (1997). 1:33, 16, 17; 1:39.1 -39.23; 1:39.11; 1:40.1-40.23; 1.40.13-15; 2:69.1-69.12; 2:76.9.

Ref. 3:

Bourdeau Je, Chen ER, Carone EA. Insulin uptake in the renal proximal tubule. Am J Physiol. (1973) 225:1399-1404.

Ref. 4:

Bilous RW, Marshall SM. International Textbook of Diabetes Mellitus. (1997)

Ref. 5:

Hanson U, Persson B, Enochsson E et al. Self-monitoring of blood glucose by diabetic women during the third trimester of pregnancy. American Journal of Obstetrics and Gynecology (1984) 150:817-21.

Ref. 6:

Freinkel N, Dooley SL, Metzgerc BE. Care of the pregnant woman with insulin-dependent diabetes mellitus. New England Journal of Medicine (1985) 313:96-103.

Ref. 7:

Molsted-Pederson L, Kuhl C. Obstetrical Management in Diabetic Pregnancy: the Copenhagen Experience. Diabetologia (1986) 29:13-16.

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8/12/03 08:47:35 AM
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Hae-Young Ahn
8/18/03 10:48:37 AM
BIOPHARMACEUTICS

**Screening of New NDAs
Division of Biometrics II, HFD-715**

NDA #: 21-536

Priority Classification: S

Trade Name:

Sponsor: Novo Nordisk

Generic Name: Insulin detemir

Indication: Diatetes Mellitus

No. of Controlled Studies: 8

Date of Submission: December 5, 2002

User Fee Goal Date: October 5, 2003

Volume numbers in statistical section: 1-124

Date of 45 Day Meeting: 1/27/03

Screened by: Lee-Ping Pian

CHECKLIST

Item	Check (NA if not applicable)
Index sufficient to locate necessary reports, tables, etc.	Yes
Original protocols & subsequent amendments available in the NDA	Yes
Designs utilized appropriate for the indications requested	Yes
Endpoints and methods of analysis spelled out in the protocols	Yes
Interim analyses (if present) planned in the protocol and appropriate adjustments in significance level made	N/A
Appropriate references included for novel statistical methodology (if present)	N/A
Sufficient data listings and intermediate analysis tables to permit a statistical review	Yes
Data from primary studies on diskettes and/or EDR submitted	EDR
Intent-to-treat analyses	Yes
Effects of dropouts on primary analyses investigated	Yes
Safety and efficacy for racial, and geriatric subgroups investigated	N/A

BRIEF SUMMARY OF CONTROLLED TRIAL

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

Trial # Place center #	ID nm/ ml	Study	bolus	Regimen Study length	Trt: N	HbA _{1c} Baseline 6 mons Difference (C.I.)	Insulin Molar ratio
1181 Eu, Aus 55	1200	NInf	HSI	2x/day 6 mons	ID: 237 NPH: 224	7.84 7.68 7.89 7.59 0.086 (-0.050, 0.221)	Basal: 3.09 Bolus: 1.18
1205 Eu 46	1200	NInf	IAsp	2x/day 6 mons	ID: 301 NPH: 148	7.99 7.60 7.92 7.64 -0.045 (-0.218, 0.128)	Basal: 3.74 Bolus: 1.18
1335 Aus, Eu 92	2400	NInf	HSI	1x/day 6 mons	ID: 492 NPH: 257	8.21 8.46 8.26 8.21 8.58 8.38 -0.11(-0.245, 0.018) -0.12 (-0.25, 0.015)	Basal: 3.27 Bolus: 1.06
1447 Eu 52	2400	Supr timing	IAsp	2x/day 16 wks	ID (M,D) 139 NPH (M,B) 129 ID (M,B) 132	8.12 7.67 8.16 7.73 8.23 7.65 p=0.64	Basal: 4.69, 4.29 Bolus: 1.12, 1.15
1448 Aus, NZ, Eu 51	2400	Supr timing	IAsp	2x/day 16 wks	ID (12 hr) 137 NPH (M,B) 132 ID (M,B) 139	8.53 7.75 8.49 7.94 8.67 7.78 p=0.08	Basal: 4.34, 4.21 Bolus: 0.97, 1.02

Table 2 Summary of 3 Phase III studies – Type 2

Trial # Location	ID nmol/ml	Regimen Study length	Trt: N	HbA _{1c} Baseline 6 mons Difference (C.I.)	Insulin Molar ratio
1166; Asia, Eu	1200	2x/day 6 mons	ID: 224 NPH: 221	9.00 9.36 8.88 8.70 0.660 (0.436, 0.885)	4.16
1336; Eu	2400	2x/day + IAsp 6 mons	ID: 341 NPH: 165	8.45 7.63 8.33 7.48 0.157 (0.003, 0.312)	Basal: 4.13 Bolus: 1.12
1337; US	2400	1x/day + metformin 6 mons	ID: 309 NPH: 158	9.40 8.40 8.5 9.35 7.89 8.0 0.51 (0.27, 0.75) 0.56 (0.326, 0.784)	Insulin: 4.98 Metformin: 2023/2050=0.99

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Todd Sahlroot
1/27/03 01:22:43 PM
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Office of Clinical Pharmacology and Biopharmaceutics
New Drug Application Filing and Review Form

General Information About the Submission

NDA Number	21-536	Brand Name	TBD
OCPB Division (I, II, III)	DPE II	Generic Name	Insulin detemir
Medical Division	HFD-510	Drug Class	protein
OCPB Reviewer	Xiaoxiong (Jim) Wei	Indication(s)	Diabetes, IDDM & NIDDM
OCPB Team Leader	Hae-Young Ahn	Dosage Form	solution
		Dosing Regimen	100 units per mL: 10 mL vial 3 mL PenFill® cartridges 3 mL InnoLet® 3 mL FlexPen®
Date of Submission	12-05-02	Route of Administration	SC
Estimated Due Date of OCPB Review	06/25/03	Sponsor	Novo Nordisk
PDUFA Due Date	10/05/03	Priority Classification	S1
Division Due Date	07/11/03		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:	X	1		
Blood/plasma ratio:				
Plasma protein binding:	X	9		
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	X	3		
multiple dose:	X	3		
Patients-				
single dose:				
multiple dose:	X	1		
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug Interaction studies -				
In-vivo effects on primary drug:	X	1		
In-vivo effects of primary drug:	X	1		
In-vitro:	X	1		
Subpopulation studies -				
ethnicity:	X	1		
gender:				

pediatrics:	X	1		
geriatrics:	X	1		
renal impairment:	X	1		
hepatic impairment:	X	1		
PD:				
Phase 2:	X	4		
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:	X	3		
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:	X	2		
replicate design; single / multi dose:				
Food-drug interaction studies:				
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		35		
Filability and QBR comments				
	"X" if yes	Comments		
Application filable ?	YES			
Comments sent to firm ?	YES	Please provide the following data in CD diskette (1) individual human PK data; (2) summary PK data; (3) individual human PK study synopsis.		
Primary reviewer Signature and Date				
Secondary reviewer Signature and Date				

Briefing In Content:

The sponsor, Novo Nordisk has submitted their NDA for insulin detemir for the treatment of type 1 and type 2 diabetes. Insulin detemir modifies human insulin in that the amino acid molecule in position B30 has been omitted and a 14-C fatty acid chain has been attached to position B29. Insulin detemir is a long-acting insulin analog produced by a process of expression of recombinant DNA and subsequent chemical synthesis.

After subcutaneous injection, insulin detemir in healthy subjects and diabetic patients has Tmax of 6-8 hours, Half-life of 5-7 hours depending on dose and bioavailability of about 60%. Insulin detemir has a small volume of distribution of about 0.1L/kg. Dose proportionality in serum concentrations was observed.

The prolonged action of insulin detemir is mediated by the slower systemic absorption from the injections site due to strong self-association of drug molecules and by albumin binding via fatty acid side chain. More than 98% of insulin detemir is albumin bound in blood. The duration of action is up to 24 hours depending on dose providing a basal insulin to patients for once or twice daily administration.

The sponsor has conducted many special population studies including children and adolescents, geriatric, obesity, ethnic and gender, renal and hepatic impairment.

Three formulations have been developed during drug development: 600, 1200 and 2400 nmol/ml. The 2400 nmol/ml is the to-be-market formulation. Two bioequivalence studies have been performed. Both studies showed that AUCs pass BE criteria, but not Cmax.

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