2 Synopsis

Trial Registration ID-number NCT00447382	**EudraCT number – 2006-004733-15**
Title of Trial A 12-months multi-national, multi-centre, double blind, randomised, parallel safety and efficacy comparison of insulin detemir produced by the current process and insulin detemir produced by the NN729 process in subjects with type 1 diabetes on a basal-bolus regimen with insulin aspart as the bolus insulin	
Investigator(s) A total of 24 principal Investigators in five countries (Germany, Republic of Macedonia, Russian Federation, Serbia, and South Africa). Prof. [redacted] was designated Signatory Investigator for the trial.	
Trial Site(s) Twenty four sites in five countries: Germany (12), The Republic of Macedonia (1), Russian Federation (4), Serbia (3) and South Africa (4)	
Publications None	
Trial Period 29 March 2007 to 09 July 2008	**Development Phase** 3

Objectives

Primary Objective:

- To compare the safety of insulin detemir based on NN729 with insulin detemir produced by the current process, as measured by development of insulin cross-reacting antibodies, in subjects with type 1 diabetes during 12 months treatment on a basal-bolus regimen with insulin detemir as basal insulin and insulin aspart as bolus.

Secondary Objectives:

Safety:

- To compare the safety profiles by measurement of insulin antibody levels (the sum of insulin detemir specific antibodies and cross-reacting antibodies) and measurement of insulin detemir specific antibodies during 12 months treatment.
- To compare the safety profiles by occurrence of adverse events during 12 months treatment (including application site disorders).
- To compare the safety profiles as measured by standard safety parameters (haematology, biochemistry), vital signs, fundoscopy/fundusphotography and weight.
- To compare the incidence of hypoglycaemic episodes during 12 months treatment.

Efficacy:

- Glycaemic control as measured by HbA1c
- Glycaemic control as measured by fasting plasma glucose (FPG, central laboratory analysis) during the trial
- Glycaemic control as measured by 9-point plasma glucose (PG) profiles during the trial.

Other:

- Assessment of hypoglycaemic impairment of work productivity and daily activity as measured by hours lost from paid work and/or daily activities and a ranking of the effect of the hypoglycaemic episode on work and daily activities.

Methodology

- The trial was a multi-national, multi-centre, double-blind, randomised parallel group trial comparing the safety

and efficacy of insulin detemir produced by the NN729 process with insulin detemir produced by the NN304 process during 12 months of treatment comprising 8 Visits.

- After successful screening, subjects were randomised to treatment with NN729 or NN304 at the same total daily dose and frequency of administration as pre-trial basal insulin. During the trial doses were individualised based on subject's plasma glucose measurements.
- The following efficacy assessments were made during the trial: HbA1c, Fasting plasma glucose and 9-point self measured plasma glucose levels.
- The following safety assessments were made during the trial: Level of cross reactive/insulin detemir specific/total insulin antibodies, adverse events, hypoglycaemia, haematology, biochemistry, vital signs, fundoscopy/fundusphotography and weight.

Number of Subjects Planned and Analysed

It was planned to randomise 300 subjects to obtain 250 subjects completing the trial. Subject disposition is summarised below:

	NN304	NN729	Total
Screened			348
Randomised	164 (100.0%)	166 (100.0%)	330 (100.0%)
Exposed	164 (100.0%)	166 (100.0%)	330 (100.0%)
Withdrawals	6 (3.7%)	6 (3.6%)	12 (3.6%)
Adverse event	1 (0.6%)	1 (0.6%)	2 (0.6%)
Inefficient therapy	1 (0.6%)	0 (0.0%)	1 (0.3%)
Non-Compliance	2 (1.2%)	0 (0.0%)	2 (0.6%)
Other	2 (1.2%)	5 (3.0%)	7 (2.1%)
Completed	158 (96.3%)	160 (96.4%)	318 (96.4%)
Full analysis set	164 (100.0%)	166 (100.0%)	330 (100.0%)
Per protocol analysis set	145 (88.4%)	145 (87.3%)	290 (87.9%)

Diagnosis and Main Criteria for Inclusion

Subjects with type 1 diabetes (duration ≥ 12 months) currently on a basal-bolus regimen for ≥3 months, age ≥18 years, BMI ≤ 35.0 kg/m^2 and HbA1c ≤ 12.0%. Subjects were excluded from the trial if they had proliferative retinopathy or maculopathy requiring acute treatment within the last six months, recurrent major hypoglycaemia, impaired hepatic or renal function, cardiac problems or uncontrolled hypertension that according to the Investigator would interfere with trial participation.

Test Product, Dose and Mode of Administration, Batch Number

Trial Product	Dose	Mode of administration	Batch Number
Insulin detemir 100 U/mL, FlexPen® (NN729 process)	Individual	Subcutaneous injection	SP51756 TP51208

Duration of Treatment

52 weeks

Reference Therapy, Dose and Mode of Administration, Batch Number

Reference therapy:

Trial Product	Dose	Mode of administration	Batch Number
Insulin detemir 100 U/mL, FlexPen® (NN304 process)	Individual	Subcutaneous injection	SP51656 TP51307

Concomitant Insulin Therapy (meal related):

Trial Product	Dose	Mode of administration	Batch Number
Insulin aspart 100 U/mL, FlexPen®	Individual	Subcutaneous injection	SP52173 TP52111 VP50336

Criteria for Evaluation – Efficacy

- HbA1c
- Fasting plasma glucose
- 9-point self measured plasma glucose levels
- Insulin dose

Criteria for Evaluation – Safety

- Cross reactive insulin antibodies (Primary endpoint)
- Insulin detemir specific insulin antibodies
- Total insulin antibodies
- Adverse events
- Hypoglyceamia
- Haematology and biochemistry
- Vital signs
- Fundoscopy/fundusphotography
- Weight

Statistical Methods

Analysis Sets:

The following analysis sets were defined:

- Full analysis set (FAS): All randomised subjects exposed to at least one dose of trial product
- Per protocol (PP) population: Excluding subjects with major violations to inclusion and exclusion criteria, study withdrawal, non-compliance with study treatment, missing relevant data for the given analysis, data recorded substantially outside the relevant visit window, basal insulin treatment not according to randomisation

Primary endpoint:

- The primary safety endpoint in this trial was the change from baseline (Visit 2) to week 52 (Visit 8) in cross-reacting insulin antibody levels.

Secondary Safety Endpoints:

- Cross-reacting antibody levels measured during the trial at 12, 26, 39 and 52 weeks of treatment.
- Insulin antibody levels (the sum of insulin detemir specific antibodies and cross-reacting antibodies) measured during the trial at 12, 26, 39 and 52 weeks of treatment.
- Insulin detemir specific antibody levels (bound/total (%)) measured during the trial at 12, 26, 39 and 52 weeks of treatment.
- Frequency of treatment emergent adverse events during 12 months of treatment.

- Application site disorders
- Clinical laboratory values (haematology, biochemistry), vital signs, fundoscopy/fundusphotography and weight after 12 months of treatment.
- Incidence of hypoglycaemic episodes during 12 months of treatment.

Secondary Efficacy Endpoints:

- HbA1c at weeks 12, 26, 39 and week 52.
- Fasting plasma glucose (FPG) level after 12, 26, 39 and 52 weeks of treatment.
- 9-point self-measured plasma glucose profile after 26 and 52 weeks of treatment.
- Insulin dose

Other secondary Endpoints:

- Hypoglycaemic Impairment of Work Productivity and Daily Activity

Analysis of the primary endpoint:

The primary endpoint was analysed using analysis of variance (ANOVA) including treatment, previous insulin detemir exposure (the stratification factor) and country as fixed effects and the baseline value as a covariate. The analysis was based on an assumption of a log-normal distribution for antibody data, and thus built on log-transformed data. If a subject did not have antibody data at Week 52, for example because the subject withdrew prior to this visit, then the missing data was replaced using last observation carried forward (LOCF). Based on this model the ratio between the two treatments was estimated and a 95% confidence interval for this estimate was calculated. A number of analyses were made to provide a sensitivity analysis for the primary endpoint including a repeated measures analysis, a PP population analysis and a separate analysis including data were unreliable antibody samples had been excluded in the primary analysis.

Analyses of the Secondary Safety Endpoints:

Insulin detemir specific antibodies and total insulin antibodies were analysed as for the primary endpoint.

The number of hypoglycaemic episodes was analysed using a negative binomial regression model. The model included the number of episodes as the dependent variable, the log-transformed exposure time as an offset variable and baseline HbA1c as a continuous covariate.

For all the remaining secondary safety endpoints, summary statistics was applied.

Analyses of Secondary Efficacy Endpoints:

The change from baseline to week 52 in HbA1c and FPG was analysed using an ANOVA model including treatment, previous insulin detemir exposure and country as fixed effects and the baseline value of HbA1c as a covariate. The estimated treatment difference based on this ANOVA is reported with the 95% confidence interval. Summary statistics was applied for 9-point SMPG profiles.

Analysis of Other Endpoints:

Summary statistics was applied for “Hypoglycaemic Impairment of Work Productivity and Daily Activity”

Demography of Trial Population

The two groups were well-matched with regard to both demographic and baseline characteristics, please see below tables.

	NN304	NN729
Number of subjects	164	166
Age (years)		
N	164	166
Mean (SD)	39.9 (14.9)	38.6 (13.6)
Median	37	37
Min ; Max	18 ; 77	18 ; 73
Gender		
Female	66 (40.2%)	79 (47.6%)
Male	98 (59.8%)	87 (52.4%)
Race		
Asian	1 (0.6%)	1 (0.6%)
Black Or African American	2 (1.2%)	4 (2.4%)
White	152 (92.7%)	152 (91.6%)
Other	9 (5.5%)	9 (5.4%)
Height (m)		
N	164	166
Mean (SD)	1.74 (0.09)	1.72 (0.10)
Median	1.74	1.72
Min ; Max	1.52 ; 1.92	1.49 ; 1.94
Body weight (kg)		
N	164	166
Mean (SD)	77.6 (14.6)	75.1 (14.9)
Median	78	74
Min ; Max	43.8 ; 123.8	43.0 ; 123.1
BMI (kg/m2)		
N	164	166
Mean (SD)	25.68 (4.05)	25.23 (3.59)
Median	25	25
Min ; Max	17.71 ; 34.9	16.80 ; 34.8
HbA1c (%)		
N	164	166
Mean (SD)	7.93 (1.31)	7.99 (1.38)
Median	8	8
Min ; Max	4.50 ; 10.9	5.20 ; 11.4
Diabetes Hist (years)		
N	164	166
Mean (SD)	14.48 (11.2)	13.66 (10.3)
Median	12	11
Min ; Max	1.02 ; 56.0	1.06 ; 51.8

Diabetic Complication		NN304	NN729
Full Analysis Set	N (%)	164 (100.0)	166 (100.0)
Duration of type 1 diabetes (yrs)	N	164	166
	Mean (SD)	14.5 (11.3)	13.7 (10.3)
	Min; Max	1.0 ; 56.0	1.1 ; 51.8
Diabetic Nephropathy	N (%)	164 (100.0)	166 (100.0)
	No (%)	145 (88.4)	149 (89.8)
	Yes (%)	19 (11.6)	17 (10.2)
Diabetic Neuropathy	N (%)	164 (100.0)	166 (100.0)
	No (%)	120 (73.2)	131 (78.9)
	Yes (%)	44 (26.8)	35 (21.1)
Diabetic Retinopathy	N (%)	164 (100.0)	166 (100.0)
	No (%)	115 (70.1)	112 (67.5)
	Yes (%)	49 (29.9)	54 (32.5)
Macro Angiopathy	N (%)	164 (100.0)	166 (100.0)
	No (%)	153 (93.3)	159 (95.8)
	Yes (%)	11 (6.7)	7 (4.2)

The treatment groups were well matched with respect to the most frequently reported concomitant illnesses (by more than 5% of subjects in either treatment group): hypertension, hyperlipidaemia and cataract. Most of the subjects in both treatment groups used a variety of concomitant medications. The treatment groups were well matched with respect to the most commonly used concomitant medications: mild anaesthetics, lipid lowering and antihypertensive drugs.

Efficacy Results

- The time profiles for HbA1c and FPG were comparable between NN729 and NN304.
- There were no statistical significant difference between NN729 and NN304 in change from baseline for HbA1c and FPG, please see table below .

NN729			NN304			NN729-NN304	
N	Mean	(SE)	N	Mean	(SE)	Diff (95% CI)	p-Value
HbA1c:							
Level at End of trial							
165	7.85	(0.07)	164	7.88	(0.07)		
Change from Baseline to End of trial							
165	-0.11	(0.07)	164	-0.08	(0.07)	-0.03 (-0.21; 0.15)	0.758
FPG:							
Level at End of trial							
165	9.64	(0.30)	164	9.73	(0.30)		
Change from Baseline to End of trial							
165	-0.02	(0.30)	164	0.07	(0.30)	-0.10 (-0.89; 0.70)	0.812

Note: Model includes adjustment for Baseline, Country and Previous detemir exposure
N: Number of subjects
Mean: Estimated change from baseline to end of trial
Diff: Estimated difference in change between treatments

- The empirical means for the 9-point plasma glucose profiles were comparable at baseline and decreased slightly (< 1 mmol/l) at all time points during the 52 weeks treatment to a similar extend with both treatments.
- The mean daily insulin detemir doses were similar in both treatment groups from start to end of trial. In both treatment groups, the mean level was approximately 0.4 units/kg throughout the trial, which does not indicate an increased demand for basal insulin during the 52 weeks treatment. The results were similar for the bolus insulin dose.

Safety Results

Antibodies:

- The analysis of change in cross-reacting insulin antibodies (primary endpoint) showed no difference between NN729 and NN304. The cross reacting antibody time profiles during 52 weeks were comparable for the two processes (NN729 and NN304): following an initial increase during the first 26 weeks, the mean levels stabilised for the remaining of the trial.
- Nor was any difference between treatments shown for total antibody or insulin detemir specific antibody level.

NN729			NN304			NN729/NN304	
N	Est.	(SE)	N	Est.	(SE)	Ratio (95% CI)	p-Value
Cross reacting antibodies:							
Level at End of trial							
152	17.21	(0.07)	158	16.47	(0.07)		
Change ratio from Baseline to End of trial							
152	1.89	(0.07)	158	1.81	(0.07)	1.04 (0.86; 1.26)	0.649
Insulin detemir specific antibodies:							
Level at End of trial							
150	4.47	(0.04)	150	4.82	(0.04)		
Change ratio from Baseline to End of trial							
150	1.06	(0.04)	150	1.14	(0.04)	0.93 (0.84; 1.03)	0.150
Total antibodies:							
Level at End of trial							
147	23.71	(0.05)	150	23.79	(0.05)		
Change ratio from Baseline to End of trial							
147	1.55	(0.05)	150	1.55	(0.05)	1.00 (0.87; 1.15)	0.966

Adverse events:

- The proportion of subjects reporting adverse events were comparable between NN729 and NN304. There was no notable difference in the overall pattern of adverse events between treatment groups. The most frequent events in both groups were upper respiratory tract infection, nasopharyngitis and influenza.
- Adverse events considered to have a probable or possible relation to trial products were reported by 9 subjects in each group (about 5% of subjects) with no major differences between treatments. Only notable difference was for application site reactions, that was only reported by subjects in the NN729 group (5 events by 3 subjects considered probably related to trial product) corresponding to a proportion of subjects of 1.8%. Further one application site disorder (unlikely related to trial product) and one lipohypertrophy (probably related to trial product) was reported in the NN729 group corresponding to 0.6% of subjects.
- Serious adverse events were reported less frequently in the NN729 group (4.8%) than in the NN304 group (11.6%), but there was no notable pattern differences between treatments. Most of the serious adverse events were considered unlikely related to trial product. Seven subjects (NN304 = 5 subjects; NN729 = 2 subjects) reported a total of eight serious adverse events that were probably or possibly related to trial drug, all related to hypoglycaemic unconsciousness or overdose.
- One subject in each treatment group was withdrawn due to adverse events related to an application site reaction (NN729) and hyperglycaemia (NN304). Both were non-serious and possibly/probably related to trial product.

Summary of Adverse events:

	NN304 N	(%)	E	R	NN729 N	(%)	E	R
Number of Subjects	164				166			
Total Exposure(year)	159.5				162.1			
All Adverse Events	93	(56.7)	284	1780	100	(60.2)	356	2197
Serious Adverse Events	19	(11.6)	25	157	8	(4.8)	10	62
Non-serious Adverse Events	87	(53.0)	259	1623	97	(58.4)	346	2135
Adverse Events by Severity								
Mild	78	(47.6)	197	1235	81	(48.8)	218	1345
Moderate	35	(21.3)	68	426	39	(23.5)	124	765
Severe	16	(9.8)	19	119	10	(6.0)	14	86
Adverse Events by Relationship								
Possible	6	(3.7)	6	38	2	(1.2)	2	12
Probable	3	(1.8)	4	25	7	(4.2)	10	62
Unlikely	90	(54.9)	274	1717	95	(57.2)	344	2122
Adverse Events leading to - Withdrawal	1	(0.6)	2	13	1	(0.6)	1	6

N: Number of subjects
%: Percentage of subjects
E: Number of events
R: Ratio - Number of events per 1000 exposure years

Most Common Adverse Events (>5% of subjects)

	NN304 N	(%)	E	R	NN729 N	(%)	E	R
Subjects	164				166			
Total Exposure(year)	159.5				162.1			
Events	93	(56.7)	284	1780.0	100	(60.2)	356	2196.5
Infections and infestations	64	(39.0)	100	626.8	66	(39.8)	118	728.1
Nasopharyngitis	26	(15.9)	33	206.8	31	(18.7)	37	228.3
Influenza	11	(6.7)	11	68.9	11	(6.6)	17	104.9
Upper Respiratory Tract - Infection	9	(5.5)	10	62.7	11	(6.6)	14	86.4
Nervous system disorders	21	(12.8)	45	282.0	24	(14.5)	66	407.2
Headache	10	(6.1)	30	188.0	17	(10.2)	59	364.0

N: Number of subjects
%: Percentage of subjects
E: Number of events
R: Ratio - Number of events per 1000 exposure years

Other safety assessments:

- There did not appear to be any major difference between treatments in the safety profiles as measured by haematology, biochemistry, vital signs, fundoscopy/fundusphotography and weight.
- There were no notable differences in hypoglycaemic impairment of work productivity and daily activity between the two treatment arms.
- No differences between treatments were found in the statistical analyses of hypoglycaemia.

Endpoint	NN304 Adj Rate	NN304 SE	NN729 Adj Rate	NN729 SE	Rate Ratio	95% Confidence Interval	p-value
All hypos	21.51	0.12	20.39	0.12	0.95	0.67, 1.33	0.76
Symptoms only	2.78	0.21	1.94	0.21	0.70	0.39, 1.25	0.22
Minor	18.35	0.13	18.10	0.13	0.99	0.69, 1.40	0.94
Major	0.09	0.36	0.12	0.33	1.37	0.53, 3.50	0.51
Daytime	18.23	0.13	17.61	0.13	0.97	0.68, 1.37	0.85
Nocturnal	3.24	0.15	2.74	0.15	0.85	0.56, 1.29	0.44

Adj rate=adjusted rate from negative binomial regression model including log-transformed exposure time as an offset variable, baseline HbA1c, previous detemir exposure and Treatment.
SE=standard error of the estimate

Conclusions

- There was no difference in the level of cross reacting antibody formation (primary endpoint) between insulin detemir produced by the NN729 or the NN304 process.
- There was no difference in the level of insulin detemir or total insulin antibody formation between insulin detemir produced by the NN729 or the NN304 process.
- There was no difference in glycaemic control (HbA1c and FPG) between the two treatments.
- Total daily basal and bolus insulin doses remained stable throughout the trial.
- The safety profile of the two treatments appeared similar in this trial. The completion rate of the trial was high and only one subject in each group was withdrawn due to an adverse event.
- Application site disorders and lipohypertrophy considered possibly or probably related to trial drug by the investigator were reported only in the NN729 group by 1.8% and 0.6% of subjects, respectively). This is not in excess of that in the current labelling.

The trial was conducted in accordance with the Declaration of Helsinki (52nd WMA, 2000. Last amended in Washington 2002 and Tokyo, 2004) and ICH Good Clinical Practice (May 1996).

The results presented reflect data available in the clinical database as of 28-aug-2008.