2 Synopsis

Trial Registration ID-number From www.clinicaltrials.gov NCT00537303	**IND Number: 51,798** **EudraCT number: 2007-000123-18**
Title of Trial A Randomised, Controlled, Parallel, Open-labelled, Multinational Trial, Comparing the Efficacy and Safety of Step-wise Addition of Insulin Aspart (NovoRapid®) According to the Largest Meals (Basic Basal Plus Regimen) or the Largest Prandial Increments (Advanced Basal Plus Regimen) in Combination with Once Daily Insulin Detemir (Levemir®) and OAD Treatment in Subjects with Type 2 Diabetes	
Investigator(s) A total of 67 principal investigators participated in the trial. Dr [redacted] and Dr [redacted] were appointed as signatory investigators for the trial.	
Trial Site(s) Denmark (1), Finland (6), France (5), Netherlands (6), Norway (5), Russian Federation (4), Serbia (2), South Africa (3), Spain (5), Sweden (3), UK (7), US (20)	
Publications None	
Trial Period First subject first visit: 01-Oct-2007 Last subject last visit: 18-Mar-2009	**Development Phase** Phase 4

Objectives

Primary Objective:

- To investigate if insulin aspart (IAsp) added step-wise (1-2-3) in a basic regimen (according to the largest meal, and titrated based mainly on pre-meal self-measured plasma glucose [SMPG]) is equivalent to IAsp added step-wise (1-2-3) in an advanced regimen (according to the largest prandial increment and titrated based mainly on postmeal SMPG) as measured by HbA_{1c} after 36 weeks of treatment in subjects with type 2 diabetes treated with once daily insulin detemir (IDet) in combination with one or more oral antidiabetic drugs (OADs).

Secondary Objectives:

- To compare HbA_{1c} levels at Week 11
- To compare the proportion of subjects achieving HbA_{1c} levels <7.0% at 11, 23 and 36 weeks with IAsp at the largest meal (Basic Basal Plus) vs. IAsp at the meal with the largest prandial increment (Advanced Basal Plus), both as add-on to IDet and OADs
- To compare the glycaemic control as measured by fasting plasma glucose (FPG) (laboratory analysis) at 36 weeks with the two regimens
- To compare the average prandial plasma glucose (PG) increments between the two regimens at 36 weeks
- To compare the proportions of subjects with postprandial PG readings above 8.0 mmol/L (144 mg/dL) or 11.1 mmol/L (199.8 mg/dL) between regimens at 12, 24 and 36 weeks of treatment
- At end of trial, to compare the safety profile as measured by occurrence of adverse events (AEs) during the trial within the two regimens
- To compare the safety profile within the two regimens as measured by changes in laboratory safety parameters (haematology, biochemistry and cardiovascular disease (CVD) risk markers), physical examination and vital signs at screening and at end of trial
- To compare the relative incidence of hypoglycaemic episodes within the two regimens during the trial
- To compare changes in body weight, body mass index (BMI), waist and hip circumference with the two regimens at 12, 24 and 36 weeks
- To evaluate the distribution of bolus injections by meal and number of boluses during the trial with the two regimens
- To evaluate the total, basal and bolus insulin doses within the two regimens at 12, 24 and 36 weeks of treatment

- To evaluate the average daily bolus insulin doses within the two regimens at 12, 24 and 36 weeks of treatment
- To assess the distribution of subjects on one, two or three boluses of IAsp during the trial with the two regimens
- To assess and compare patient reported outcomes (e.g. ,treatment satisfaction) with the two treatments after 0, 12 and 36 weeks

Methodology

This was a 50-week, open-labelled, multinational, randomised, parallel-group, treat-to-target (TTT) trial comparing two different Basal Plus regimens in subjects with type 2 diabetes not achieving glycaemic targets on basal insulin plus OADs:

1) A Basic Basal Plus regimen with addition of meal-time IAsp stepwise (1-2-3) at the largest meals (as reported by the subject) and titration of IAsp based mainly on pre-meal SMPG
2) An Advanced Basal Plus regimen with addition of meal-time IAsp stepwise (1-2-3) at the meals with the largest prandial increments and titration of IAsp based mainly on post-meal SMPG.

In both regimens, IAsp was added to once-daily IDet and OADs by application of a TTT approach.

The trial included a total of 14 clinic visits, 3 laboratory visits and 17 telephone contacts. A screening visit was made to assess the eligibility of the subjects. Approximately 2 weeks after screening, subjects who met the inclusion criteria initiated an open 12-weeks forced titration period (run-in) with IDet once daily as add-on to current metformin ± SU ± TZD treatment. After the 12-week run-in period, subjects who did not meet the HbA_{1c} target <7.0% were randomised to one of the two treatment regimens, and treatment was intensified by either the basic regimen or the advanced regimen. SU treatment was discontinued when the first IAsp bolus injection was added. The trial consisted of three 12-week treatment periods and intensification with addition of 1, 2 or 3 IAsp boluses was possible only at fixed time points every 12 weeks. The titration of IDet continued for the rest of the trial in both regimens.

Number of Subjects Planned and Analysed

A total of 512 subjects were planned to be screened for this trial. Subject disposition is shown in the table below:

	Advanced		**Basic**		**Total**	
	N	(%)	N	(%)	N	(%)
Screened					560	
Entered run-in period					345	(100)
Not Randomised					49	(14.2)
Randomised	146	(100)	150	(100)	296	(100)
Exposed	146	(100)	150	(100)	296	(100)
Withdrawals	26	(17.8)	25	(16.7)	51	(17.2)
Completed Trial	120	(82.2)	125	(83.3)	245	(82.8)
Full Analysis Set (FAS)	146	(100)	150	(100)	296	(100)
PP Analysis Set	108	(74)	118	(78.7)	226	(76.4)
Safety Analysis Set	146	(100)	150	(100)	296	(100)

Randomised subjects were stratified according to previous OAD use: metformin only: 62 subjects (42.5%) (Advanced) and 64 subjects (42.7%) (Basic); metformin + other OADs: 84 subjects (57.5%) and 86 subjects (57.3%).

Diagnosis and Main Criteria for Inclusion

Eligible subjects were to have had type 2 diabetes mellitus ≥6 months, be ≥18 years and have an HbA_{1c} ≥7.5% and <10.0% at screening. Their BMI should be <40.0 kg/m^2. Previous basal insulin treatment (NPH once or twice daily, insulin glargine once daily or IDet once daily) was to have been of at least 3 months duration at screening, in addition to treatment with 1-3 OADs (metformin ≥ 1500 mg daily ± SU ≥ 50% of maximum dose ± pioglitazone or rosiglitazone.

Test Product, Dose and Mode of Administration, Batch Number

Trial Product	Strength	Batch Number	Administration
Insulin detemir, Levemir® FlexPen®, 3 ml	100 U/ml	TP51137	Injected subcutaneously once daily at bedtime, preferably in the thigh. Dose adjusted individually according to protocol defined titration guideline
Insulin aspart, NovoRapid® FlexPen®, 3 ml	100 U/ml	TP51087	Injected subcutaneously 1-3 times daily before main meal(s), preferably in the abdomen. Dose adjusted individually according to protocol defined titration guideline.

Duration of Treatment

The trial consisted of a 12-week run-in period with IDet followed by a 36-week treatment period with IDet and IAsp, adding up to a total of 48 weeks of treatment. With 2 weeks between screening and treatment initiation (run-in) the total trial length was 50 weeks.

Reference Therapy, Dose and Mode of Administration, Batch Number

Not applicable, as subjects in both treatment groups were treated with IAsp and IDet

Criteria for Evaluation – Efficacy

Primary efficacy endpoint

- HbA_{1c} after 36 weeks of treatment

Secondary efficacy endpoints:

- HbA_{1c} at Week 12
- Subjects reaching HbA_{1c} < 7.0%
- Fasting plasma glucose
- Average prandial plasma glucose increment
- Subjects with postprandial plasma glucose above 8.0 mmol/L or 11.0 mmol/L
- Body weight, BMI and ratio of waist-hip circumference
- Insulin dose
- Number of bolus injections
- Insulin treatment satisfaction questionnaire (ITSQ)

Criteria for Evaluation – Safety

- Hypoglycaemic episodes
- Adverse events (AEs)
- Cardiovascular disease risk markers
- Laboratory safety variables within haematology, biochemistry, and lipids
- Physical examination, fundoscopy/fundusphotography, electrocardiogram (ECG) and vital signs

Statistical Methods

Demographics and baseline characteristics were summarised using descriptive statistics for the full analysis set (FAS) by regimen and strata.

Efficacy endpoints: the primary analysis aimed to show equivalence of the two regimens, basic and the advanced, with respect to **HbA_{1c} after 36 weeks of treatment**. A clinically meaningful margin for equivalence was defined at 0.4%. The analysis was performed using an ANCOVA model including regimen, region and previous OAD use as factors and baseline value as a covariate. A two-sided 95% confidence interval (CI) was constructed for the estimated

difference in means between the two regimens. If this CI was included within the interval from –0.4 to 0.4 for both the FAS and the PP, the two regimens were declared equivalent with respect to HbA_{1c}.
The primary analysis model was also used to analyse **HbA_{1c} after 12 weeks** of treatment and **FPG after 36 weeks.** The model was used with number of bolus injections added as a factor for analysis of **average prandial PG increments** after 36 weeks. In addition, the model was used with number of bolus injections and pretrial use of IDet added as factors to analyse **body weight, BMI, ratio of waist-hip circumference** and **ITSQ score. The number of subjects reaching HbA_{1c} <7.0%,** and **number of subjects with postprandial PG >8mmol/L and > 11.1mmol/L** was analysed at week 11, 24 and 36 using logistic regression including regimen, previous OAD use and baseline HbA_{1c}. The analysis was repeated with number of bolus injections included at Week 23 and Week 36. **Insulin dose** and **number of bolus injections** was summarised using descriptive statistics.

Safety endpoints: the number, percentage and rate of **hypoglycaemic episodes** occurring during the trial was summarised by regimen and classification. The **rate ratio of hypoglycaemic episodes** for the Advanced Basal Plus Regimen was estimated relative to the Basic Basal Plus regimen using a negative binomial regression model including regimen and previous OAD use, and natural logarithm of exposure time as offset.
Treatment emergent (serious) adverse events (TEAE/TESAE) were summarised by number of subjects experiencing a TEAE/TESAE, percentage of FAS, number of events, and event rate per subject year of exposure, presented by regimen and number of bolus injections. Severity and relationship to trial product were tabulated.
Cardiovascular disease risk markers, haematology, biochemistry and lipid measurements were presented by box plots for screening and/or baseline and end of trial, and by shift tables showing changes from baseline to end of trial. Descriptive statistics by visit was presented for physical examination and ECG at baseline and at end of trial, for fundoscopy/fundusphotography at screening, and for vital signs at screening, baseline, Week 12, 24 and at end of trial.

Demography of Trial Population

	Advanced		Basic		Total	
Number of subjects	146		150		296	
Age (years)						
N	146		150		296	
Mean (SD)	58.3	(8.29)	58.3	(8.54)	58.3	(8.4)
Age group						
18 - 65	117	(80.1%)	122	(81.3%)	239	(80.7%)
> 65	29	(19.9%)	28	(18.7%)	57	(19.3%)
Gender						
Female	70	(47.9%)	67	(44.7%)	137	(46.3%)
Male	76	(52.1%)	83	(55.3%)	159	(53.7%)
Race						
Asian	6	(4.1%)	6	(4%)	12	(4.1%)
Black Or African American	8	(5.5%)	9	(6%)	17	(5.7%)
Not Known *)	12	(8.2%)	13	(8.7%)	25	(8.4%)
White	120	(82.2%)	122	(81.3%)	242	(81.8%)
Ethnicity						
Hispanic Or Latino	26	(17.8%)	34	(22.7%)	60	(20.3%)
Not Hispanic Or Latino	108	(74%)	103	(68.7%)	211	(71.3%)
Not Known *)	12	(8.2%)	13	(8.7%)	25	(8.4%)

Baseline Body weight (kg)						
N	145		147		292	
Mean (SD)	88.8	(15.8)	88.0	(16.3)	88.4	(16)
Baseline BMI (kg/m^2)						
N	145		147		292	
Mean (SD)	31.26	(4.26)	31.38	(4.92)	31.32	(4.60)
Baseline HbA_{1c} (%)						
N	143		148		291	
Mean (SD)	8.89	(1.16)	8.67	(0.97)	8.78	(1.07)
Diabetes history (years)						
N	146		150		296	
Mean (SD)	11.82	(5.99)	12.68	(6.68)	12.25	(6.35)

SD: Standard deviation *) Race and ethnicity information is not collected in France

Efficacy Results

Primary Endpoint

- IAsp added step-wise (1-2-3) in an Advanced Basal Plus regimen (according to the largest prandial increment, and titrated based mainly on postmeal SMPG) was equivalent to IAsp added step-wise (1-2-3) in a Basic Basal Plus regimen (according to the largest meal, and titrated based mainly on premeal SMPG) as measured by HbA_{1c} after 36 weeks of treatment in subjects with type 2 diabetes treated with once daily IDet in combination with OAD(s).
- The mean observed HbA_{1c} after 36 weeks of treatment was 7.7% in the Advanced Basal Plus treatment group and 7.5% in the Basic Basal Plus treatment group (FAS)
- The mean (absolute) change in HbA_{1c} was -1.3% in the Advanced Basal Plus treatment group and -1.1% in the Basic Basal Plus treatment group (FAS)
- The mean estimated treatment difference in HbA_{1c} after 36 weeks of treatment (Advanced Basal Plus treatment – Basic Basal Plus treatment) was 0.06 %, with a 95% CI of [–0.17; 0.29]% for the FAS

Secondary Endpoints

- The mean observed HbA_{1c} after the first 12 weeks of treatment (IDet in combination with OAD(s) and one IAsp bolus injection) was 8.4% in the Advanced Basal Plus treatment group and 8.3 % in the Basic Basal Plus treatment group.
  - The mean estimated treatment difference (Advanced Basal Plus – Basic Basal Plus) was 0.14% with a 95% CI of [-0.03; 0.32]%
  - Between the Advanced Basal Plus and the Basic Basal Plus treatment groups, there were no difference in the number and percentage of subjects reaching $HbA_{1c} < 7\%$ after 12, 24 or 36 weeks of treatment. For both treatment groups together, the percentage of subjects reaching $HbA_{1c} < 7\%$ was approximately 5%, 18% and 29% after 12, 24 and 36 weeks of treatment, respectively.
- The mean observed FPG after 36 weeks of treatment was 7.4 mmol/L in the Advanced Basal Plus treatment group and 7.5 mmol/L in the Basic Basal Plus treatment group
  - The mean estimated treatment difference (Advanced Basal Plus – Basic Basal Plus) was -0.27 mmol/L with a 95% CI of [-0.99; 0.44] mmol/L.
- There was no difference in the average prandial PG increment after 36 weeks of treatment, between the Advanced Basal Plus and the Basic Basal Plus treatment groups. The mean estimated treatment difference (Advanced Basal Plus – Basic Basal Plus) was -0.07 mmol/L with a 95%CI of [-0.38; 0.25] mmol/L.
  - The mean (absolute) change in prandial PG increment from randomisation to end of treatment was -1.8 mmol/L in the Advanced Basal Plus treatment group and -2.0 mmol/L in the Basic Basal Plus treatment group
  - The mean estimated treatment difference (Advanced Basal Plus – Basic Basal Plus) in the average breakfast PG increment after 36 weeks of treatment was -0.94 mmol/L with a 95% CI of [–1.41;-0.47] mmol/L
  - The mean estimated treatment difference (Advanced Basal Plus – Basic Basal Plus) in the average lunch PG

increment after 36 weeks of treatment was 0.69 mmol/L with a 95% CI of [0.13; 1.25] mmol/L
  - The mean estimated treatment difference (Advanced Basal Plus – Basic Basal Plus) in the average dinner PG increment after 36 weeks of treatment was -0.10 mmol/L with a 95% CI of [–0.62; 0.42] mmol/L
- Between the Advanced Basal Plus and the Basic Basal Plus treatment groups, there were no differences in the number and percentage of subjects achieving a postprandial PG below 11 mmol/L or below 8 mmol/L after 12, 24 or 36 weeks of treatment (all meals together)
  - For both treatment groups, the proportion of subjects achieving a postprandial PG below 11 mmol/L or below 8 mmol/L increased during the course of the study
  - After the third treatment period, 90% of subjects in the Advanced Basal Plus treatment group and 91% of subjects in the Basic Basal Plus treatment group had achieved postprandial PG values below 11 mmol/L
  - After the third treatment period, 53% of subjects in the Advanced Basal Plus treatment group and 61% of subject in the Basic Basal Plus treatment group had achieved postprandial PG values below 8 mmol/L
- Between the Advanced Basal Plus and the Basic Basal Plus treatment groups, there was no clinically significant difference in body weight, BMI or waist-hip circumference ratio after 12, 24 or 36 weeks of treatment
  - The mean (absolute) change in body weight from randomisation to end of treatment was +2.0 kg in the Advanced Basal Plus treatment group and +2.7 kg in the Basic Basal Plus treatment group. After 36 weeks of treatment, the mean estimated treatment difference (Advanced Basal Plus – Basic Basal Plus) in body weight was -0.67 kg with a 95% CI of [-1.60, 0.27]kg.
  - The mean (absolute) change in BMI from randomisation to end of treatment was +0.7 kg/m^2 in the Advanced Basal Plus treatment group and +1.0 kg/m^2 in the Basic Basal Plus treatment group. After 36 weeks of treatment, the mean estimated treatment difference (Advanced Basal Plus – Basic Basal Plus) in BMI was -0.28 kg/m^2 with a 95% CI of [-0.61; 0.06] kg/m^2.
  - The mean (absolute) change in waist-hip circumference ratio was -0.02 in the Advanced Basal Plus treatment group and 0.0 in the Basic Basal Plus treatment group. After 36 weeks of treatment, the mean estimated treatment difference (Advanced Basal Plus – Basic Basal Plus) in waist-hip circumference ratio was 0.017 with a 95% CI of [0.006, 0.029]. This difference was statistically significant, but was not considered to be clinically relevant.
- After 12 and 36 weeks of treatment, there was no statistically significant difference in the insulin treatment satisfaction questionnaire (ITSQ) score between the Advanced Basal Plus and the Basic Basal Plus treatment groups

Safety Results

Insulin Doses

- The average IDet dose at the beginning of the run-in period was 0.41 U/kg, increasing to 0.57 U/kg at randomisation
- During the first 12-week treatment period, the average IDet doses were similar for the Advanced Basal Plus and the Basic Basal Plus treatment group, but during the second and third treatment periods, the IDet dose continued to increase in the Advanced Basal Plus treatment group and stabilised in the Basic Basal Plus treatment group
- After 36 weeks of treatment, the average IDet dose was 0.84 U/kg in the Advanced Basal Plus and 0.72 U/kg in the Basic Basal Plus treatment group
- The daily dose of IAsp increased continuously during the three treatment periods, starting at 0.05 U/kg at randomisation and increasing to 0.53 U/kg in both the Advanced Basal Plus and the Basic Basal Plus treatment group. The daily doses of IAsp were similar in the two treatment groups during all three treatment periods.

Adverse Events

- Approximately 61% of subjects in both treatment groups experienced AEs during the trial
  - In both treatment groups, approximately 50% of the subjects reported mild AEs, while approximately 30% of subjects reported moderate and approximately 3% reported severe AEs
- A total of 4 SAEs in 4 subjects were reported in the Advanced Basal Plus treatment group, and a total of 9 SAEs in 8 subjects were reported in the Basic Basal Plus treatment group
- A total of 5 AEs led to subject withdrawal, 1 in the Advanced Basal Plus treatment group (possible relation to trial product), and 4 in the Basic Basal Plus treatment group (unlikely relation to trial product)

- A total of 28 AEs were assessed as being probably or possibly related to IDet, and 24 AEs were assessed as being probably or possibly related to IAsp
  - Of these, 19 AEs were reported as being probably or possibly related to both IDet and IAsp at the same time
  - The majority of AEs with relation to trial insulin were application site disorders or wrong drug administration
- No clustering or specific pattern in the reported AEs was observed

Hypoglycaemia

- Approximately 75% of all subjects reported hypoglycaemic episodes during the trial
- A tendency towards a higher rate of nocturnal hypoglycaemic episodes was observed in the Basic treatment group compared to the Advanced Basal Plus treatment group
- Major hypoglycaemic episodes were reported by one subject in the Advanced Basal Plus treatment group (one event, caused by wrong drug administration) and by 2 subjects in the Basic Basal Plus treatment group (2 events each)

Other Safety Endpoints

- No clinically relevant differences between treatment groups were observed from screening (or baseline) to the end of the treatment in any of the laboratory parameters, including CVD risk markers
- There were no clinically relevant changes in vital signs, physical examination or ECG in either treatment group during the trial
- Application site disorders, the majority of mild severity, were reported by 6.4% of all screened and exposed subjects. No cases of lipodystrophy or potentially allergic reactions were reported

Conclusions

Stepwise addition of IAsp (1-2-3) in a Basic basal plus regimen (according to the largest meal, and titrated based mainly on premeal SMPG) or stepwise addition of IAsp (1 2 3) in an Advanced basal plus regimen (according to the meal with the largest prandial increment, and titrated based mainly on postmeal SMPG) for 36 weeks in subjects with type 2 diabetes treated with once-daily IDet in combination with OAD(s) resulted in the following conclusions:

- Glycaemic control, as measured by HbA_{1c} after 36 weeks of treatment, was improved to a similar extent in the Advanced Basal Plus and the Basic Basal Plus treatment groups
- There was no statistically significant differences in laboratory measured FPG between the two treatment groups after 12, 24 and 36 weeks of treatment
- Prandial plasma glucose increments were reduced after 12, 24 and 36 weeks of treatment, with no clinically relevant differences between the Advanced Basal Plus and the Basic Basal Plus treatment groups
- After 36 weeks of treatment, 90% of subjects in the advanced treatment group had a 2-hour postprandial plasma glucose <11 mmol/L, while 53% reached a 2-hour PPG < 8 mmol/L
- After 36 weeks of treatment 91% of subjects in the Basic Basal Plus treatment group had a 2-hour PPG <11 mmol/L, while 61% reached a 2-hour PPG < 8 mmol/L
- There was no statistically significant difference between the treatment groups in terms of the proportion of subjects reaching PPG levels below 8 or 11 mmol/L
- The mean body weight increased in both treatment group, with no statistically significant difference between the two treatments
- Safety data did not reveal any unexpected findings and no specific patterns or clustering of AEs were observed in any of the two treatment groups. The safety profile as reflected by vital signs, physical examination and clinical laboratory parameters did not show any clinically relevant differences from baseline to end of treatment, or between the two treatment groups.
- Application site disorders were reported by 6.1% of exposed subjects, no lipodystrophy or potentially allergic reactions were reported, and the collected antibody data did not give rise to any concerns
- In general, the rate of hypoglycaemic episodes was low, and there was no statistically significant differences in the overall rate of hypoglycaemic episodes between the Advanced Basal Plus and the Basic Basal Plus treatment groups
- A slightly higher rate of nocturnal hypoglycaemic episodes was observed in the Basic Basal Plus treatment group, approaching a statistically significant difference
- Treatment satisfaction scores indicated a similar degree of satisfaction with both treatments

The trial was conducted in accordance with the Declaration of Helsinki and ICH Good Clinical Practice (refer to

applicable edition).

The results presented reflect data available in the clinical database as of 14-Oct-2009.