2 Synopsis

Trial Registration ID-number	**EudraCT number**
NCT00331604	2005-005378-58

Title of Trial

Inhaled pre-prandial human insulin with the AERx® iDMS versus s.c. insulin aspart in type 2 diabetes: A 104-week, open-label, multicentre, randomised trial followed by 12-week re-randomised extension to investigate safety and efficacy.

Investigators

In total, 67 principal investigators participated in the trial. Signatory Investigator is Dr [redacted]

Trial Sites

The trial was conducted at 67 sites in 11 countries: Brazil, Denmark, France, Germany, Hong Kong, Israel, Italy, Singapore, Spain, Taiwan, and United Kingdom.

Publications

None

Trial Period	**Development Phase**
31 August 2006 to 5 May 2008	Phase 3a

Objectives

Primary Objective

- To compare the effect of pre-prandial inhaled human insulin administered with AERx to subcutaneous injections of pre-prandial insulin aspart (both in combination with insulin detemir) on glycaemic control (as measured by change in HbA_{1c} from baseline) in subjects with type 2 diabetes after 52 weeks treatment.

Secondary Objectives

- To compare the effect of pre-prandial inhaled human insulin administered with AERx to subcutaneous injections of pre-prandial insulin aspart (both in combination with insulin detemir) on glycaemic control (as measured by change in HbA_{1c}) in subjects with type 2 diabetes after 104 and 116 weeks treatment
- To assess and compare the effect on fasting plasma glucose
- To evaluate 8-point plasma glucose profiles
- To assess the percentage of subjects achieving HbA_{1c} ≤7.5%, ≤7.0%, and ≤6.5% after 52 and 104 weeks
- To assess the proportion of subjects achieving HbA_{1c} ≤7.0% without symptomatic hypoglycaemia confirmed by a plasma glucose value of <4.0 mmol/L (<72 mg/dL) or any single plasma glucose value of < 3.1 mmol/L (<56 mg/dL) in the last 12 weeks of treatment before the visit at 52, 104 and 116 weeks
- To assess the plasma glucose intra-subject variability performed before breakfast, lunch, dinner and bedtime during five days in the last week before the visit at 52 weeks
- To evaluate the lipid profile
- To evaluate body weight changes
- To evaluate basal/bolus insulin doses
- To assess and compare the incidence of hypoglycaemic episodes in the treatment groups (nocturnal (11 pm - 6 am) and over the entire day (24 hours))
- To assess and compare Pulmonary Function Test
- To evaluate biomarkers (urine microalbumin/creatinine ratio, hsCRP, PAI-1, fibrinogen and adiponectin)
- To assess and compare Patient Reported Outcomes
- To investigate reversibility of changes in insulin antibodies
- To investigate reversibility of changes in pulmonary function
- To assess the safety and tolerability

Due to the early termination of the trial not all objectives were assessed.

Methodology

- This trial was designed as a 104-week multi-centre, multinational, open-label, active-controlled, treat-to-target, parallel group trial followed by a 12-week re-randomisation extension. Subjects were randomised in a 1:1 fashion with respect to human soluble insulin administered by AERx and subcutaneous injected insulin aspart both in combination with basal insulin (insulin detemir) for treatment of type 2 diabetes. After 104 weeks of treatment, the subjects in the AERx treatment group were planned to be re-randomised in a 1:1 fashion to either continue the AERx treatment or switch to insulin aspart. The subjects who initially were randomised to insulin aspart should continue this treatment for an additional 12 weeks.
- The trial was planned to include a screening visit to assess the subject's eligibility and 12 visits to the clinic and at least 16 telephone contacts in the first 52 weeks. The subsequent 52 weeks were planned to include 7 visits to the clinic and at least 6 telephone contacts. The 12 weeks re-randomisation period was planned to contain 2 visits to the clinic.
- Safety and efficacy assessments were measured at regular intervals during the trial

On 14 January 2008 Novo Nordisk A/S announced the decision to terminate the development of the AERx® iDMS for delivery of inhaled soluble human insulin. As a consequence, the trial was discontinued. All subjects in the discontinued trial were switched to the treatment alternative recommended by their doctor. Novo Nordisk offered to fund anti-diabetic medication, strips for blood glucose measurements and medical supervision for the duration of the remaining trial period, if permitted by local law.

Apart from the inconvenience caused by the termination of the trials, the termination was considered to have no impact or implications for the safety of the enrolled subjects. Due to the termination of the development of AERx® iDMS for delivery of inhaled soluble human insulin and the premature discontinuation of this trial, this is an abridged report, in which the major efficacy and safety results of the trial are described.

Number of Subjects Planned and Analysed

It was planned to screen 710 subjects so that at least 546 were randomised. In total, 829 subjects were screened, of which 211 were screening failures, while 618 subjects were randomised of which 597 subjects were exposed to trial product. Due to the early termination of the trial no subjects completed the trial. The subject disposition is shown below:

	AERx + insulin detemir	insulin aspart + insulin detemir	Total
Screened subjects			829
Screening failures			211(25.45%)
Randomised Subjects	309(100.00%)	309(100.00%)	618(100.00%)
Randomised but not treated	15(4.85%)	6(1.94%)	21(3.40%)
Randomised and treated subjects	294(95.15%)	303(98.06%)	597(96.60%)
Withdrawn Subjects (before 14/1/2008)	86(27.83%)	53(17.15%)	139(22.49%)
- Adverse Event	16(5.18%)	6(1.94%)	22(3.56%)
- Non-Compliance with protocol	14(4.53%)	9(2.91%)	23(3.72%)
- Ineffective therapy	9(2.91%)	1(0.32%)	10(1.62%)
- Withdrawal Criteria	4(1.29%)	4(1.29%)	8(1.29%)
- Other	43(13.92%)	33(10.68%)	76(12.30%)
- Missing	0(0.0%)	0(0.0%)	0(0.0%)
Withdrawn subjects (after 14/1/2008)	223(72.17%)	256(82.85%)	479(77.51%)
Completed subjects	0(0.0%)	0(0.0%)	0(0.0%)

Diagnosis and Main Criteria for Inclusion

Male and female non-smoking subjects, aged ≥ 18 years, a BMI ≤ 40 kg/m^2, FEV_1 ≥ 70 % of predicted value, HbA_{1c} ≤ 11.0% (analysis from central laboratory) and with a diagnosis of type 2 diabetes according to clinical judgement. Current treatment with any regimen of insulin for ≥ 3 months (with or without a maximum of one oral antidiabetic drug. Subjects with pulmonary diseases (excluding asthma), a total daily insulin dosage of > 100 IU/day, a history of 2 or more severe hypoglycaemic episodes within the last year prior to trial, or currently treated with systemic steroids were excluded from this trial.

Test Product, Dose and Mode of Administration, Batch Number

Human insulin inhalation solution, for inhalation, was administered via the AERx® iDMS (P3 device) using insulin strips (2.6 mg per insulin strip (50 µl, 10U per insulin strip). Batch numbers by subject are provided in Appendix 16.1.6. Individualised insulin doses were administered by inhalation immediately (within 5 minutes) before main meals. Insulin doses from 2 to 10 AERx units could be administered from one AERx insulin strip. One AERx unit was considered comparable to one s.c. unit. Starting dose was decided based on the subject's previous insulin regimen and according to local practice. Insulin doses were adjusted according an insulin dosing guideline (Appendix C of the Protocol, Appendix 16.1.1).

Duration of Treatment

The planned duration of treatment was 116 weeks. However, due to the decision to discontinue the development of the AERx® iDMS for delivery of inhaled soluble human insulin, the mean number of treatment days was 299 (2-521) days with AERx-detemir and 330 (7-560) days with IAsp-detemir. No subjects were exposed for more than 80 weeks.

Reference Therapy, Dose and Mode of Administration, Batch Number

- Insulin aspart, 3 mL FlexPen®, 100 U/mL
- Insulin detemir, 3 mL FlexPen®, 100 U/mL

Insulin aspart and insulin detemir were administered subcutaneously using the FlexPen® and NovoFine® 30G 8 mm needles. Insulin aspart was used as comparative treatment as well as escape therapy for subjects in the AERx-detemir treatment group if administration of inhaled human insulin using the AERx® iDMS was not possible. Insulin doses were adjusted according an insulin dosing guideline (Appendix C of the Protocol, Appendix 16.1.1).

Criteria for Evaluation – Efficacy

Primary efficacy endpoints

- HbA_{1c} change from baseline after 52 weeks of treatment

Secondary efficacy endpoints

- HbA_{1c} change from baseline after 104 and 116 weeks
- Fasting plasma glucose after the visits at 52, 104 and 116 weeks
- 8-point plasma glucose profile (pre- and post meals, bedtime, 3am) performed during the last week prior to Visits 2, 9, 11, 13, 18 and 20
- The proportion of subjects achieving a HbA_{1c} ≤ 7.5%, ≤ 7.0%, and ≤ 6.5% after the visit at 52 and 104 weeks
- The proportion of subjects achieving a HbA_{1c} ≤ 7.0% without symptomatic hypoglycaemia confirmed by a plasma glucose value of < 4.0 mmol/L (< 72 mg/dL) or any single plasma glucose value of < 3.1 mmol/L (< 56mg/dL) in the last 12 weeks of treatment before the visits at 52, 104 and 116 weeks
- The proportion of subjects achieving HbA_{1c} ≤ 7.0 % without any episodes of major hypoglycaemia during the last month of treatment before the visits at 52 and 104 weeks
- Plasma glucose measurements for variability performed before breakfast, lunch, dinner and bedtime during five days in the last week before the visit at 52 weeks
- Basal and bolus insulin doses at the visits at 52 and 104 weeks

Due to the early termination of the trial the only secondary efficacy endpoint analysed was fasting plasma glucose. Further, the analyses of HbA_{1c} and fasting plasma glucose were made on the change from baseline to the last available observation in the treatment period instead of the change from baseline to 52 weeks.

Criteria for Evaluation – Safety

Safety endpoints

- Change in laboratory assessments (haemoglobin, biochemistry, lipids, insulin antibodies) baseline to the visits at

52 and 104 weeks
- Incidence of hypoglycaemic episodes (minor, major, symptomatic) analysed from 12 weeks treatment. Incidence of nocturnal hypoglycaemic episodes (11 pm – 6 am) and over the entire day (24 hours) analysed from 12 weeks treatment
- Change in Pulmonary Function Test (FEV_1, FVC, FRC, RV, TLC, and $D_{L,CO}$) after 52, 104 and 116 weeks of treatment as percent of predicted value
- Change in body weight during treatment
- Assessment of reversibility of insulin antibodies
- Assessment of reversibility of pulmonary function
- Change in X-ray from baseline to Visit 13 and to Visit 20
- Change in High Resolution CT Scan from baseline to Visit 20
- Change in other parameters from baseline to End-of-Trial including ECG, fundoscopy/fundosphotography, vital signs, physical examination
- Correlation of pulmonary safety with passive smoking exposure
- Frequency and severity of adverse events

Other endpoints
- Patient Reported Outcomes at Visit 2, 9, 13, 17 and 20
- Number and type of AERx® iDMS complaints
- AERx device performance
- Assessments of biomarkers (urine microalbumin/creatinine ratio, hsCRP, PAI-1, fibrinogen; adiponectin;) at the visits at 52 and 104 weeks

Due to the discontinuation of the trial not all analyses or assessments were made.

Statistical Methods

All efficacy endpoints were analysed for the Full Analysis Set. All tests were made using two-sided alternative hypothesis and a significance level of 5%. Two-sided 95% confidence intervals were presented for treatment comparisons. Standard descriptive statistics (mean, standard deviation, median, min and max) were presented for all endpoints by visit and for the last observed value. For most endpoints the main analyses were based on changes from baseline to the last available observation in the treatment period. The baseline was defined as the last available value before randomisation. For the primary endpoint, the change in HbA_{1c} from baseline to the end of the treatment period was compared between treatments using an analysis of variance model with treatment and country as fixed factors and with baseline HbA_{1c} as a covariate. The mean changes were estimated for each treatment and the treatment difference was estimated and described with 95% confidence interval and the p-value for the hypothesis of no difference between treatments.

Demography of Trial Population

The trial population consisted of 260 female and 337 male subjects, aged from 25 to 79 years; 132 (22%) subjects were ≥65 years. About 83% of all subjects were White. All subjects had type 2 diabetes. Mean duration of diabetes was approximately 14 years, mean BMI 30.33 kg/m^2, and mean HbA_{1c} and FPG_{Lab} were 8.33% and 9.43 mmol/L, respectively. Mean total cholesterol was 4.59 mmol/L and mean triglycerides 1.65 mmol/L.

Efficacy Results

Due to the early termination of the trial, only the primary efficacy endpoint (change in HbA_{1c} from baseline after 52 weeks of treatment) and the secondary efficacy endpoint (change in FPG_{Lab} from baseline after 52 weeks of treatment) were analysed. However, as a consequence of the early termination of the trial, the evaluation was made on the change from baseline to the last available observation in the treatment period instead of the change from baseline to 52 weeks.

- There was a greater reduction in HbA_{1c} with IAsp-detemir (-0.80 percentage points) compared to AERx-detemir (-0.42 percentage points). This difference in HbA1c reduction was found to be statistically significant (0.39 percentage points, 95% C.I.: [0.22; 0.56], $p<0.0001$). However, the result should be interpreted with caution due to the early termination of the trial and consequential high number of withdrawn subjects and consequential unequal length of the individual treatment periods.
- No marked difference in reduction in FPG_{Lab} between AERx-detemir (-0.89 mmol/L) and IAsp-detemir (-0.90 mmol/L) was seen. The difference in FPG_{Lab} was not statistically significant (0.01 mmol/L, 95% C.I.: [-0.48;

050], p=0.9682). However, the result should be interpreted with caution due to the early termination of the trial and consequential high number of withdrawn subjects and consequential unequal length of the individual treatment periods.

Safety Results

With 597 subjects treated for a mean duration of 315 days (range 2 to 560 days) before the trial was terminated, the following summary of events was found.

Safety Endpoints

- The overall proportion of subjects with AEs was comparable between the two treatments groups; 85.7% of the subjects with AERx-detemir and 85.5% of the subjects with IAsp-detemir reported AEs. The majority of AEs in both treatment groups were considered non-serious and unlikely related to trial products and the majority of the AEs were classified as mild or moderate in severity.
- One treatment emergent fatal case was reported in the AERx-detemir group (pneumonia). In addition, 1 non-treatment emergent fatal case was reported in each treatment group; abdominal neoplasm with AERx-detemir and pulmonary oedema with IAsp-detemir. The non-treatment emergent cases occurred after the subjects were withdrawn from the trial. Further, 1 non-treatment emergent case occurred in the screening period before the subject was exposed to trial product. The treatment emergent case was judged unlikely related to trial product by the investigator whereas Novo Nordisk judged the relationship as possible as it could not be excluded that the AE might have been related to the route of administration of the AERx solution.
- In all 101 subjects reported a treatment emergent SAE; 44 (15.0%) subjects with AERx-detemir and 57 (18.8%) subjects with IAsp-detemir. In both treatment groups the majority of SAEs were considered either moderate or severe in severity. No pronounced differences in reported SAEs, frequency and severity were seen between the two treatment groups.
- Eight subjects had an SAE in which the relationship to the AERx insulin device could not be ruled out as the cause of the SAE. In three of the eight cases, the device was analysed and found normal. By mistake five of the devices were not returned for analysis and storage.
- The overall distribution of AEs with a probable and possible relation to trial products was twice as high with AERx-detemir as with IAsp-detemir; 103 (35%) subjects with AERx-detemir had 225 probably/possibly related AEs and 47 (16%) with IAsp-detemir had 87 probably/possibly related AEs. The higher frequency of probably/possibly related AEs with AERx-detemir is mainly seen in the SOCs “Respiratory, thoracic and mediastinal disorders”, “Investigations” and "Infections and infestations" where 17%, 10% and 7% of subjects with AERx-detemir had probably/possibly related AEs in these three SOCs compared to 0%, 2% and <1% of subjects in the IAsp-detemir group. The AEs causing the higher frequency related to PFTs and cough which could be related to the pulmonary route of insulin administration.
- In all 19 subjects withdrew from the trial due to a treatment emergent AE; 13 subjects in the AERx-detemir group and 6 subjects in the IAsp-detemir group. Seven subjects in the AERx-detemir group had either a respiratory or PFT related AE that led to withdrawal. No subjects in the IAsp-detemir group withdrew due to a respiratory or PFT related AE.
  - For one subject the AE was PFT related ($D_{L,CO}$ decrease). The AE was serious and considered possibly related to trial product.
  - For six subjects the AEs were respiratory related: dyspnoea, allergic respiratory disease, chronic obstructive pulmonary decease, cough, pharyngolaryngeal pain, throat irritation, dysphonia, rhinorrhoea and productive cough. All the respiratory related AEs were non-serious and considered probable/possible related to trial product, except for chronic obstructive pulmonary decease that was considered unlikely related.
- A slightly higher number of subjects in the IAsp-detemir group compared with the AERx-detemir group reported a hypoglycaemic episode. In the AERx-detemir group 28 hypoglycaemic episodes reported by 17 subjects (6%) were characterised as major, 2210 episodes reported by 186 subjects (63%) were minor and 656 episodes reported by 133 subjects (45%) were symptoms only. In the IAsp-detemir group 41 episodes were characterised as major by 28 subjects (9%), 2505 episodes reported by 228 subjects (75%) were minor and 1151 episodes reported by 169 subjects (56%) were symptoms only. Nocturnal hypoglycaemic episodes were reported by 46% of subjects with AERx-detemir and 52% with IAsp-detemir. In both treatment groups, 7 subjects (2%) had a nocturnal hypoglycaemic episode characterised as major.

- Five hypoglycaemic episodes considered probably or possibly related to trial product were reported by 5 subjects (2%) with AERx-detemir compared with 13 episodes reported by 9 subjects (3%) with IAsp-detemir. For 2 subjects with AERx-detemir the hypoglycaemic episodes led to withdrawal; both episodes were considered probably related to trial product. No subjects with IAsp-detemir had a hypoglycaemic episode that led to withdrawal.
- There were no pronounced changes from baseline to End of Trial in ECG, funduscopy, vital signs or physical examination in either treatment group or between treatment groups.
- An average increase in body weight was seen in both treatment groups. For subjects with AERx-detemir the mean increase was 1.3 kg and for subjects with IAsp-detemir the mean increase was 3.0 kg. For 2 subjects with AERx-detemir and 3 subjects with IAsp-detemir the increase in weight was recorded as an AE and for one subject with IAsp-detemir the AE led to withdrawal. All the AEs were considered mild or moderate in severity, non-serious and with a probable/possible relation to treatment.
- There were no marked changes from baseline to End of Trial in laboratory assessments (haemoglobin, biochemistry and lipid) in either treatment group or differences between treatment groups. In all 27 subjects had a change in laboratory assessment reported as an AE; 13 subjects with AERx-detemir and 14 subjects with IAsp-detemir. None of the AEs were considered related to treatments and all AEs were non-serious, except for one AE in the AERx-group (anaemia).
- An increase in insulin antibody level was seen at End of Trial in the AERx-detemir group; the increase predominantly related to an increase in IgG antibodies. This has also been seen on other AERx trials.
- The mean changes from baseline to End of Trial in PFTs showed no marked differences for either AERx-detemir or IAsp-detemir and analyses of all the PFTs (% of predicted normal value) did not show any statistically significant differences between AERx-detemir and IAsp-detemir. The proportion of subjects with changes above 15% in PFTs showed no pronounced differences between the treatment groups.
- For the majority of subjects in both treatment groups the findings in chest X-ray were stable from baseline to End of Trial and the majority of findings was cardiomegaly, linear opacity or related to "other" (diskarthrosis, hyperostosis and syndesmophytes). In all 6 subjects had either a new finding or a worsened finding in chest X-ray at End of Trial; 2 subjects with AERx-detemir (cardiomegaly and linear opacity) and 4 subjects with IAsp-detemir (cardiomegaly, micronodules and irregular opacity).
- In all, 116 subjects with AERx-detemir and 120 subjects with IAsp-detemir had an HRCT scan. For one subject in each treatment group pulmonary fibrosis was seen both at baseline and End of Treatment. In addition, one subject in the AERx-detemir group had pulmonary fibrosis at baseline where the HRCT scan was missing (not done at the same anatomical level) at End of Treatment.

Other Endpoints

- In all 50 AERx insulin devices were visually inspected and 10 devices were tested for Mouth Piece Temperature and Automated Piston Position Accuracy. No critical or dose accuracy related observations were recorded and the AERx insulin devices satisfied visual inspection, Mouth Piece Temperature and Automated Piston Position Accuracy acceptance criteria for End of Trial testing.
- In all 139 subjects had 394 AERx complaints: 254 (64%) related to the device, 109 (28%) to the insulin strips, 30 (8%) to the battery and one "Other".

Conclusions

Treatment with AERx or insulin aspart in combination with insulin detemir in subjects with type 2 diabetes resulted in the following conclusions in this discontinued trial:

- Due to the early termination of the trial and consequential high number of withdrawn subjects and consequential unequal length of the individual treatment periods the efficacy results from comparing AERx-detemir to IAsp-detemir treatment should be interpreted with caution. In this trial, treatment with IAsp-detemir showed a greater reduction in HbA_{1c} than AERx-detemir treatment whereas no difference was seen in FPG_{Lab} between the two treatment groups.
- Overall, the pulmonary safety, as determined by PFTs, chest X-rays, HRCT scan (subgroup) and respiratory related AEs, did not give rise to any safety concerns.
  - Analyses of PFTs (% of predicted normal value) showed no statistically significant differences between the AERx-detemir group and the IAsp-detemir group.

- Findings in chest X-ray did not show any marked differences between AERx-detemir and IAsp-detemir; in both treatment groups the majority of findings were stable from baseline to End of Trial and the majority of these findings were non-pulmonary or listed as "other".
- HRCT scan did not show any differences between AERx-detemir and IAsp-detemir.
- There were more AEs associated with the respiratory system that were judged related to AERx (88) than to the comparator trial products (0). The same was seen for AEs associated with decreased PFTs judged related to AERx (33) than to the comparator trial products (2). This was expected due to the pulmonary route of insulin administration of AERx.

- Overall, there was no statistical difference between the two treatment groups in hypoglycaemic episodes; however a slightly higher number of subjects in the IAsp-detemir group reported a hypoglycaemic episode.
- The safety profile as reflected by adverse events, standard laboratory parameters, vital signs and changes in ECG, fundoscopy/fundosphotography, and biomarkers did not show any differences between the two groups.
- AERx insulin device performance showed no critical or dose accuracy related observations.
- No safety concerns were raised by this trial.

The trial was conducted in accordance with the Declaration of Helsinki (2004) and ICH Good Clinical Practice.