2 Synopsis

Trial Registration ID-number	**EudraCT number**
NCT00469586	2006-004623-12

Title of Trial

Inhaled human insulin with the AERx® iDMS as prandial monotherapy compared to combination therapy with metformin and glimepiride in type 2 diabetes: an eighteen-week, open-label, multicentre, randomised, parallel group trial with an eight-week extension to investigate efficacy and safety

Investigators

In total, 58 principal investigators participated in the trial. Signatory Investigator is Dr. [redacted]

Trial Sites

42 sites in 11 countries: Argentina, Austria, Belgium, Bulgaria, Canada, France, India, Israel, Mexico, Poland and Turkey

Publications

Not applicable

Trial Period	**Development Phase**
26 April 2007 to 4 March 2008	Phase 3a

Objectives

Primary Objective:

- To compare the effect of periprandial inhaled insulin administered with AERx with the effect of glimepiride and metformin combination therapy, on glycaemic control after 18 weeks of treatment (as measured by change in HbA_{1c} from baseline) in previously inadequately controlled subjects with type 2 diabetes.

Key Secondary Objective:

- To compare the effect of preprandial inhaled insulin administered with AERx with the effect of post-prandial inhaled insulin administered with AERx on glycaemic control after 18 weeks of treatment (as measured by change in HbA_{1c} from baseline) in previously inadequately controlled subjects with type 2 diabetes.

Secondary Objectives:

- To assess and compare the effect on fasting plasma glucose measured as change in fasting plasma glucose from baseline
- To assess and compare the effect on 8-point plasma glucose profiles
- To assess and compare the percentage of subjects achieving a $HbA_{1c} \leq 7.5\%$, $\leq 7.0\%$, and $\leq 6.5\%$ after 18 weeks of treatment
- To assess and compare HbA_{1c} after 26 weeks of treatment
- To assess and compare fasting lipid profile
- To assess and compare the effect on body weight
- To assess and compare the incidence of hypoglycaemic episodes
- To assess and compare health economic parameters and patient reported outcomes (PRO)
- To assess and compare pulmonary function tests (PFT)
- To assess the safety and tolerability of AERx.

Other Objective:

- To evaluate the number and type of AERx complaints.

Methodology

This trial was designed as an 18-week open-label, multicentre, randomised, active-controlled, parallel group trial with an eight-week extension. A total of 8 visits were planned during the 26 weeks: Visit 1 (screening at – 2wks), Visit 2 (baseline at 0 wks) and Visits 3-8 (at 4, 6, 8, 12, 18 and 26 wks). Subjects with type 2 diabetes were randomised in a 2:1 manner to either human soluble insulin administered with AERx® iDMS (AERx) or to glimepiride plus metformin combination therapy (oral anti-diabetic combination therapy (OAD)). Subjects randomised to insulin administered by inhalation were re-randomised in a 1:1 manner to inhale insulin either 5-10

minutes before a meal or within 20 minutes after starting the meal throughout the trial period. Titration of the AERx dose was possible throughout participation. OAD was titrated to a daily maintenance dose of 2,000 mg metformin and 4 mg glimepiride; these daily doses could be reduced to minimum 1,500 mg metformin and 2 mg glimepiride in case of unacceptable side effects.

On 14 January 2008 Novo Nordisk A/S announced the decision to terminate the development of the AERx® iDMS system for delivery of inhaled soluble human insulin. As a consequence, the trial was discontinued. All subjects in the discontinued trial were switched to the alternative treatment recommended by their doctor. Novo Nordisk offered to fund anti-diabetic medication, strips for blood glucose (BG) 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 all safety results of the trial are described.

Number of Subjects Planned and Analysed

The planned number of randomised subjects was 345. At the time of the early termination of the trial announced by Novo Nordisk on 14 January 2008, only 165 subjects had been randomised and treated (AERx: 108; OAD: 57) and only 70 subjects had completed the trial. The 165 treated subjects constitute the full analysis set as well as the safety analysis set. Please see the subject disposition table below for numbers screened, screening failures, run-in failures, randomised and withdrawn before and after January 14 2008.

	AERx	Metformin + Glimepiride	Total
Screened subjects			369
Screening Failures			144 (39.0%)
Run-In Failures			55 (14.9%)
Randomised Subjects	113 (100.0%)	57 (100.0%)	170 (100.0%)
Randomised but not treated	5 (4.4%)	0 (0.0%)	5 (2.9%)
Randomised and treated subjects	108 (95.6%)	57 (100.0%)	165 (97.1%)
Withdrawn Subjects (before 14/1/2008)	15 (13.3%)	7 (12.3%)	22 (12.9%)
- Adverse Event	2 (1.8%)	1 (1.8%)	3 (1.8%)
- Non-Compiliance with protocol	1 (0.9%)	2 (3.5%)	3 (1.8%)
- Ineffective therapy	0 (0.0%)	1 (1.8%)	1 (0.6%)
- Other	9 (8.0%)	3 (5.3%)	12 (7.1%)
- Withdrawal Criteria	3 (2.7%)	0 (0.0%)	3 (1.8%)
Withdrawn subjects (after 14/1/2008)	47 (41.6%)	26 (45.6%)	73 (42.9%)
Completed subjects	46 (40.7%)	24 (42.1%)	70 (41.2%)

Diagnosis and Main Criteria for Inclusion

Diagnosis: Type 2 diabetes; Main criteria for inclusion: (at screening): Informed consent; Current treatment with an insulin secretagogue (sulfonylurea) or metformin at the maximum therapeutic dose for at least 3 months before screening; 8.0% ≤ glycosylated haemoglobin (HbA_{1C}) ≤ 11.0%; Age ≥ 18 years; Body mass index (BMI) ≤ 40.0 kg/m^2; Forced expiratory volume (FEV_1) ≥ 70% of predicted value; Able and willing to perform self-monitoring of plasma glucose; Able and willing to receive treatment with glimepiride and metformin or change to inhaled human insulin with the AERx insulin device; (at randomisation): mean fasting plasma glucose (FPG) ≥ 135 mg/dL (≥ 7.5 mmol/L) and ≤ 240 mg/dL (≤ 13.3 mmol/L). A number of exclusion criteria applied.

Test Product, Dose and Mode of Administration, Batch Number

Insulin human inhalation solution, 2.6 mg per insulin strip (50 µL, 10U per insulin strip) administered using the AERx insulin device. Dose: variable according to the AERx iDMS Insulin Dosing Guideline.

For batch numbers of trial products and devices, please refer to Section 16.1.6.

Duration of Treatment

Planned duration in protocol of 23 November 2006: 18 weeks. Planned duration in global substantial Protocol amendment of 14 August 2007 and updated Protocol of 23 August 2007: 26 weeks. A total of 73 subjects were withdrawn before the planned 26 weeks of trial treatment due to early termination of the trial announced on 14 January 2008, whereas 22 subjects had withdrawn before 14 January 2008. A total of 70 subjects (41%) completed the trial.

Reference Therapy, Dose and Mode of Administration, Batch Number

Glimepiride 1 and 2 mg tablets – oral administration. Maximum dose: 4 mg/day

Metformin 500 mg tablets – oral administration. Maximum dose: 2,000 mg/day

For batch numbers of trial products, please refer to Section 16.1.6.

Criteria for Evaluation – Efficacy

HbA_{1c} change from baseline after 18 weeks of treatment (primary efficacy analysis) and HbA_{1c} change from baseline after 18 weeks of treatment (pre-prandial versus post-prandial inhaled insulin) (key secondary efficacy analysis). Due to early termination only one secondary efficacy endpoint was analysed: change in FPG from baseline after 18 weeks of treatment. Other planned efficacy analyses were not performed.

Criteria for Evaluation – Safety

Frequency and severity of treatment emergent adverse events (TEAEs); Incidence of hypoglycaemic episodes; Changes in the following from baseline to end-of-trial: Pulmonary function test (PFT) (FEV_1; FVC; FEV_1/FVC; FRC; RV; TLC; $D_{L,CO}$); Laboratory tests (haematology; biochemistry; insulin antibodies; fasting lipids; urinalysis); Chest X-rays; Vital signs; ECG; Physical examination; Fundoscopy / fundusphotography; Body weight

Statistical Methods

Due to early termination of the trial, focus was switched from efficacy to safety and therefore superiority / non-inferiority of the efficacy analyses were not considered. The change in HbA_{1c} from baseline to the end-of-treatment (Week 18) was compared between treatments using an analysis of variance model with treatment, pre-trial medication and country as fixed factors and with baseline HbA_{1c} as a covariate. From the analysis model, mean changes were estimated for each treatment. The treatment difference was estimated and described with 95% confidence interval and the p-value for the hypothesis of no difference between treatments. The key secondary and the secondary efficacy analyses were done as described for the primary efficacy analysis.

Demography of Trial Population

The trial population consisted of 92 male (56%) and 73 female (44%) subjects. Mean age was 54 years with a range from 27 to 78 years; 23 subjects (14%) were ≥ 65 years. The majority of the subjects (58%) were White. Mean BMI was 30 kg/m2 (range 20 to 40 kg/m2). Duration of diabetes ranged from 3 months to 31 years, mean FPG and mean HbA_{1c} were 10.3 mmol/L and 9.2%, respectively. Baseline characteristics were similar for the AERx and OAD groups.

Efficacy Results

Due to the early termination of the trial, many subjects were withdrawn and only 70 subjects completed the trial; the efficacy analyses should therefore be interpreted with caution. Efficacy analyses were performed on the end-of-trial data using the last observation carried forward.

- Mean HbA_{1c} values at the end-of-trial (Week 18) for AERx preprandial, AERx postprandial and OAD were 8.3%, 8.2% and 7.7%, respectively. The changes in HbA_{1c} from baseline were -1.00% for AERx preprandial, -1.19% for AERx postprandial and -1.62% for OAD. The differences between AERx preprandial and AERx postprandial vs. OAD were 0.62% (p=0.008) and 0.43% (p=0.075)
- No difference in HbA_{1c} was seen between AERx preprandial and AERx postprandial (p=0.421)
- Mean values for FPG at the end-of-trial (Week 18) for AERx preprandial, AERx postprandial and OAD were 9.0, 8.3 and 8.5 mmol/L, respectively. The change in FPG from baseline to end-of-trial was -1.69 mmol/L for AERx and -1.66 mmol/L for OAD (p=0.944).

Safety Results

The evaluation of safety includes all 165 subjects treated for a mean duration of 103.8 days (range 2 to 202 days); mean (median) length of exposure was comparable between treatment groups: 103.2 (123) days for AERx and 104.9

(125) days for metformin + glimepiride. A total of 12 subjects in the AERx group took insulin aspart as escape therapy.

Adverse Events

- A total of 83 subjects (50.3%) reported 200 TEAEs. The percentage of subjects with TEAEs was slightly higher in the subjects in the AERx group (52.8%) than in the subjects in the OAD group (45.6%), whereas the number of TEAEs by subject was slightly higher for OAD (75 in 26 subjects) than for AERx (125 in 57 subjects)
- Differences in the percentages of subjects with TEAEs were seen for the SOCs Investigations (AERx 18%; OAD 9%), Respiratory, thoracic and mediastinal disorders (AERx 12%; OAD 5%; the difference was caused by cough reported by 10 subjects in the AERx group and 1 subject in the OAD group) and Gastrointestinal disorders (AERx 5%; OAD 12%)
- The vast majority of TEAEs were mild (66%) or moderate (33%); only 2 severe TEAEs (1%) were recorded (AERx: hypersensitivity; OAD: myocardial infarction)
- Relationship probable or possible was reported for 31 TEAEs in 17 subjects in the AERx group (16%) and for 10 TEAEs in 4 subjects (7%) in the OAD group; nasopharyngitis (AERx: 6 events in 5 subjects), cough (AERx: 5 events in 5 subjects), nausea (OAD: 3 events in 3 subjects), carbon monoxide diffusing capacity decreased (AERx: 2 events in 2 subjects), pyrexia (AERx: 2 events in 2 subjects) and TLC decreased (AERx: 2 events in 2 subjects) were considered related in more than one case
- Respiratory-related events were seen in the SOCs Infections and infestations (AERx: 18 events; OAD: 11 events), Investigations (AERx: 23; OAD: 7) and Respiratory, thoracic and mediastinal (AERx: 14; OAD: 3). Of the 78 respiratory-related TEAEs (AERx: 55; OAD: 21), 67 events were mild and 11 events moderate; no severe respiratory-related TEAEs were reported. All subjects except 6 had recovered from the event at end-of-trial
- Of the 31 treatment-related TEAEs in the subjects in the AERx group, 20 were related to the respiratory tract system: nasopharyngitis (6), cough (5), carbon monoxide diffusing capacity decreased (2) and TLC decreased (2) were reported more than once. None of the 10 treatment-related TEAEs in subjects in the OAD group were considered related to the respiratory tract system
- A total of 7 TESAEs were reported: AERx: 3 in 3 subjects (3%) and OAD: 4 in 4 subjects (7%). Of these, 2 were considered related to trial treatment (AERx): PFT (moderate), TLC decreased (mild). One SAE, myocardial infarction in a subject that received OAD was severe. No deaths occurred
- Only 1 MESI (AERx: decline in FVC) was reported
- A total of 3 subjects withdrew due to TEAEs: 2 received AERx and 1 OAD
- A case of pregnancy with a subsequent non-treatment related spontaneous abortion occurred in a subject, who received AERx.

Clinical Laboratory Evaluation

- Total cholesterol, HDL, LDL and triglycerides increased slightly from baseline to end-of-trial; no differences were seen between the two treatment groups
- For haematology and biochemistry, no marked changes were seen from Visit 1 to end-of-trial; no marked differences were seen between AERx and OAD treatment
- There was a +15.75% increase in total insulin antibodies in the subjects in the AERx group compared to a decrease of -0.05% in the subjects in the OAD group. Exogenous insulin was not introduced in the subjects, who received OAD.

Vital Signs, Physical Findings and Other Observations related to Safety

- There was no difference in vital signs between treatment groups
- A total of 3 clinically significant changes in fundoscopy from baseline to end-of-trial were seen in subjects in the OAD group
- The ECG recordings showed no QTc interval > 500 msec at the end-of-trial and no clinically significant changes were seen from Visit 1 to end-of-trial in either treatment group
- No statistically significant differences in FEV_1; FVC; FEV_1/FVC; FRC; TLC; and $D_{L,CO}$ from baseline to end-of-trial were seen between treatment groups. For RV, a treatment difference was seen for the Linear trend (L/year) (all data): -0.08 L/year for AERx and 1.00 L/year for OAD (p=0.045); for technically accepted data the difference in RV was not significant
- At the comparative blind readings of chest X-rays, normal findings at both visits were seen for 19% and 26% of

the subjects in the AERx and OAD groups, respectively. At the end-of-trial, abnormal findings seen at Visit 1 were either stable (AERx: 51; OAD: 23), improved (AERx: 1; OAD: 0) or not assessable or missing (AERx: 33; OAD: 15) . The primary abnormal finding was vertebral arthrosis in the spine. No new findings and no worsenings were seen at the end-of-trial compared to Visit 1. Thus, the comparative blind readings indicate no difference between the 2 treatment groups

- A total of 31 subjects in the AERx group (29%) and 16 subjects in the OAD group (28%) had at least one hypoglycaemic episode. Of the 152 episodes, 2 episodes were major (AERx: 1; OAD: 1), 121 were minor (AERx: 59; OAD: 62) and 29 were "symptoms only" (AERx: 26; OAD: 3); thus more minor episodes tended to occur in the subjects in the OAD group and more "symptoms only" in subjects in the AERx group. A total of 17 nocturnal episodes occurred in 12 subjects in the AERx group (11%) and 3 in 3 subjects in the OAD group (5%). The overall rate of hypoglycaemic episodes per year was similar between treatment groups: 3.02 for AERx and 2.98 for OAD (p=0.9695)
- Body weight increased slightly more in the AERx (2.7 kg) than in the OAD group of subjects (1.6 kg)
- In all, 18 subjects in the AERx group had a total of 41 AERx device-related complaints. No SAEs were caused by device-related issues.

Conclusions

Due to the early termination of the trial, only 70 of the planned 345 patients completed the trial. The results should therefore be interpreted with caution. In this trial AERx was found less effective than metformin + glimepiride as measured by HbA1c in subjects with type 2 diabetes previously treated with oral anti-diabetic drugs; no difference was seen between AERx preprandial and AERx postprandial. The changes in fasting plasma glucose were similar between trial treatments.

Overall there were no clinically relevant changes in pulmonary function and chest X-rays and no deaths or lung cancers were reported. Although the TEAE profiles of the 2 trial treatments in general were similar, more respiratory events were reported for AERx. The higher frequency of respiratory related events and decreased PFTs judged related to trial product in the AERx arm is expected due to the pulmonary route of insulin administration of AERx. The rate of all hypoglycaemic events per patient year was similar between treatment groups. Increased insulin antibody concentrations were seen only in the AERx group as could be expected when comparing insulin treatment to oral anti-diabetic treatment. In conclusion, no safety issues related to AERx treatment were found in this trial.

The trial was conducted in accordance with the Declaration of Helsinki (Tokyo 2004) and ICH Good Clinical Practice (1 May 1996).