2 Synopsis

Trial Registration ID-number	**EudraCT number**
NCT00348712	2006-000796-15

Title of Trial

Inhaled pre-prandial human insulin with the AERx® iDMS plus metformin versus rosiglitazone plus metformin in type 2 diabetes: a 26-week, open-label, multicentre, randomised, parallel trial to investigate efficacy and safety

Investigators

In total, 51 principal investigators participated in the trial. Signatory Investigator is Dr. [redacted]

Trial Sites

The trial was conducted at 55 sites in nine countries: Austria, Finland, France, Germany, Ireland, the Netherlands, Spain, Switzerland, and United Kingdom.

Publications

None

Trial Period	**Development Phase**
30 October 2006 to 5 March 2008	Phase 3a

Objectives

Primary Objective

- To compare the effect of pre-prandial inhaled human insulin administered with AERx to rosiglitazone, both in combination with metformin, on glycaemic control (as measured by change in HbA_{1c} from baseline) in subjects with type 2 diabetes, after 26 weeks of treatment.

Secondary Objectives

- To assess and compare the effect on fasting plasma glucose
- To evaluate 8-point plasma glucose profiles
- To assess the percentage of subjects achieving $HbA_{1c} \leq 7.5\%$, $\leq 7.0\%$, and $\leq 6.5\%$ after 26 weeks
- To evaluate the lipid profile
- To evaluate body weight changes
- To assess the incidence of hypoglycaemic episodes
- To assess and compare pulmonary function tests
- To assess and compare patient reported outcomes
- To assess and compare health economics parameters
- To assess the safety and tolerability

Other objectives

- Evaluate the number and type of AERx® iDMS complaints

Methodology

- The trial was designed as a 26-week, multi-centre, multinational, open-label, randomised, active-controlled, treat-to-target, and parallel group trial. Following a run-in period of 6 weeks on metformin, the subjects were randomised in a 2:1 fashion with respect to human soluble insulin administered by AERx and rosiglitazone both in combination with metformin for treatment of type 2 diabetes.
- The trial was planned to include 10 visits; 1 screening visit to assess the subject's eligibility, 1 run-in visit, 1 randomisation visit after the 6-week run-in period and 7 visits during the treatment period, and at least 13 telephone contacts during the 26 weeks of treatment
- 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 all safety results of the trial are described.

Number of Subjects Planned and Analysed

It was planned to randomise 345 subjects. However, due to discontinuation of the trial only 298 subjects were randomised. In total, 568 subjects were screened, of which 260 were screening failures, while 298 subjects were randomised and 290 of these subjects were exposed to trial product.

When the trial was discontinued, 180 subjects had completed the trial (123 with AERx- metformin and 57 with rosiglitazone-metformin) and 66 subjects were ongoing in the trial (46 to AERx-metformin and 20 to rosiglitazone-metformin). The subject disposition is shown below:

	AERx + Metformin	Rosiglitazone + Metformin	Total
Screened subjects			568
Screening Failures			260 (45.8%)
Run-In Failures			10 (1.8%)
Randomised Subjects	200 (100.0%)	98 (100.0%)	298 (100.0%)
Randomised but not treated	7 (3.5%)	1 (1.0%)	8 (2.7%)
Randomised and treated subjects	193 (96.5%)	97 (99.0%)	290 (97.3%)
Withdrawn Subjects (before 14 Jan 08)	31 (15.5%)	21 (21.4%)	52 (17.4%)
- Adverse Event	4 (2.0%)	2 (2.0%)	6 (2.0%)
- Non-Compliance with protocol	5 (2.5%)	0 (0.0%)	5 (1.7%)
- Ineffective therapy	2 (1.0%)	16 (16.3%)	18 (6.0%)
- Other	19 (9.5%)	2 (2.0%)	21 (7.0%)
- Withdrawal Criteria	1 (0.5%)	1 (1.0%)	2 (0.7%)
Withdrawn subjects (after 14 Jan 08)	46 (23.0%)	20 (20.4%)	66 (22.1%)
Completed subjects	123 (61.5%)	57 (58.2%)	180 (60.4%)

Diagnosis and Main Criteria for Inclusion

Male and female subjects, aged ≥ 18 years, a BMI ≤ 40 kg/m^2, FEV_1 ≥ 70 % of predicted value and with a diagnosis of type 2 diabetes according to the following criteria:

- Current treatment with one or two oral antidiabetic drug(s) (insulin secretagogues, insulin sensitizers, metformin, glitazones, alpha-glucosidase inhibitors) for ≥ 2 months. Subjects on monotherapy should be at least on half maximum dose for ≥ 2 months
- 7.5% ≤ HbA_{1c} ≤ 11.0% in subjects on oral antidiabetic drug monotherapy, and 7.0% ≤ HbA_{1c} ≤ 10.0% in subjects on oral antidiabetic drug combination therapy (analysis from central laboratory)

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).

Duration of Treatment

The planned duration of treatment was 26 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 143 days with AERx-metformin and 135 days with rosiglitazone-metformin. In all 180 subjects completed the trial; 123 with AERx- metformin and 57 with rosiglitazone-metformin.

Reference Therapy, Dose and Mode of Administration, Batch Number

- Rosiglitazone 4 mg tablets. Batch numbers by subject are provided in Appendix 16.1.6. Rosiglitazone was administered orally. After 6 weeks dosage of rosiglitazone the dose was increased from 4 mg once daily to 4 mg twice daily. The dose of rosiglitazone was reduced from 4 mg twice daily to 4 mg once daily in the event of unacceptable hypoglycaemia or other adverse events at the discretion of the Investigator. Likewise, the rosiglitazone dose was increased to 4 mg twice daily again.
- Metfomin 500 mg tablets. Batch numbers by subject are provided in Appendix 16.1.6. Subjects started on 500-1500 mg per day at the investigator's discretion. During the 6-week run-in period they were titrated with weekly increments of 500 mg to a final dose of 2000 mg per day. Subjects already treated with metformin at trial entry were titrated from their current dose. Subjects treated with 2000 mg metformin per day at trial entry remained at this dose during the run-in and treatment period. Subjects treated with > 2000 mg metformin per day at trial entry had the dose reduced to 2000 mg metformin per day and remained on this dose during the run-in and treatment period.
- Rapid-acting insulin aspart PenFill®, 100 U/mL, 3 mL cartridge was used as escape therapy in the AERx-metformin group if administration of inhaled human insulin using the AERx® iDMS was not possible.

Criteria for Evaluation – Efficacy

Primary efficacy endpoints

- HbA_{1c} change from baseline after 26 weeks of treatment

Secondary efficacy endpoints

- Fasting plasma glucose after 26 weeks of treatment
- 8-point plasma glucose profile (pre- and post meals, bedtime, 3 am).
- The proportion of subjects achieving a $HbA_{1c} \leq 7.5\%$, $\leq 7.0\%$, and $\leq 6.5\%$ after 26 weeks of treatment
- Change in the lipid profile after 26 weeks of treatment

Due to discontinuation of the trial analyses were only done on HbA_{1c} and fasting plasma glucose.

Criteria for Evaluation – Safety

Safety endpoints

- Change in laboratory assessments (haemoglobin, biochemistry, insulin antibodies) from Visit 1 to Visit 10
- Change in body weight during treatment
- Incidence of hypoglycaemic episodes (major, minor, symptoms only) from 12-26 weeks of treatment. Incidence of nocturnal (11 pm – 6 am) episodes and overall episodes (24 hours) from 12-26 weeks of treatment
- Change in pulmonary function tests (FEV_1, FVC, FRC, RV, TLC, and $D_{L,CO}$) after 26 weeks of treatment as percent of predicted value
- Change in chest X-ray from Visit 1 to Visit 10
- Change in other parameters from Visit 1 to Visit 10 including ECG, fundoscopy/fundusphotography, vital signs, physical examination
- Frequency and severity of adverse events

Other endpoints

- Patient reported outcomes
- Health economics parameters
- Number and type of AERx complaints
- AERx device performance

Due to the discontinuation of the trial no analyses or assessments of Patient Reported Outcomes, Health Economic Parameters and AERx device performance were made. Further, the incidence of hypoglycaemic episodes was analysed for the entire treatment period and not from 12-26 weeks of treatment.

Statistical Methods

All tests were made using two-sided alternative hypothesis and a significance level of 5%. Two-sided 95% confidence intervals were presented for pair wise treatment comparisons. 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 randomization. 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. From the analysis model the 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.

Demography of Trial Population

The trial population consisted of 92 male and 198 female subjects, aged from 33 to 80 years; 81 (28%) subjects were ≥ 65 years. About 97% of all subjects were White. All subjects had type 2 diabetes. Mean duration of diabetes was approximately 10 years (66 days to 47 years), mean BMI 30.62 kg/m^2, and mean HbA_{1c} and FPG_{Lab} were 8.64% and 11.09 mmol/L, respectively. Mean total cholesterol was 4.67 mmol/L and mean triglycerides 1.99 mmol/L. Baseline characteristics were similar between the two treatment groups.

Efficacy Results

Due to the early termination of the trial, only the primary efficacy endpoint (change in HbA_{1c} from baseline after 26 weeks of treatment) and the secondary efficacy endpoint (change in FPG_{Lab} from baseline after 26 weeks of treatment) were analysed.

- There was a greater reduction in HbA_{1c} with AERx-metformin (-1.39 percentage points) compared to rosiglitazone-metformin (-0.54 percentage points). This difference in HbA_{1c} reduction was found to be statistically significant (-0.86 percentage points, 95% C.I.: [-1.11; -0.61], $p<0.0001$). However, these results should be interpreted with caution due to the early termination of the trial and consequential high number of withdrawn subjects.
- There was a greater reduction in FPG with AERx-metformin (-2.55 mmol/L) compared to rosiglitazone-metformin (-1.78 mmol/L). This difference in FPG reduction was found to be statistically significant (-0.76 mmol/L, 95% C.I.: [-1.30; -0.23], p=0.0051). However, these results should be interpreted with caution due to the early termination of the trial and consequential high number of withdrawn subjects.

Safety Results

With 290 subjects treated for a mean duration of 104.4 days (range 2 to 203 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; 63.7% of the subjects with AERx-metformin and 54.6% of the subjects with rosiglitazone-metformin 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.
- Proportion of subjects with AEs with a possible/probable relation to trial products was comparable; 16% with AERx-metformin and 14% with rosiglitazone-metformin. No AEs with a possible/probable relation to trial products were reported more frequently than others, except for cough which was reported by 8 (4%) of subjects with AERx-metformin and no subjects with rosiglitazone-metformin. Cough could be related to the pulmonary route of insulin administration.
- In all 18 respiratory related AEs (events reported in the system organ classes: Infections and infestations, Investigations and Respiratory, thoracic and mediastinal disorders) with a possible/probable relation to trial product were reported in the AERx-metformin group. No respiratory related AEs with a possible/probable relation to trial product were reported in the rosiglitazone-metformin group. Respiratory related AEs may be expected in the AERx-metformin group since AERx is delivered via inhalation while rosiglitazone is taken orally.
- In all 12 subjects reported a SAE during the trial; 10 (5.2%) subjects in the AERx-metformin group had 11 events and 2 (2.1%) subjects in the rosiglitazone-metformin group had 2 events. Eight out of the 11 events with AERx-metformin were considered unlikely related and 3 possibly/probably related to trial product (hypoglycaemia, dyspnoea and interstitial lung disease). Both events with rosiglitazone-metformin were considered unlikely related to trial product. Two of the SAEs in the AERx-metformin group were respiratory related; interstitial lung disease

and dyspnoea, and both events led to withdrawal. No subjects in the rosiglitazone-metformin group had a SAE that led to withdrawal. No SAEs were reported more than once in either treatment group and no pattern within or between treatment groups were seen.

- Five subjects withdrew from the trial due to a treatment emergent AE; 3 (1.6%) subjects in the AERx-metformin group had 5 AEs and 2 (2.1%) subjects in the rosiglitazone-metformin group had 2 AEs. For two of the subjects in the AERx-metformin group the events were respiratory related; interstitial lung disease, cough and dyspnoea. All 3 events were considered possibly/probably related to treatment. Further, one subject in the AERx-metformin group withdrew from the trial due to flatulence and diarrhea; both events were considered unlikely related to AERx but related to metformin. For both subjects in the rosiglitazone-metformin group the events (drug eruption and nausea) were considered probably related to treatment.
- In the AERx-metformin group 3 hypoglycaemic episodes reported by 2 subjects (1%) were characterised as major, 121 episodes reported by 50 subjects (26%) were minor and 58 episodes reported by 31 subjects (16%) were symptoms only. In the rosiglitazone-metformin group no episodes were characterised as major, 5 episodes reported by 3 subjects (3%) were minor and 5 episodes reported by 2 subjects (2%) were symptoms only. In all 18 subjects (9%) had a nocturnal hypoglycaemic episode; all in the AERx-metformin group. All the nocturnal hypoglycaemic episodes were characterised as minor or symptoms only. One of the major episodes in the AERx-metformin group was serious and considered probably related. None of the hypoglycaemic episodes led to withdrawal.
- There were no pronounced changes from baseline to End of Trial in ECG, funduscopy, vital signs, physical examination or body weight in either treatment group or between treatment groups.
- There were no marked changes from baseline to End of Trial in laboratory assessments (haemoglobin, biochemistry) in either treatment group or between treatment groups. For one subject in the AERx-metformin group a decrease in white blood cell count was reported as an AE and for 3 subjects an increase in blood potassium, creatinine or cholesterol were reported as an AE. In the rosiglitazone-metformin group 2 subjects had an increase in blood cholesterol reported as an AE. All the events were considered non-serious, mild or moderate in severity and unlikely related to trial products.
- An increase in insulin antibody level was seen at End of Trial in the AERx-metformin group; 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-metformin or rosiglitazone-metformin, and analysis of all the PFTs (% of predicted normal value) did not show any statistically significant differences between AERx-metformin and rosiglitazone-metformin. However, a higher proportion of subjects with AERx-metformin compared with rosiglitazone-metformin had changes higher than 15% of predicted normal in the PFTs. Overall there were no differences between the two treatment groups in frequency and type of PFTs reported as an AE; however PFT related AEs considered possibly or probably related to treatment were only seen in the AERx-metformin group (in all 6 events: decrease in $D_{L,CO}$, TLC and PFT). All the PFT related AEs were considered to be mild in severity, except one decrease in PFT in the AERx-metformin group that was considered moderate in severity. None of the PFTs reported as AEs led to withdrawal and none were serious.
- Three subjects had either a new finding or a worsened finding in chest X-ray at End of Trial. In the AERx-metformin group one subject had a new finding and one subject had a worsened finding (both findings were cardiomegaly). In the rosiglitazone-metformin group one subject had a new finding (micronodules). For the majority of subjects in both treatment groups the findings in chest X-ray were stable from baseline to End of Trial; 78% of the findings with AERx-metformin and 73% with rosiglitazone-metformin. The majority of findings were non-pulmonary or listed as “other”. The most common abnormality type in both treatment groups were nodules and cardiomegaly. Further, a number of the findings were not assessable; 18% of the findings with AERx-metformin and 23% with rosiglitazone-metformin. The chest X-rays were not accessible because the subject chose not to complete the End of Trial procedure or for technical reasons such as poor quality X-rays.

Other Endpoints

- One subject had a SAE (dyspoea) in which the relationship to the AERx device was considered possible by the investigator and Novo Nordisk. This event, however, was not reported as an AERx SAE by the investigator. Since the event was not reported as an AERx SAE the device was not analysed or stored.

- In all 25 subject had 51 AERx complaints: 42 related to the device, 8 to the insulin strips and 1 to the battery.

Conclusions

Treatment with AERx or rosiglitazone in combination with metformin 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 the efficacy results from comparing AERx-metformin to rosiglitazone-metformin treatment should be interpreted with caution. In this trial, treatment with AERx-metformin resulted in a greater reduction in HbA_{1c} and FPG than rosiglitazone-metformin treatment.
- Overall, the pulmonary safety (as determined by PFTs and chest X-rays) did not give rise to any safety concerns.
  - Pulmonary function tests showed no statistically significant difference between the AERx-metformin group and the rosiglitazone-metformin group.
  - Findings in chest X-ray did not show any marked differences between AERx-metformin and rosiglitazone-metformin; 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".
  - There were more AEs associated with the respiratory system that were judged related to AERx (18) than to the comparator trial products (0). This was expected due to the pulmonary route of insulin administration of AERx.
- There was a higher number of hypoglycaemic episodes reported with AERx-metformin. This was expected due to the rapid onset of action of insulin (AERx) compared to an oral antidiabetic agent as rosiglitazone.
- The safety profile as reflected by standard laboratory parameters, vital signs and changes in ECG and fundoscopy/fundosphotography did not show any differences between the two groups.
- 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.