2 Synopsis

Trial Registration ID-number	**EudraCT number**
NCT00472953	2006-004731-29

Title of Trial

Inhaled preprandial human insulin with the AERx® iDMS versus subcutaneous injected insulin aspart in subjects with diabetes and chronic obstructive pulmonary disease: A 52-week, open-label, multicentre, randomised, parallel trial to investigate long-term safety

Investigator(s)

In total, 31 principal investigators were planned to participate in the trial (one investigator was planned to be investigator on two sites). The Signatory Investigator is Dr. [redacted].

Trial Site(s)

In total, 31 sites were planned to participate in the trial. Of these, 5 sites in 3 countries (India, Romania, and Argentina) randomised subjects.

Publications

None

Trial Period	**Development Phase**
15 May 2007 to 5 March 2008	Phase 3a

Objectives

Primary Objective

- The primary objective of this trial is to evaluate the long term pulmonary safety profiles comparing preprandial inhaled human insulin with preprandial subcutaneous (s.c.) injections of insulin aspart, both in combination with basal insulin and/or OADs, in subjects with diabetes and COPD

Secondary Objectives

- Long term safety profiles as measured by laboratory parameters, ECG, fundoscopy/fundusphotography, body weight, vital signs, physical examination and adverse events.
- Incidence of hypoglycaemic episodes
- Glycaemic control as measured by HbA_{1c} and fasting plasma glucose (FPG_{Lab})
- Patient Reported Outcomes (PRO)
- Bolus insulin doses

Other objectives

- Evaluate the number and type of AERx®iDMS complaints

Methodology

- This trial was designed as 52-week, multicentre, multinational, open-label, active-controlled, treat-to-target, parallel group trial with the aim of randomising subjects with type 1 or type 2 diabetes and COPD in a 2:1 manner to either inhale insulin at each of three meals with AERx or inject insulin aspart (IAsp) at each of three meals. Both treatments were given in combination with the subject's current basal insulin treatment and/or oral antidiabetic agents (OADs)
- The trial was planned to include a screening visit to assess the subject's eligibility, followed by 12 clinic visits and at least 11 telephone contacts
- Safety and efficacy assessments were measured at regular intervals during the trial
- On 14 January 2008, Novo Nordisk A/S announced the decision to discontinue the development of the AERx®iDMS for delivery of inhaled soluble human insulin. At that time only 36 subjects were exposed to trial products: 26 to AERx and 10 to IAsp.

Number of Subjects Planned and Analysed

It was planned to randomise 225 subjects. However, due to discontinuation of the trial only 64 subjects were screened. All randomised subjects were withdrawn from the trial as a consequence of discontinuation of the trial, except for 2 subjects in the IAsp group that were withdrawn from the trial before 14 January 2008; 1 withdrew

consent and 1, who by mistake was randomised although [redacted] COPD stage IV. This subject was withdrawn immediately after the mistake was discovered and was only exposed to IAsp for [redacted] days.

	AERx	Insulin Aspart	Total
Screened subjects			64
Screening failures			26(40.63%)
Randomised subjects	26(100.00%)	12(100.00%)	38(100.00%)
Randomised but not treated	0(0.00%)	0(0.00%)	0(0.00%)
Randomised and treated subjects	26(100.00%)	12(100.00%)	38(100.00%)
Withdrawn Subjects (before 14/1/2008)	0(0.0%)	2(16.67%)	2(5.26%)
- Adverse Event	0(0.0%)	0(0.0%)	0(0.0%)
- Non-Compliance with protocol	0(0.0%)	0(0.0%)	0(0.0%)
- Ineffective therapy	0(0.0%)	0(0.0%)	0(0.0%)
- Other	0(0.0%)	2(16.67%)	2(5.26%)
Withdrawn subjects (after 14/1/2008)	26(100.00%)	10(83.33%)	36(94.74%)
Completed subjects	0(0.0%)	0(0.0%)	0(0.0%)
Full analysis set	26	12	36

Diagnosis and Main Criteria for Inclusion

Male and female subjects, aged ≥ 30 years, a BMI ≤ 40 kg/m^2, and with a diagnosis of type 1 or type 2 diabetes according to the following criteria:

- Type 1 diabetes with an HbA_{1c} ≤ 11.0 % and treated continuously with basal/bolus insulin for at least six months or
- Type 2 diabetes with an HbA_{1c} ≤ 11.0 % and treated continuously with basal/bolus insulin for at least three months or
- Type 2 diabetes with an HbA_{1c} ≥ 7.5% and ≤ 11.0 % and treated continuously with basal insulin (with or without an OAD(s) (except rosiglitazone if not approved in combination with insulin) for at least two months or
- Type 2 diabetes with an HbA_{1c} ≥ 7.5% and ≤ 11.0 % and treated continuously with one or more OADs (except rosiglitazone if not approved in combination with insulin) for at least two months

Further, the subjects should have a clinical diagnosis of stable COPD (GOLD stages I-III).

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 [75 units] 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.

Duration of Treatment

The planned duration of treatment was 52 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 151 days to AERx and 135 days to IAsp; no subjects were exposed for more than 36 weeks.

Reference Therapy, Dose and Mode of Administration, Batch Number

- Rapid-acting insulin aspart PenFill®, 100 U/mL, 3 mL cartridge. Batch numbers by subject are provided in Appendix 16.1.6. Individualised insulin doses were administered by s.c. injections immediately (within 5 minutes) before main meals. Starting dose was decided based on the subject's previous insulin regimen and according to local practice.
- Rapid-acting insulin aspart PenFill®, 100 U/mL, 3 mL cartridge was used as escape therapy in the AERx group if

administration of inhaled human insulin using the AERx® iDMS was not possible.

Criteria for Evaluation – Efficacy

The Protocol did not specify any efficacy objective or efficacy endpoints; however, HbA_{1c} and FPG_{Lab} were measured and reported for completeness.

Criteria for Evaluation – Safety

Primary safety endpoints

- Changes in PFTs (FEV_1, FEV_6, FVC, FRC, RV, TLC, and $D_{L,CO}$) as percent of predicted value from baseline to 52 weeks of treatment
- Distribution of overall classification of COPD according to GOLD classification at end of 52 weeks of treatment
- Type and frequency of inhaled and systemic medication for pulmonary symptomatology (COPD medication) during 52 weeks of treatment
- Type, duration and frequency of COPD exacerbations, both severe (hospitalisation) and non-severe, (systemic steroids, antibiotics) during 52 weeks of treatment
- Change in X-ray from baseline to 52 weeks of treatment

Secondary safety endpoints

- Changes in laboratory assessments (haematology, biochemistry, urinalysis, insulin antibodies), ECG, fundoscopy/fundusphotography, vital signs, body weight and physical examination from baseline to 52 weeks of treatment
- Frequency and severity of AEs
- Incidence of hypoglycaemic episodes (minor, major, symptomatic) analysed for the last 12 weeks of treatment. Incidence of nocturnal hypoglycaemic episodes (11 pm – 6 am) and over the entire day (24 hours) analysed for the last 12 weeks of treatment
- Bolus insulin doses after 52 weeks of treatment
- Patient Reported Outcomes (PRO) during the trial using the St. George Respiratory Questionnaire (SGRQ) (not evaluated due to early termination of the trial).

Other endpoints

- Number and type of AERx complaints
- AERx insulin device performance (not evaluated due to early termination of the trial)

Due to discontinuation of the trial, PROs and AERx insulin device performance were not assessed.

Statistical Methods

Data were extensively described. PFT parameters at End of Trial were compared between treatments using an analysis of variance model. In addition, trends in PFT parameters were investigated using a linear mixed effect model.

Demography of Trial Population

The trial population consisted of 29 male and 9 female subjects, aged from 43 to 71 years; 11 subjects were ≥ 65 years. About 92% of all subjects were White, while 8% were Asian. Two subjects had type 1 diabetes and 36 type 2 diabetes. Mean duration of diabetes was approximately 6 years, mean BMI 28.5 kg/m^2, and mean HbA_{1c} and FPG_{Lab} were 8.4% and 9.5 mmol/L, respectively. Mean duration of COPD was approximately 8 years. Of the 38 subjects, 1 had mild COPD, 15 moderate, 21 severe, and 1 very severe COPD (this subject was by mistake randomised although [redacted] had very severe COPD and was withdrawn from the trial after having been exposed to IAsp for only [redacted] days). In all, 36 of the 38 subjects were previous smokers with a mean duration of smoking of approximately 31 years.

Efficacy Results

The Protocol did not specify any efficacy objectives or efficacy endpoints. There were no differences in HbA_{1c} and FPG_{Lab} between the treatment groups; however no conclusion on the efficacy of AERx®iDMS can be made based on these trial results.

Safety Results

Primary Safety Endpoints

- For all the PFTs the changes from baseline to End of Trial were mainly minor.
- Two subjects in the AERx group had a change in COPD classification from baseline to End of Trial; 1 from

moderate to severe, and 1 from severe to very severe. The changes in classification were associated with very small changes in lung function.

- Two subjects in the AERx group reported COPD exacerbation. Both cases were non-serious, considered to be severe and unlikely related to trial product; the absolute change in FEV_1 was small. For both subjects the COPD exacerbations were recorded at the End of Trial Visit. These two subjects also changed COPD classification; one from severe to very severe, and one from moderate to severe.
- In both treatment groups the most frequently used classes of COPD medication were Tiotropium, Theophylline, and Beclometasone.
- All findings in chest x-ray were present at baseline and remained stable to End of Trial and no new findings were reported.

Secondary Safety Endpoints

- There were no marked changes from baseline to End of Trial in ECG, funduscopy, vital signs, physical examination or body weight.
- There were no marked changes from baseline to End of Trial in laboratory assessments (haemoglobin, biochemistry, and insulin antibodies).
- No SAEs were reported and no subjects withdrew due to an AE.
- The overall proportion of subjects with AEs was comparable between the two treatments groups. All the AEs were considered non-serious and unlikely related to trial products. The majority of the AEs were classified as mild or moderate in severity.
- One non-treatment emergent (total lung capacity decreased) was reported by 1 subject in the IAsp group. The MESI was non-serious, considered mild in severity and unlikely related to trial product.
- Hypoglycaemic episodes characterised as “minor” or “symptoms only” were reported by 5 subjects (3 in the AERx group, 2 in the IAsp group). In all cases, the subjects were able to treat themselves. No subjects experienced a nocturnal hypoglycaemic episode.
- Mean total daily bolus insulin doses at baseline were 0.4 U/kg and 0.3 U/kg for AERx and IAsp, respectively. At End of Trial the doses were 0.5 U/kg and 0.4 U/kg for AERx and IAsp, respectively.

Other Safety Endpoints

- No AERx SAEs were reported.
- One subject reported two AERx complaints; one related to the device and one related to the battery.

Conclusions

Owing to the small number of subjects treated with the AERx®iDMS in this trial, it is not possible to draw any conclusions concerning effects on lung function in subjects with COPD.

The trial was conducted in accordance with the Declaration of Helsinki (2002) and ICH Good Clinical Practice.