2 Synopsis

Trial Registration ID-number NCT00184600	**EudraCT number** 2004-000514-38

Title of Trial

A 36-month, Multi-centre, Open-label, Randomised, Parallel-group Trial Comparing the Safety, Efficacy and Durability of Adding a Basal Insulin versus a Twice Daily Insulin Mixture versus a Meal-time Rapid-Acting Insulin in Subjects with Type 2 Diabetes Inadequately Controlled on Therapy with Oral Agents, and Assessing the Requirement for more Complex Insulin Regimens to Achieve and Maintain Glycaemic Control, their Efficacy and Durability

Investigator(s)

Steering Committee — [redacted] (chair), [redacted]
Data and Safety Monitoring Board — [redacted] (chair), [redacted] (chair), [redacted]
Site Investigators: [redacted]

Trial Site(s)

58 sites across the UK (54 sites) and Ireland (4 sites)

Publications

Addition of biphasic, prandial, or basal insulin to oral therapy in type 2 diabetes.
Holman RR, Thorne KI, Farmer AJ, Davies MJ, Keenan JF, Paul S, Levy JC; 4-T Study Group.
N Engl J Med. 2007 Oct 25;357(17):1716-30.

- Addition of Insulin to Oral Therapy in Type 2 Diabetes.
  Holman RR.
  N Engl J Med 2008;358:1198.

Three-year efficacy of complex insulin regimens in type 2 diabetes.
Holman RR, Farmer AJ, Davies MJ, Levy JC, Darbyshire JL, Keenan JF, Paul SK; 4-T Study Group.
N Engl J Med. 2009 Oct 29;361(18):1736-47.

Insulin Regimens in Type 2 Diabetes.
Holman RR, Darbyshire, JL.
N Engl J Med. 2010 Mar 11; 362(10):959-960.

Trial Period	**Development Phase**
November 2004 – August 2009	3b

Objectives

2.1 Primary Study Objectives

The 4-T study will explore the efficacy and safety of treatment with biphasic, basal and prandial analogue insulin regimens in participants with T2DM inadequately controlled by two oral anti-diabetic drugs (OADs). As this is a glycosylated haemoglobin (HbA_{1c}) treat-to-target study it is expected that the HbA_{1c} levels in the three treatment groups will be similar but that there may be substantive differences in concomitant measures such as rates of hypoglycaemia, changes in weight and Quality of Life scores.

2.1.1 Co-primary objective at one year:

To compare the ability of three different single insulin formulation regimens to achieve good glycaemic control, defined as HbA_{1C} levels ≤6.5 %, when added to current OAD treatment in subjects with inadequately controlled type 2 diabetes.

2.1.2 Co-primary objective at three years:

To determine the efficacy and durability of the three different insulin regimens in the longer term, and to assess the need for the addition of a second insulin formulation to achieve good glycaemic control.

2.1.3 Co-primary objective at one year:

To derive algorithms to estimate individual starting insulin dose requirements and insulin adjustment scales in populations such as this.

2.2 Secondary Study Objectives

2.2.1 Secondary objectives at one year:

- To compare the three treatment arms in terms of:
- Proportions of participants who achieve HbA_{1c} values ≤6.5 %.
- Proportions of participants who achieve HbA_{1c} values ≤6.5 % without grade 2 (minor) or grade 3 (major) hypoglycaemia (as defined in the protocol) in the last 4 weeks of year one.
- Proportion of participants who have clinically unacceptable hyperglycaemia (defined as two consecutive HbA_{1c} values ≥8.0 % or a single HbA_{1c} value ≥10.0 % at or after 24 weeks) despite therapy with a single insulin formulation.

2.2.2 Secondary objectives at three years:

- To compare the three treatment arms in terms of:
- Proportions of participants who achieve HbA_{1c} values ≤6.5 %.
- Proportions of participants who achieve HbA_{1c} values ≤6.5 % without grade 2 or grade 3 hypoglycaemia (as defined in the protocol) in the last 4 weeks of the Study.
- Proportion of participants who have required a second insulin formulation.

2.2.3 Secondary objectives at one and three years:

- To compare the three treatment arms in terms of:
- The frequency of grade 1 (symptoms only), grade 2 (minor) or grade 3 (major) hypoglycaemia (as

defined in the protocol) in a 24-hour period (00:00-24:00).

- The frequency of grade 1, 2 or 3 nocturnal hypoglycaemia (23:00-05:59).
- The frequency of grade 1, 2 or 3 daytime hypoglycaemia (06:00-22.59).
- Changes in body weight.
- Eight-point capillary plasma glucose profiles (self-measured).
- Within-subject variation in pre-breakfast, pre-lunch and pre-dinner capillary plasma glucose levels (self-measured).
- Changes in urinary albumin to creatinine ratio.
- Reasons for inability to achieve target HbA_{1c} levels.
- Changes in quality of life and beliefs about medicines, both generic and disease-specific measures for people with diabetes treated with insulin.
- Safety data.

Methodology

This trial was undertaken as an academic collaboration between the [redacted] and Novo Nordisk (NN). A Steering Committee, consisting of nominated [redacted] and NN representatives, with two independent advisers (an academic diabetologist and a lay member of the public), had overall responsibility for the management of the trial. The [redacted] had primary responsibility for the academic aspects of the trial to ensure impartiality with respect to data collection, analysis and reporting. NN was the sponsor and had primary responsibility for the operational aspects of the trial.

The trial aimed to determine the degree to which good glycaemic control can be achieved, defined as an $HbA_{1c} \leq 6.5$ % over time, by the addition of a single insulin regimen in patients with Type 2 diabetes inadequately controlled on their existing OAD therapy. The first year of the trial examined the utility of three different single insulin regimens: adding a basal insulin analogue, adding a biphasic insulin analogue or adding a prandial insulin analogue. In the second and third years, the need for a second insulin formulation to be added (with cessation of sulphonylurea (SU) therapy, if taken) was examined and the degree to which good glycaemic control could now be achieved, determined. The more complex insulin regimens used were: the addition of a prandial insulin analogue to the basal insulin analogue arm, the addition of a prandial insulin analogue to the biphasic insulin analogue arm and the addition of a basal insulin analogue to the prandial insulin analogue arm.

The trial was a multi-centre, open-label, randomised, parallel-group trial in subjects with type 2 diabetes inadequately controlled on OAD monotherapy with metformin or SU, or with both agents in combination. Subjects were randomised to one of three primary insulin regimens in the ratio 1:1:1, namely a basal insulin analogue once (or twice) daily: a biphasic insulin analogue twice daily: a rapid-acting insulin analogue thrice daily with meals. Subjects allocated to the basal insulin analogue were asked to take it once daily, as a pre-bed injection, with the option to add a second pre-breakfast injection if pre-breakfast but not pre-dinner meal plasma glucose targets were met.

For the first year, subjects were asked to remain on their existing OAD and their randomly allocated single insulin formulation regimen, unless they had unacceptable hyperglycaemia defined as two consecutive

HbA_{1c} values ≥8.0 % or a single HbA_{1c} value ≥10.0 % after 24 weeks. In this event they discontinued their SU (if taken) and added a second insulin formulation, as described below.

In the second and third years, a second insulin formulation was added if subjects failed to achieve or to maintain good glycaemic control, defined as two consecutive HbA_{1C} measurements >6.5 % or a single measurement >7.5%. This resulted in the three single insulin formulation regimens being enhanced as follows:

- Those allocated to a basal insulin analogue once (or twice) daily were asked to add a rapid acting insulin analogue thrice daily with meals
  i.e. a basal-bolus insulin analogue regimen.

- Those allocated to a biphasic insulin analogue twice daily were asked to add a rapid acting insulin analogue at lunchtime (midday)
  i.e. an augmented pre-mixed insulin analogue regimen.

- Those allocated to a mealtime rapid acting insulin analogue thrice daily were asked to add a basal insulin analogue once or twice daily
  i.e. a basal-bolus insulin analogue regimen.

The primary objective of the Single Insulin Formulation phase was to compare the glycaemic efficacy of insulin detemir, biphasic insulin aspart, and insulin aspart, as assessed by HbA_{1c} levels, in subjects with type 2 diabetes over a 1 year period. The primary objective of the Extended Insulin Regimen phase was to compare the efficacy of the three treatment regimens in reducing then maintaining HbA_{1c} at acceptable levels over a three year period.

The primary efficacy endpoint HbA_1c after 12 months and after 36 months of treatment were analysed by an analysis of covariance (ANCOVA) with randomised primary insulin regimen, clinical centre and subject's existing OAD treatment as fixed effects and their baseline HbA_1c value as a covariate (see Statistics section, Section 16). Differences in the three different insulin regimens will be examined with respect to:

- Baseline OAD therapy: metformin monotherapy, SU monotherapy or metformin and SU combination therapy.
- HbA_{1C} level: < 8.5% or ≥ 8.5%.

Exploratory analyses were performed to examine whether there are identifiable subgroups who may benefit more from particular randomised insulin sequences. The ANCOVA methodology was used, with additional baseline variables included in the model as explanatory variables, along with first order interactions between the factors and treatment. The factors investigated were gender, ethnicity, educational attainment, duration of type 2 diabetes, oral agents used, waist measurement, and Body Mass Index (BMI).

The duration of the trial was 158 weeks. This period includes a recruitment visit (2 weeks before randomisation), a randomisation visit, a randomised insulin treatment period of 156 weeks with on-going dose titration to achieve and maintain glycaemic targets. In addition there was a follow-up period of 28 days.

Number of Subjects Planned and Analysed

Planned: 1000 screened / 700 randomised / 594 completed

Screened: 936

Randomised: 708

Withdrawn: 130

Completed: 578

Intent to Treat (ITT) group: 708

Per protocol (PP) group: 680

Diagnosis and Main Criteria for Inclusion

2.3 *Inclusion Criteria*

1. Informed consent obtained before any trial-related activities. Trial-related activities are any procedure that would not have been performed during normal management of the subject.
2. Subjects with type 2 diabetes of at least 12 months duration who are insulin naïve. Short term insulin treatment (7 days or less at any one time) is allowed.
3. OAD treatment for at least 4 months with metformin and a SU. Subjects treated only with metformin or a SU are also eligible if they have shown previous intolerance to SU or metformin respectively.
4. The individual OAD dose(s) prior to inclusion must be either highest tolerated dose or at least half maximum recommended dose according to the local labelling for the OAD in question for the last 4 months before inclusion.
5. The OAD dose(s) should be unchanged for the last 4 weeks prior to inclusion.
6. Males and females, age ≥18 years.
7. BMI ≤ 40.0 kg/m^2.
8. 7.0 % ≤ HbA_{1c} ≤ 10.0% at screening and based on analysis from the central laboratory.
9. Able and willing to use insulin injections for the entire trial period.
10. Able and willing to perform self-monitoring of plasma glucose.

2.4 *Exclusion Criteria*

1. Type 2 diabetic subjects currently receiving or having previously received insulin for more than 7 days at any one time.

2. Current or previous treatment with thiazolidinediones within the last 6 months.
3. Current or previous treatment with an alpha-glucosidase inhibitor, repaglinide or nateglinide within the past 30 days.
4. OAD treatment with three or more OADs within the last 6 months.
5. Diabetes other than Type 2 diabetes mellitus.
6. Known sight-threatening retinopathy as judged by the investigator.
7. Plasma creatinine ≥130 µmol/l.
8. Cardiac disease defined as:
    - Unstable angina pectoris within the last 6 months
    - Myocardial infarction (MI) within last 6 months
    - Congestive heart failure New York Heart Association (NYHA) class III and IV[1]
9. Evidence of hepatic disease as determined by Alanine aminotransferase (ALT) values ≥2 x upper limit of normal.
10. Known hypoglycaemia unawareness or recurrent major hypoglycaemia as judged by the Investigator.
11. Anticipated change in dose of concomitant medication, which may interfere with glucose regulation, such as monoamine oxidase inhibitors (MAOI), beta-adrenergic agents, anabolic steroids or systemic glucocorticoids.
12. Uncontrolled hypertension measured as systolic blood pressure ≥ 180 mmHg and / or diastolic pressure ≥ 105 mmHg.
13. Known or suspected allergy to trial products or related products.
14. Any condition that the Investigator and / or the Sponsor feel would interfere with trial participation or the evaluation of results.
15. Mental incapacity, unwillingness or language barrier precluding adequate understanding or cooperation.
16. Pregnant or planning to become pregnant within the next 36 months, breast-feeding, or judged to be using inadequate contraceptive methods. Adequate contraceptive methods are sterilisation, intrauterine device (IUD), oral contraceptives or consistent use of barrier methods.
17. Receipt of any investigational trial drug within 3 months prior to participation in this trial.
18. Subjects previously screened for participation or having already participated in this trial.

Test Product, Dose and Mode of Administration, Batch Number

Insulin detemir (Levemir®) injected subcutaneously, either in the thigh or abdomen, once daily before bed and administered in combination with current OAD treatment. Subjects had the option to add a second pre-breakfast basal insulin analogue injection if pre-breakfast but not pre-dinner meal plasma glucose targets were met.

Insulin detemir supplied in 3ml pre-filled, disposable pen device (FlexPen®) 100U/ml.

Insulin detemir batch numbers:

PP50277

RP50468

SP51184

TP52028

Biphasic insulin aspart 30 (NovoMix 30®) injected subcutaneously, either in the thigh or abdomen, twice daily with meals (breakfast and dinner) and administered in combination with current OAD treatment.

Biphasic insulin aspart 30 supplied in 3ml pre-filled, disposable pen device (FlexPen®) 100U/ml.

Biphasic insulin aspart 30 batch numbers:

PP50576

RP51005

SP50833

TP50436

TP51225

VP51338

Insulin aspart (NovoRapid®) injected subcutaneously, either in the thigh or abdomen, at meal-times (breakfast, lunch and dinner) and administered in combination with current OAD treatment.

Insulin aspart supplied in 3ml pre-filled, disposable pen device (FlexPen®) 100U/ml.

Insulin aspart batch numbers:

PP50573

RP51129

SP52173

TP51251

VP51396

Duration of Treatment
All patients were treated for a total of three years (156 weeks) from randomisation

Reference Therapy, Dose and Mode of Administration, Batch Number
This section is not applicable.

Criteria for Evaluation – Efficacy

Analyses were conducted on the following data sets.

Intention to Treat (ITT) Analysis Data Set

The ITT data analysis set included all randomised study participants irrespective of whether they commenced their allocated insulin therapy. The same set of participants was used for the one and, where still available, for the three year analyses.

Per Protocol (PP) Analysis Data Sets

There is a one-year and a three-year PP data analysis set. These include all randomised study participants who completed one and three years of follow up respectively without a major protocol violation. The participants within these two sets may differ since they may be valid for inclusion at one year but not at three years.

Efficacy variables for the study were:

- HbA1c
- Fasting plasma glucose
- Self-measured capillary glucose (SMCG)
- Eight-point plasma glucose profile
- Body weight
- Waist circumference measurements

Criteria for Evaluation – Safety

Safety Population (SP) Analysis Data Set

The SP data analysis set comprises those participants in the ITT population who received at least one dose of their study medication. Participants who were dispensed Study Medication but were immediately lost to follow-up have not been counted among those known to have been dosed. An additional table entitled "Subject Evaluation Groups" identifies the number and details of people screened for entry into 4-T.

Safety data was made available continuously on demand to Novo Nordisk HQ during the trial via a secure password-protected FTP server.

Treatment emergent adverse events (AEs) and treatment emergent serious adverse events (SAEs) were coded by Novo Nordisk using the Medical Dictionary for Regulatory Activities (MedDRA). SAEs and AEs were tabulated by treatment group by preferred term and by high-level term, with totals for each term. Counting was done by patient and by event. Between treatment group comparisons were performed using

Fisher's Exact Test.

2.7.1 Other Safety Variables

Visit-based Box and Whisker plots were produced for safety variables, for blood pressure and for waist circumference by randomised treatment. Supplementary analyses were only performed where these summaries suggested that there may be clinically significant differences.

The trial safety assessments included:

- Adverse events, including serious adverse events
- Hypoglycaemic episodes
- Blood pressure
- Plasma ALT, creatinine and lipid levels
- Unrinary albumin:creatinine ratio

Statistical Methods

The statistical analyses reflect the two distinct phases of the study:

Phase 1

The Single Insulin Formulation phase was analysed after all patients had completed one year in the study.

Phase 2

The Extended Insulin Regimen phase was analysed after all patients had completed three years in the study.

The methodology for each phase is as described below unless otherwise noted. The two phases of the study are regarded as separate experiments with their own primary null hypothesis and their own type I error rate of 5%. Accordingly, no adjustment needs to be made for multiple comparisons and each study phase was analysed independently. All statistical tests will be two sided.

Analyses were conducted prior to the end of each phase using dummy randomisation codes to help test statistical programs, examine study data distributions and design templates for tables and figures in preparation for final analysis.

All statistical analyses were adjusted for possible 'centre' effects as is usual for multi-centre clinical trials[1]. Mixed effect models were used with centre included as a random effect, assuming that the 4-T centres are a random sample of all UK diabetes centres.

Demography of Trial Population:

The 708 patients assigned randomly at baseline to the three study groups had a mean (± standard deviation (SD)) age of 61.7±9.8 years and a median duration of disease of 9 years; most were white and overweight, with no significant differences in baseline variables among the groups. The total numbers of patients who did not complete three years did not differ significantly among the biphasic (34 of 235, or 14.4%), prandial

[1] *Statistics in Medicine (2000) Vol 19 pp: 1115-1139*

(51 of 239, or 21.3%), or basal (45 of 234, or 19.2%) groups (P=0.15 for all comparisons). At baseline, the 130 patients who did not complete the study did not differ from those who continued.
Efficacy Results: The mean (SE) HbA_{1c} levels converged after one year and remained stable in all groups, with an overall value at three years of 7.2±0.1 that did not differ between groups (p=0.28). At three years, the mean reduction from baseline was 1.3% in the biphasic group, 1.4% in the prandial group, and 1.2% in the basal group. During the study, the percentage of patients whose prescribed insulin doses were within ±10% of the trial management system recommendation was 89.7% for the biphasic group, 80.4% for the prandial group and 90.2% for the basal group.
Safety Results: No clinically relevant changes occurred in plasma creatinine or ALT levels, although the difference in ALT was statistically significant. Fourteen patients discontinued metformin therapy according to the study protocol after two successive measures of plasma creatinine showed values of more than 1.7 mg per deciliter (150 μmol per liter). Although the proportions of patients with SAEs differed between groups (P=0.012) being greatest in the prandial group but no differences were seen between proportions of patients with individual serious adverse events or the numbers of AEs. Nineteen patients died, seven in the biphasic, nine in the prandial and three in the basal group; P = 0.23); of these patients, 14 died from cardiovascular disease (4 in the biphasic group, 9 in the prandial group, and 1 in the basal group; P = 0.002). As compared with the cohort as a whole, the median rates of grade 2 hypoglycaemia were lower in the biphasic and prandial groups but higher in the basal group, with per-patient rates of 1.7 in the biphasic group, 2.3 in the prandial group, and 4.3 in the basal group per year, with no reports of any grade 3 episodes. Median HbA_{1c} levels were 6.9%, 7.0%, and 7.9%, respectively.
Conclusions More patients achieved HbA_{1c} targets using a basal or prandial than a biphasic insulin based regimen, but those commencing with a basal insulin had fewer hypoglycemic episodes and less weight gain.
The trial was conducted in accordance with the Declaration of Helsinki (October 2000) and ICH Good Clinical Practice (01May1996).

The results presented reflect data available in the clinical database as of 31st August 2009.

[1] The Criteria Committee of The New York Heart Association. Nomenclature and Criteria for Diagnosis of Disease of The heart and Great Vessels. Boston (Mass): Little Brown and Co; 1994; 253-256.