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Treating To Target in Type 2 diabetes

Submission date	Recruitment status	[X] Prospectively registered
02/08/2004	No longer recruiting	[_] Protocol
Registration date	**Overall study status**	[_] Statistical analysis plan
14/09/2004	Completed	[X] Results
Last Edited	**Condition category**	[_] Individual participant data
31/07/2017	Nutritional, Metabolic, Endocrine	

Plain English summary of protocol
Not provided at time of registration

Study website
http://www.dtu.ox.ac.uk/4-T

Contact information

Type(s)
Scientific

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Additional identifiers

EudraCT/CTIS number

IRAS number

ClinicalTrials.gov number

Secondary identifying numbers
NN304-1613

Study information

Scientific Title
Treating To Target in Type 2 diabetes

Acronym
4-T

Study objectives
Current hypothesis as of 06/07/07:
The United Kingdom Prospective Diabetes Study (UKPDS) demonstrated that improved glycaemic control reduces the risk of complications in type 2 diabetes. It showed also that type 2 diabetes is a progressive condition in which HbA1c levels rise inexorably, secondary to declining beta cell function. As a result, oral therapy needs to be escalated repeatedly with the majority of patients requiring insulin in the longer term.

There remains, however, considerable uncertainty as to which insulin regimen should be used when oral therapy becomes insufficient. Analogue insulin preparations have been shown to reduce the risk of hypoglycaemia whilst minimising weight gain, but there is no consensus about whether to commence therapy with a short acting, a long acting or a biphasic preparation. It is also uncertain how best to select an appropriate starting dose given that insulin requirements are often 2 - 3 times higher in type 2 than in type 1 diabetes.

The 4-T trial is a three-year, randomised controlled study in 57 centres that is comparing the efficacy and safety of three different analogue insulin regimens in 708 patients with type 2 diabetes inadequately controlled on maximally tolerated sulphonylurea and metformin therapy (not glitazones).

Patients are allocated to open-label therapy with:
1. Twice-daily biphasic insulin aspart 30
2. Once-daily determir insulin (twice if required)
3. Aspart insulin with meals three times daily

During the first year of the trial (Phase 1) insulin therapy is restricted to a single insulin formulation (unless unacceptable hyperglycaemia occurs), aiming to achieve HbA1c levels less than or equal to 6.5%. During the second and third years (Phase 2) more complex insulin regimens will be introduced if HbA1c levels are greater than 6.5%. 4-T is designed to provide the evidence base that will assist:
1. The choice of an appropriate insulin regimen when treatment with sulphonylurea and/or metformin becomes insufficient
2. Determination of an appropriate insulin starting dose for individual patients
3. Managing cessation of sulphonylurea therapy and transition to a more complex insulin regimen should hyperglycaemia recur

Previous hypothesis:
In year one, to determine the degree to which the randomised addition to existing oral therapies of:
1. Long-acting analogue insulin once-daily (or twice if needed)

2. Prandial rapid-acting analogue insulin thrice-daily
3. Pre-mixed long and rapid acting (biphasic) analogue insulin twice-daily can achieve HbA1c values less than 6.5%.

In years two and three, to determine the degree to which HbA1c values less than 6.5% can be achieved when existing sulphonylurea therapy is replaced by a second insulin preparation.
To derive algorithms that predict likely starting and adjustment doses of insulin for Type 2 diabetic patients with inadequate glycaemic control on oral agents.

Ethics approval required
Old ethics approval format

Ethics approval(s)
West Hertfordshire Local Research Ethics Committee, 13/09/2004, ref: 04/Q0203/33

Study design
Multicentre open-label randomised parallel-group trial

Primary study design
Interventional

Secondary study design
Randomised parallel trial

Study setting(s)
Hospital

Study type(s)
Treatment

Participant information sheet

Health condition(s) or problem(s) studied
Type 2 diabetes

Interventions
1. Insulin detemir (Levemir)
2. Insulin Aspart (NovoRapid)
3. Biphasic Insulin Aspart (NovoMix30)

Intervention Type
Drug

Phase
Phase I/II

Drug/device/biological/vaccine name(s)
Metformin, sulphonylurea

Primary outcome measure

Current primary outcomes measures as of 06/07/2007:
The 4-T study will explore the efficacy and safety of treatment with biphasic, basal and prandial analogue insulin regimens in participants with type 2 diabetes mellitus (T2DM) inadequately controlled by two OADs. As this is an HbA1c treat-to-target study it is expected that the HbA1c 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.

Co-primary objective at one year:
To compare the ability of three different single insulin formulation regimens to achieve good glycaemic control, defined as HbA1C levels less than or equal to 6.5 %, when added to current OAD treatment in subjects with inadequately controlled type 2 diabetes.

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.

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.

Secondary outcome measures
Current secondary outcome measures as of 06/07/2007:
At one and three years, to compare the three treatment arms in terms of:
1. Proportions of participants who achieve HbA1c values less than or equal to 6.5%
2. Proportions who achieve HbA1c values of 6.5% or less without grade 2 (minor) or grade 3 (major) hypoglycaemia (as defined in the protocol) in the last four weeks of year one
3. Proportion who have clinically unacceptable hyperglycaemia (defined as two consecutive HbA1c values 8.0 % or more, or a single HbA1c value 10.0 % or more at or after 24 weeks) despite therapy with a single insulin formulation
4. 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)
5. The frequency of grade 1, 2 or 3 nocturnal hypoglycaemia (23:00 - 05:59)
6. The frequency of grade 1, 2 or 3 daytime hypoglycaemia (06:00-22.59)
7. Changes in body weight
8. Changes in eight-point capillary plasma glucose profiles (self-measured)
9. Within-subject variation in pre-breakfast, pre-lunch and pre-dinner capillary plasma glucose levels (self-measured)
10. Changes in urinary albumin-to-creatinine ratio
11. Reasons for inability to achieve target HbA1c levels
12. Changes in quality of life and beliefs about medicines, both generic and disease-specific measures for people with diabetes treated with insulin

Overall study start date
01/11/2004

Completion date
31/07/2009

Eligibility

Key inclusion criteria
Current inclusion criteria as of 06/07/2007:
1. Informed consent
2. People with type 2 diabetes for at least 12 months who are insulin naive
3. On maximally tolerated metformin and sulphonylurea therapy for at least four months
4. Males and females, aged 18 years or more
5. Body mass index of 40.0 kg/m^2 or less
6. HbA1c in the range 7.0 to 10.0% inclusive
7. Able and willing to use insulin injections and perform self-monitoring of plasma glucose for the entire trial period

Previous inclusion criteria:
1. 700 subjects with type 2 diabetes
2. Males and females
3. Aged 18 years or over
4. Body mass index (BMI) less than or equal to 40kg/m^2 currently treated with oral antidiabetic drugs (OADs) (metformin and/or a sulphonylurea) and with an HbA1c in the range 7.0% to 10.0% inclusive

Participant type(s)
Patient

Age group
Adult

Lower age limit
18 Years

Sex
Both

Target number of participants
Target number: 700. As of 06/07/2007, recruitment was completed with 708 participants

Key exclusion criteria
Current exclusion criteria as of 06/07/2007:
1. Current or previous treatment with thiazolidinediones within the last six months
2. Current or previous treatment with an alpha-glucosidase inhibitor, repaglinide or nateglinide within the past 30 days
3. Oral Antidiabetic (OAD) treatment with three or more OADs within the last six months
4. Diabetes other than type 2 diabetes mellitus
5. Known sight-threatening retinopathy as judged by the investigator
6. Plasma creatinine 130 micromoles/l or more
7. Cardiac disease defined as:
7.1. Unstable angina pectoris within the last six months
7.2. Myocardial infarction (MI) within last six months
7.3. Congestive heart failure New York Heart Association (NYHA) class III and IV
8. Evidence of hepatic disease as determined by alanine aminotransferase (ALT) values of twice the upper limit of normal or more
9. Known hypoglycaemia unawareness or recurrent major hypoglycaemia as judged by the

Investigator
10. 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
11. Uncontrolled hypertension with systolic blood pressure repeatedly 180 mmHg or more, or diastolic blood pressure 105 mmHg or more
12. Known or suspected allergy to trial products or related products
13. Any condition that the Investigator and/or the Sponsor feel would interfere with trial participation or the evaluation of results
14. Mental incapacity, unwillingness or language barrier precluding adequate understanding or cooperation
15. Pregnant or planning to become pregnant within the next 36 months, breastfeeding, or judged to be using inadequate contraceptive methods. Adequate contraceptive methods are sterilisation, intrauterine device (IUD), oral contraceptives or consistent use of barrier methods.
16. Receipt of any investigational trial drug within three months prior to participation in this trial
17. Subjects previously screened for participation or having already participated in this trial

Date of first enrolment
01/11/2004

Date of final enrolment
06/07/2007

Locations

Countries of recruitment
England

Ireland

United Kingdom

Study participating centre
Churchill Hospital
Oxford
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Sponsor information

Organisation
Novo Nordisk Limited (UK)

Sponsor details
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Sponsor type
Industry

Website
http://www.novonordisk.co.uk/documents/home_page/document/index.asp

ROR
https://ror.org/0415cr103

Funder(s)

Funder type
Industry

Funder Name
Novo Nordisk Limited (UK)

Results and Publications

Publication and dissemination plan
Not provided at time of registration

Intention to publish date

Individual participant data (IPD) sharing plan

IPD sharing plan summary
Not provided at time of registration

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article	results	25/10/2007		Yes	No
Results article	results	29/10/2009		Yes	No
Results article	results	01/10/2010		Yes	No
Results article	results	01/09/2017		Yes	No