Clinical trial results:
A comparison of the effects of insulin Detemir with insulin Glargine on weight gain in female adolescents and young adults with Type 1 Diabetes (T1D) on a basal bolus regime

Summary

EudraCT number	2007-004144-74
Trial protocol	GB
Global end of trial date	12 January 2017

Results information

Result version number	v1 (current)
This version publication date	06 July 2017
First version publication date	06 July 2017

Trial information

Trial identification

Sponsor protocol code	DG07

Additional study identifiers

ISRCTN number	ISRCTN49492872
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Cambridge University Hospitals NHS Foundation Trust
Sponsor organisation address	Hills Road, Cambridge, United Kingdom, CB2 0QQ
Public contact	Professor David Dunger, Dept of Paediatrics, University of Cambridge, +44 1223762943, dbd25@cam.ac.uk
Scientific contact	Professor David Dunger, Dept of Paediatrics, University of Cambridge, +44 1223762943, dbd25@cam.ac.uk

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	14 June 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	12 January 2017
Global end of trial reached?	Yes
Global end of trial date	12 January 2017
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To explore the hypothesis that use of insulin Detemir vs. insulin Glargine will lead to reduced weight gain in young women with Type 1 Diabetes.

Protection of trial subjects:

Informed consent/assent was obtained for all participants. Where participant were under 16, parental consent was obtained in addition to participants assent.
Adverse events were recorded at each visit during the trial.
All subjects were allocated a unique Study ID number based on their specific site and sequence of recruitment, which was translated into a barcode used for all subsequent correspondence, transfer of samples and data input. Confidential data has been retained at the study sites in a secure study file. At all times the confidentiality of the subjects was maintained, and reports to meetings and publications did not include confidential or data identifying individuals.

Background therapy:

N/A

Evidence for comparator:

Intensification of insulin therapy through a traditional basal bolus regime in young women with T1D may increase weight gain and rates of hypoglycaemia and induce ovarian hyperandrogenism secondary to peripheral hyperinsulinaemia. Particularly in young women, fear of inappropriate weight gain may impede compliance with treatment and contribute to increased risks of microvascular complications. Incorporation of insulin detemir as part of a basal bolus regime may reduce weight gain thereby improving compliance in this vulnerable population. Preferential hepatic uptake by insulin detemir may lead to relative reductions in peripheral insulin concentrations with subsequent effects on ovarian hyperandrogenism.

Actual start date of recruitment	11 April 2008
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 97
Worldwide total number of subjects	97
EEA total number of subjects	97

Notes:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	75
Adults (18-64 years)	22
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

First participant was recruited 11/04/2008. Last participant was recruited 10/12/2015. Recruitment was carried out at 25 sites in the UK.

Pre-assignment

Screening details:

Participants, on a basal bolus regimen, were recruited from paediatric and young adult diabetes clinics.
Of the 97 consented to the study, 4 withdrew prior to randomisation.
Of those randomised: 46 were allocated to Insulin Detemir and 47 to Insulin Glargine.

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

n/a as unblinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Detemir

Arm description:

Participants randomised to Insulin Detemir

Arm type	Active comparator
Investigational medicinal product name	Insulin Detemir
Investigational medicinal product code	MA No EU/1/04/278/005
Other name	Levemir
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Levemir 1ml contains 100U insulin Detemir(equivalent to 14.2mg).
Doses are titrated to fasting glucose aiming for target of 4-8mmol/l.

Arm title	Glargine

Arm description:

Participants randomised to insulin Glargine

Arm type	Active comparator
Investigational medicinal product name	Insulin Glargine
Investigational medicinal product code	MA No EU/1/00/134/006 & EU/1/00/134/030-37
Other name	Lantus
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Lantus 1ml contains 100U insulin Glargine (equivalent to 3.64mg).
Doses are titrated to fasting glucose aiming for target of 4-8mmol/l.

Number of subjects in period 1[1]	Detemir	Glargine
Started	47	46
Completed	31	34
Not completed	16	12
Consent withdrawn by subject	8	7
Physician decision	-	2
Adverse event, non-fatal	2	1
Pregnancy	-	1
Lost to follow-up	2	-
non-compliance	4	1

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: The baseline data counted all subjects who consented to the study (n=97). 4 participants withdrew prior to randomisation and are therefore not counted in the enrolled numbers which were based on those randomised (n=93)

Baseline characteristics

Reporting groups	
Reporting group title	Detemir
Reporting group description: Participants randomised to Insulin Detemir	
Reporting group title	Glargine
Reporting group description: Participants randomised to insulin Glargine	

Reporting group values	Detemir	Glargine	Total
Number of subjects	47	46	93
Age categorical			
Age at consent			
Units: Subjects			
Adolescents (12-17 years)	36	35	71
Adults (18-64 years)	11	11	22
Age continuous			
Age			
Units: years			
arithmetic mean	16.44	16.49	
standard deviation	± 2.21	± 2.25	-
Gender categorical			
Units: Subjects			
Female	47	46	93
Male	0	0	0

End points

End points reporting groups	
Reporting group title	Detemir
Reporting group description: Participants randomised to Insulin Detemir	
Reporting group title	Glargine
Reporting group description: Participants randomised to insulin Glargine	

Primary: BMI SDS	
End point title	BMI SDS
End point description: The primary endpoint of the trial was change in BMI SDS between baseline and 12 months.	
End point type	Primary
End point timeframe: 12 months	

End point values	Detemir	Glargine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	31	34		
Units: z-score				
arithmetic mean (standard error)	0.048 (± 0.074)	-0.022 (± 0.071)		

Statistical analyses

Statistical analysis title	Detemir vs Glargine comparison
Statistical analysis description: Differences between groups are explored using one-way analysis of variance with appropriate transformation of variables which are not normally distributed to allow parametric testing. With each outcome variable, any effect of the baseline value is explored as a covariate.	
Comparison groups	Detemir v Glargine
Number of subjects included in analysis	65
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.49
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.07

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.136
upper limit	0.276
Variability estimate	Standard error of the mean
Dispersion value	0.103

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were recorded from date of consent until completion of the final study visit.

Adverse event reporting additional description:

AEs were recorded at each visit and reviewed locally. SAEs were reported to the coordinating centre within 24hr of knowledge.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.0

Reporting groups

Reporting group title	Detemir

Reporting group description:

Participant randomised to Insulin Detemir

Reporting group title	Glargine

Reporting group description:

Participants randomised to Insulin Glargine

Serious adverse events	Detemir	Glargine	
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 47 (10.64%)	5 / 46 (10.87%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Investigations			
Endoscopy upper gastrointestinal tract			
subjects affected / exposed	0 / 47 (0.00%)	1 / 46 (2.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Hypoglycaemic seizure			
subjects affected / exposed	1 / 47 (2.13%)	0 / 46 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Chronic fatigue syndrome			

subjects affected / exposed	1 / 47 (2.13%)	0 / 46 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Diabetic retinopathy			
subjects affected / exposed	0 / 47 (0.00%)	1 / 46 (2.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Depression			
subjects affected / exposed	0 / 47 (0.00%)	1 / 46 (2.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Pyelonephritis			
subjects affected / exposed	1 / 47 (2.13%)	0 / 46 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Diabetes mellitus inadequate control			
subjects affected / exposed	1 / 47 (2.13%)	0 / 46 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemia			
subjects affected / exposed	1 / 47 (2.13%)	2 / 46 (4.35%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Detemir	Glargine	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	33 / 47 (70.21%)	37 / 46 (80.43%)	
Surgical and medical procedures			

Influenza immunisation			
subjects affected / exposed	3 / 47 (6.38%)	0 / 46 (0.00%)	
occurrences (all)	3	0	
Nervous system disorders			
Dizziness			
subjects affected / exposed	3 / 47 (6.38%)	0 / 46 (0.00%)	
occurrences (all)	4	0	
Headache			
subjects affected / exposed	9 / 47 (19.15%)	11 / 46 (23.91%)	
occurrences (all)	16	32	
Migraine			
subjects affected / exposed	0 / 47 (0.00%)	3 / 46 (6.52%)	
occurrences (all)	0	3	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	3 / 47 (6.38%)	6 / 46 (13.04%)	
occurrences (all)	3	15	
Diarrhoea			
subjects affected / exposed	2 / 47 (4.26%)	4 / 46 (8.70%)	
occurrences (all)	2	4	
Nausea			
subjects affected / exposed	5 / 47 (10.64%)	4 / 46 (8.70%)	
occurrences (all)	7	4	
Vomiting			
subjects affected / exposed	5 / 47 (10.64%)	9 / 46 (19.57%)	
occurrences (all)	6	10	
Respiratory, thoracic and mediastinal disorders			
Oropharyngeal pain			
subjects affected / exposed	5 / 47 (10.64%)	2 / 46 (4.35%)	
occurrences (all)	5	5	
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	3 / 47 (6.38%)	3 / 46 (6.52%)	
occurrences (all)	3	4	
Viral upper respiratory tract infection			

subjects affected / exposed	17 / 47 (36.17%)	22 / 46 (47.83%)	
occurrences (all)	30	41	
Metabolism and nutrition disorders			
Hyperglycaemia			
subjects affected / exposed	3 / 47 (6.38%)	5 / 46 (10.87%)	
occurrences (all)	5	8	
Hypoglycaemia			
subjects affected / exposed	2 / 47 (4.26%)	4 / 46 (8.70%)	
occurrences (all)	3	8	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
25 October 2007	Protocol V7 – First working protocol Approved by MREC - 26/10/07
30 May 2008	Protocol V8 - Addition of new prefilled device for injection of Glargine. Approved by MREC 04/06/2008
04 February 2009	Protocol V9 - Addition of new sites. Approved by MREC 16/02/09
01 May 2009	Protocol version 10 - amended to no longer collect blood for HbA1c for central analysis. Correction of serum IGF1, IGFBP-3 instead of plasma. Removal of specifically named measure for waist circumferences. Addition of new sites plus removal of 2 sites. Re-submitted to MREC as Protocol 10.1
18 June 2009	Protocol version 10.1 - Revised inclusion criteria - HbA1c increased to =/<12%. Approved by MREC 15/06/09
10 December 2009	Protocol version 11 - Revision to eligibility criteria. The protocol has therefore been amended to facilitate recruitment and include girls who are in late puberty but have not yet attained menarche. Study timeline revised. List of participating sites was updated. Approved by MREC 02/12/09
20 April 2010	Protocol V12 - revised to include additional information stating what will happen in the event of a positive pregnancy test. Approved by MREC 30/03/2010
08 October 2010	Protocol version 13 - protocol revised to update study timeline, extending recruitment. Update of the list of participating centres. References to the measurement of HbA1c will allow for the change from % to mmol/mol which was coming into effect. The possibility of combining screening (randomisation) and baseline visits into one visit has been allowed for. The use of finger prick HbA1c measurement by some sites means that there is no longer a delay in assessing HbA1c eligibility criteria. The label template for the study drugs has been amended to include the text 'For Clinical Trial Use Only' Approved by MREC 28/09/2010

24 April 2012	Protocol V14 - Revision of Protocol This includes the following:- •Text has been amended to allow for the use of email as well as, or instead of, telephone contact. Introduction of an email contact sheet •List of study sites has been updated – •Method of reporting HbA1C has been changed from DCCT to IFFC in line with recent changes. •Removal of Barry Widmer as Data manager (now left). •Change of text (from in to by) to allow for the possibility of future archiving being off site rather than within the department. • A Protocol section has been created to include information about sponsorship, finance and insurance. •Participant information sheets have been amendment to allow for email as a method of contact. •Consent and Assent forms have been updated to reflect changes to the information sheets. •Once participants have completed the study we would like to thank them for their help. We propose to send out a thank you letter and certificate of achievement. • We propose to send out a letter to participants GPs notifying them that they have now finished the study. Submitted to MREC only
25 February 2013	Protocol V15 - Revision of Protocol. This includes the following: •Text amended throughout the protocol to allow for the exclusion of DEXA scan in centres where access is not available to appropriate facilities and /or software (paediatric) •Participant information sheets amended to allow for the exclusion of DEXA scans •Consent and Assent forms updated to reflect changes to the information sheets •Wording for consent forms amended in Clause 3 so there is uniformity across the forms and in line with ethical recommendations •Minor typo corrections – Primarily BMI SDS minimisation altered from ≤2.5 to < or ≥ 1, and > sign for other minimisation criteria corrected to ≥ •Dr Rachel Williams' role as Co-ordinating Investigator has been recognised •Study time line extended. Submitted to MREC only
02 June 2014	Protocol 16 - •In accordance with the protocol, a Data Monitoring committee has been convened and details listed in the appendix •Detail of a proposed Interim analysis •The list of study sites has been amended and updated •Typo correction to Power Calculation on Page 23 •Clarification that NOVO Nordisk will only be notified of SADR's relating to their product (Detemir) • Appetite assessment forms will only be done at 3,6,9 & 12 month visits, Submitted to MREC only.
25 April 2016	Protocol version 17 - Clarification regarding pregnancy reporting. Additional information defining the end of the study. Additional information relating to document management and archiving. Approved by MREC 04/05/2016

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported