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Liraglutide Efficacy and Action in Non-Alcoholic Steatohepatitis

Submission date	Recruitment status	[X] Prospectively registered
17/02/2010	No longer recruiting	[X] Protocol
Registration date	**Overall study status**	[_] Statistical analysis plan
24/03/2010	Completed	[X] Results
Last Edited	**Condition category**	[_] Individual participant data
03/10/2018	Digestive System	

Plain English summary of protocol
Not provided at time of registration

Contact information

Type(s)
Scientific

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Clinical Trials Information System (CTIS)
2009-016761-29

ClinicalTrials.gov (NCT)
NCT01237119

Protocol serial number
HE2013

Study information

Scientific Title
A 48-week phase II, randomised, double blinded placebo controlled, parallel-group, multicentre trial on liraglutide's safety, efficacy and action on liver histology and metabolism in overweight patients with non-alcoholic steatohepatitis, with or without type II diabetes

Acronym
LEAN

Study objectives
Background:
Non-alcoholic fatty liver disease (NAFLD) is responsible for an increasing prevalence of liver disease and is becoming the commonest cause of liver disease in the western world. NAFLD is recognised to be the hepatic manifestation of the metabolic syndrome, which is a cluster of metabolic abnormalities characterised by abdominal obesity, insulin resistance, impaired glucose metabolism, hypertension and dyslipidaemia. In its mildest form there is an accumulation of fat in the liver (steatosis) without any liver damage, however in many cases it progresses to non-alcoholic steatohepatitis (NASH), and cirrhosis.

Current treatment options for NASH are limited in efficacy, necessitating the development of more effective options. New agents such as Glucagon-like Peptide-1 (GLP-1) agonists that improve diabetic control and facilitate weight loss have been suggested as therapies in NASH.

No published studies to date have assessed the impact of the GLP-1 agonist, Liraglutide, on liver histology and metabolism in obese patients with NASH. This study hypothesises that treatment with liraglutide will result in a significant improvement in histological disease activity in obese patients with NASH, in the presence or absence of Type 2 Diabetes (T2DM).
Objectives

The primary objective is to investigate whether 48 weeks treatment with once-daily injections of liraglutide improves liver histology in overweight patients with NASH enough to warrant further investigation.

The secondary objectives are to investigate whether 48 weeks treatment with once-daily injections of liraglutide in overweight patients with NASH results in a clinically significant effect on the:
1. Individual histological features of NASH including steatosis, hepatocyte inflammation and injury, and fibrosis.
2. Non-invasive clinical markers of steatosis, steatohepatitis and fibrosis.
3. Clinical components of metabolic syndrome
4. Insulin resistance and hepatic lipogenesis
5. Patients Quality of Life (QOL)
6. Clinical safety profile

Ethics approval required
Old ethics approval format

Ethics approval(s)
Leicestershire, Northamptonshire and Rutland Research Ethics Committee 2 approved in May 2010

Study design

Multicentre international phase II double blind randomised placebo controlled parallel group drug efficacy and safety trial

Primary study design
Interventional

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Non-alcoholic Steatohepatitis (NASH)

Interventions
Please note that as of 14/08/2010 this Birmingham, UK site is open/active to recruitment.

1. Placebo/Control Group:
Treatment with once-daily subcutaneous injection of inactive placebo-control (i.e. identical to experiment drug minus the active substance liraglutide - Supplied by Novo Nordisk ®) for 48 weeks.
2. Interverntion group:
Treatment with once-daily subcutaneous injections 1.8mg active Liraglutide (Victoza) (Supplied by Novo Nordisk ®) for 48 weeks.
Group 1 and 2 will contain the same proportion of non-diabetics and Type II diabetics, and the same proportion of patients enrolled from UK and Germany.
Participants will attend two screening visits in the first two weeks. Then if eligible will commence study treatment for 48 weeks (336 days), during which time they will be asked to attend 5 study visits. A follow up visit will take place 24 weeks after completion of 48 weeks study treatment. Therefore the estimated duration of the study is 74 weeks from screening to end of follow up.

Intervention Type
Drug

Phase
Phase II

Drug/device/biological/vaccine name(s)
Liraglutide (Victoza®)

Primary outcome(s)
The primary outcome measure is the proportion of patients with an improvement in liver histology after 48-weeks of treatment as defined by;
1. Disappearance of Steatohepatitis (i.e. Disappearance of hepatocyte ballooning)
2. No worsening of the fibrosis score

Key secondary outcome(s))
1. Change in the NAS pre and post-treatment on liver biopsy, assessed at baseline (from pre-study liver biopsy within 6 months of screening) and 48 weeks
2. Steatosis, lobular inflammation, hepatocyte ballooning and liver fibrosis on liver biopsy, assessed at baseline (from pre-study liver biopsy within 6 months of screening), 48 weeks and follow-up (1 visit 24 weeks after End of Treatment [EOT])

3. Serological markers of steatosis, steatohepatitis and fibrosis using the Fibromax panel, assessed at baseline (screening), 48 weeks and follow-up
4. NAFLD fibrosis score, assessed at baseline (screening), 24 and 48 weeks and follow-up
5. Transient Elastography (Fibroscan®), assessed at baseline (screening), 48 weeks and follow-up
6. Change in weight (Kg), BMI (Kg/m2) and waist:hip ratio, assessed at baseline, 4, 12, 24, 36, 48 weeks and follow-up
6. Glycaemic control (HbA1c, Fasting plasma glucose [central laboratory], fasting self-measured plasma glucose [SMPG]), assessed at baseline, 4, 12, 24, 36, 48 weeks and follow-up
7. Serological markers of insulin sensitivity and lipid profile, assessed at baseline, 12, 24, 26 and 48 weeks
8. Total body, hepatic, muscle, and adipose insulin sensitivity using hyperinsulinaemic euglycaemic and adipose microdialysis studies, assessed at baseline (screening) and 12 weeks
9. De-novo hepatic lipogensis (DNL) using stable isotope experiments, assessed at baseline (screening) and 12 weeks
10. Quality of life (SF-36v2) and Nutrition (Block Brief 2000 FFQ) questionnaires, assessed at baseline (screening), 48 weeks and follow-up
11. Safety measures (History and clinical examination, hypoglycaemia rates, routine bloods tests, TFTs and calcitonin, insulin detemir [Levemir®] and liraglutide [Victoza®] antibodies), assessed at baseline, 4, 12, 24, 36, 48 weeks and follow-up

Completion date
01/06/2013

Eligibility

Key inclusion criteria
1. NASH criteria (all):
1.1. Liver biopsy must be performed within 6 months of screening for the trial.
1.2. 'Definite' diagnosis of NASH by two independent expert histopathologists from the central trial site (Birmingham, UK). (Definite diagnosis of NASH defined as moderate macrovesicular steatosis, hepatocyte ballooning [+/- Mallorys hyaline], and lobular inflammation [mixed infiltrate, related to foci of ballooning] in the presence or absence of fibrosis)
1.3. Non-alcoholic Fatty Liver Disease (NAFLD) Activity Score (NAS) ≥ 3, comprising of a minimum of 1 point from each of the individual steatosis, lobular inflammation and hepatocyte ballooning scores
2. Age ≥ 18, < 70 at randomisation
3. Body Mass Index (BMI) ≥ 25 , ≤45 at randomisation
4. Type 2 Diabetes Mellitus criteria:
4.1. Subjects oral hypoglycaemic therapy at a stable dose for ≥ 3 months prior to randomisation, including one of the following:
4.1.1. Metformin monotherapy
4.1.2. Sulphonylurea monotherapy
4.1.3. Metformin and Sulphonylurea
5. Non-Diabetic criteria (based on two separate fasting plasma glucose levels > 48 hours apart and/or Oral Glucose Tolerance Test [OGTT]):
5.1. Impaired fasting glucose (IFG), defined using the European Criteria between 6.1 and 6.9 mmol/L
and/or
5.2. Impaired glucose tolerance (IGT), defined as two-hour plasma glucose levels between 7.8 and 11.0 mmol/ on the 75-g OGTT
or

5.3. Normal Fasting Plasma Glucose (FPG) < 6.1 mmol and Normal two-hour plasma glucose levels < 7.8 on the 75g OGTT

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 years

Sex
All

Key exclusion criteria
1. Generic exclusion criteria:
1.1. Patients with a BMI > 45 kg/m2
Despite the fact that there is no limit in BMI in the approved labelling of liraglutide, the vast majority of published data that exists from clinical trials for the safety and efficacy of liraglutide in non-diabetic and diabetic patients was in individuals with a BMI of 45 kg/m2 or less.
1.2. Refusal or lacks capacity to give informed consent to participate in the trial
1.3. Participation in any clinical trial of an investigational therapy or agent within 3 months of randomisation
1.4. Patient (or carer) deemed not competent at using the correct site and technique for subcutaneous injection of the trial treatment (containing dummy drug on practice) at visit 2
1.5. Neonatal Abstinence Syndrome (NAS) score < 3
1.6. Childs B or C cirrhosis
1.7. Past medical history of multiple drug allergies (defined as anaphylactoid drug reactions in >2 drug groups)
1.8. Presence of any acute/chronic infections or illness that at the discretion of the chief investigator might compromise the patients health and safety in the trial
1.9. Pregnancy or breastfeeding
1.10. Women, of child-bearing age, who are not willing to practise effective contraception (i.e. barrier, oral contraceptive pill, impenon or PMHx hysterectomy) for the 48 week duration of the trial and for one-month after the last administration of the drug.
1.11. Men, sexually active with women of child-bearing age, who are not willing to practise effective contraception for the 48 week duration of the trial and for one-month after the last administration of the drug.
1.12. Liver disease of other aetiologies (i.e. drug-induced, viral hepatitis, autoimmune hepatitis, PBC, PSC, haemochromatosis, A1AT deficiency, Wilsons disease)
1.13. Past medical/surgery history of;
1.13.1. Gastric bypass surgery
1.13.2. Orthotopic liver transplant (OLT) or listed for OLT
1.13.3. Hepatocellular, pancreatic, thyroid carcinoma
1.13.4. Acute or chronic pancreatitis
1.13.5. Total Parenteral Nutrition within 6 months of randomisation
1.14. Diagnosis of malignancy within the last 3 years (with the exception of treated skin

malignancies)
1.15. Hepatocellular Carcinoma dysplastic or intermediate nodules to be excluded. Borderline cases to be discussed at Birminghams tertiary hepato-biliary multidisciplinary team (MDT) meeting. Regenerative and other nodules to be included at the discretion of the chief investigator and the MDT.
1.16. Clinical evidence of decompensated chronic liver disease:
1.16.1. Radiological or clinical evidence of ascites
1.16.2. Current or previous hepatic encephalopathy
1.16.3. Evidence of portal hypertensive haemorrhage or varices on endoscopy
1.17. Abnormal clinical examination of thyroid (i.e. unexplained goitre or palpable nodules)
1.18. ALT or AST > 10 x upper limit of normal
1.19. Average alcohol consumption per week > 21 units (168g) male, >14 units (112g) female within the last 5 years.
1.20. >5% weight loss since the diagnostic liver biopsy was obtained.
1.21. Recent or concomitant use of the following drugs within 6 months of randomisation;
1.21.1. Inducers of Hepatic steatosis steroids (oral), methotrexate, amiodarone
1.21.2. Weight-reducing therapies Orlistat, Sibutramine
1.22. Addition or significant change (as judged by the chief investigator) in dose of the following drugs, within 6 months of randomisation;
1.22.1. Angiotensin converting enzymes (ACE)-inhibitors
1.22.2. Angiotensin receptor blockers (ARBs)
1.22.3. Multi-vitamins (containing Vitamin E)
1.23. Known positivity for antibody to Human Immunodeficiency virus (HIV)
1.24. Serum creatinine > 150 µmol/L or currently being treated with renal replacement therapy (i. e. Haemodialysis or Peritoneal Dialysis)
2. Subjects with Type II Diabetes exclusion criteria:
2.1. Current or previous insulin therapy, with exception of previous short-term insulin treatment in connection with intercurrent illness is allowed (≥ 3 months prior to screening), at the discretion of the chief investigator.
2.1. Subjects receiving Thiazolidinediones (TZDs), Dipeptidy Peptidase (DPP) IV inhibitors and other GLP-1 agonists (i.e. Exenatide)
2.3. HbA1c ≥ 9.0%
2.4. Recurrent major hypoglycaemia or hypoglycaemic unawareness as judged by the chief investigator

Date of first enrolment
01/06/2010

Date of final enrolment
01/06/2013

Locations

Countries of recruitment
United Kingdom

England

Germany

Study participating centre
University of Birmingham
Birmingham
United Kingdom
B15 2TT

Sponsor information

Organisation
University of Birmingham (UK)

ROR
https://ror.org/03angcq70

Funder(s)

Funder type
Research organisation

Funder Name
Wellcome Trust (UK)

Alternative Name(s)

Funding Body Type
Private sector organisation

Funding Body Subtype
International organizations

Location
United Kingdom

Funder Name
Novo Nordisk (Denmark)

Alternative Name(s)
Novo Nordisk Global

Funding Body Type
Private sector organisation

Funding Body Subtype
For-profit companies (industry)

Location
Denmark

Results and Publications

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	01/02/2016		Yes	No
Results article	results	13/02/2016		Yes	No
Protocol article	protocol	04/11/2013		Yes	No