



Clinical trial results:

A 48-WEEK PHASE II, RANDOMISED, DOUBLE BLINDED PLACEBO CONTROLLED, PARALLEL-GROUP, MULTI-CENTRE 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

Summary

| | |
|--------------------------|----------------|
| EudraCT number | 2009-016761-29 |
| Trial protocol | GB |
| Global end of trial date | 02 July 2014 |

Results information

| | |
|-----------------------------------|---|
| Result version number | v1 (current) |
| This version publication date | 26 September 2020 |
| First version publication date | 26 September 2020 |
| Summary attachment (see zip file) | Lean Study Protocol V7.0 (Protocol version 7.0 (Cleaned).pdf) |

Trial information

Trial identification

| | |
|-----------------------|-----------|
| Sponsor protocol code | RG_09-190 |
|-----------------------|-----------|

Additional study identifiers

| | |
|------------------------------------|---|
| ISRCTN number | ISRCTN85774727 |
| ClinicalTrials.gov id (NCT number) | NCT01237119 |
| WHO universal trial number (UTN) | - |
| Other trial identifiers | UK Competent authority (MHRA) Reference: 21761/0247/001-0001, NHS (UK) Ethics Ref number: 10/H0402/32 |

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | The University of Birmingham |
| Sponsor organisation address | Research Support Group, Finance Office, Aston Webb building, Birmingham, United Kingdom, B15 2TT |
| Public contact | Dr Sean Jennings, The University of Birmingham, +44 (0)121 415 8011, s.jennings@bham.ac.uk |
| Scientific contact | Professor Philip Newsome, The University of Birmingham, +44 (0)121 414 5614, p.n.newsone@bham.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 | 20 August 2015 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 02 July 2014 |
| Global end of trial reached? | Yes |
| Global end of trial date | 02 July 2014 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

To investigate the safety and efficacy of 48 weeks treatment with once-daily injections of liraglutide in damaged liver tissue in overweight patients with non-alcoholic steatohepatitis [NASH] (i.e. the more severe, inflammatory form of fatty liver disease). To investigate whether the effect of liraglutide on NASH warrants further investigation.

Protection of trial subjects:

No specific measures were included within the study protocol specifically for the protection of trial subjects outside the normal safety monitoring that is included in a phase II (safety and efficacy) study. This monitoring included, but not limited to blood tests (Full blood counts and Biochemistry panel); physical exam and collection/evaluation of adverse event and serious adverse event data. These procedures were performed/repeated at multiple visits throughout the treatment period (monthly - 3 monthly visits) and the results of these procedures were recorded in the Case Report Form (CRF)

In addition a facility for 24/7 unblinding of study medication was available for medical physicians if required. This could be accessed by any physician who was treating a patient irrespective of whether they were directly involved in the clinical study. Trial subjects were provided with a participant study card which included details of the clinical trial and 24/7 emergency number. Limited medical advice was also available from this resource.

Background therapy:

The study did not include any Non-Investigational Medicinal Products (NIMPS). A full record of any medications that a trial subject was taking during the study period was recorded in the individual subjects Case Report Form (Concomitant medication page).

Evidence for comparator:

This clinical trial was a randomised, double blind phase II safety and efficacy study. The comparator was a liraglutide-matched Placebo provided by Novo-Nordisk Ltd (UK). The placebo included everything except the active ingredient.

| | |
|---|-----------------|
| Actual start date of recruitment | 19 October 2010 |
| 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: 52 |
| Worldwide total number of subjects | 52 |
| EEA total number of subjects | 52 |

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) | 0 |
| Adults (18-64 years) | 49 |
| From 65 to 84 years | 3 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

All trial participants were recruited / randomised into the clinical study between 19th October 2010 and 3rd May 2013. The trial participants were all recruited in the United Kingdom from 4 participating centres; Queen Elizabeth Hospital: Birmingham, Queens Medical Centre: Nottingham, Hull Royal Infirmary: Hull, St James University Hospital: Leeds

Pre-assignment

Screening details:

Patients were screened using study inclusion and exclusion criteria detailed in the study protocol.

Key screening inclusion criteria were:

1. Age ≥ 18
2. BMI ≥ 25
3. Non-alcoholic steatohepatitis (NASH): Kleiner classification on liver biopsy within ≤ 6 months prior to randomisation.

Presence of any other liver aetiologies were excluded

Period 1

| | |
|------------------------------|---|
| Period 1 title | Randomisation |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |
| Roles blinded | Subject, Investigator, Monitor, Carer, Assessor |

Blinding implementation details:

After screening and completion of the inclusion / exclusion criterion patients were randomly assigned to either treatment or placebo on a 1:1 basis using a computer generated randomisation. This randomisation was stratified to ensure equal numbers in each treatment group. Stratification variables were;

1. Type II diabetes (vs. non-diabetics)
2. Trial/ participating centre

All randomised patients were allocated a unique trial identification number.

Arms

| | |
|------------------------------|---------|
| Are arms mutually exclusive? | Yes |
| Arm title | Group 1 |

Arm description:

Control group: Treatment with once daily subcutaneous injection of inactive treatment (liraglutide placebo) - supplied by Novo Nordisk Ltd, UK.

| | |
|--|---|
| Arm type | Placebo |
| Investigational medicinal product name | liraglutide placebo - supplied by Novo Nordisk Ltd, UK. |
| Investigational medicinal product code | PLACEBO |
| Other name | |
| Pharmaceutical forms | Injection |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

1.8mg daily after a 14 day dose escalation period

| | |
|------------------|---------|
| Arm title | Group 2 |
|------------------|---------|

Arm description:

Group 2: Experimental group. Treatment with once daily subcutaneous injections 1.8 mg active liraglutide (Victoza) supplied by Novo Nordisk Ltd, UK

| | |
|----------|--------------|
| Arm type | Experimental |
|----------|--------------|

| | |
|--|------------------|
| Investigational medicinal product name | Liraglutide |
| Investigational medicinal product code | Active |
| Other name | Victoza |
| Pharmaceutical forms | Injection |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

1.8mg Subcutaneous daily injection after a 2 week dose escalation period for a period of 48 weeks.

| Number of subjects in period 1 | Group 1 | Group 2 |
|--------------------------------|---------|---------|
| Started | 26 | 26 |
| Completed | 26 | 26 |

Period 2

| | |
|------------------------------|---|
| Period 2 title | On Study Treatment and Follow-up |
| Is this the baseline period? | No |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |
| Roles blinded | Subject, Investigator, Monitor, Carer, Assessor |

Blinding implementation details:

After screening and completion of the inclusion / exclusion criterion patients were randomly assigned to either treatment or placebo on a 1:1 basis using a computer generated randomisation. This randomisation was stratified to insure equal numbers in each treatment group. Stratification variables were;

1. Type II diabetes (vs. non-diabetics)
2. Trial/ participating centre

All randomised patients were allocated a unique trial identification number which was used to identify the patient.

Arms

| | |
|------------------------------|-------------------|
| Are arms mutually exclusive? | Yes |
| Arm title | Group 1 - Placebo |

Arm description:

Placebo

| | |
|--|---|
| Arm type | Placebo |
| Investigational medicinal product name | liraglutide placebo - supplied by Novo Nordisk Ltd, UK. |
| Investigational medicinal product code | PLACEBO |
| Other name | |
| Pharmaceutical forms | Injection |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

1.8mg daily after a 14 day dose escalation period

| | |
|------------------|--|
| Arm title | Group 2 - Liraglutide - Active Treatment Group |
|------------------|--|

Arm description:

Active- experimental

| | |
|--|------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Liraglutide |
| Investigational medicinal product code | Active |
| Other name | Victoza |
| Pharmaceutical forms | Injection |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

1.8mg Subcutaneous daily injection after a 2 week dose escalation period for a period of 48 weeks.

| Number of subjects in period 2 | Group 1 - Placebo | Group 2 - Liraglutide - Active Treatment Group |
|---|-------------------|--|
| | | |
| Started | 26 | 26 |
| Completed | 22 | 23 |
| Not completed | 4 | 3 |
| end Trt / No end of study biopsy- Patient choice | 3 | - |
| patient choice- end Trt/ No biospy @ 48 week | - | 3 |
| No Treatment received / ineligible after entry | 1 | - |

Baseline characteristics

Reporting groups

| | |
|---|---------|
| Reporting group title | Group 1 |
| Reporting group description: | |
| Control group: Treatment with once daily subcutaneous injection of inactive treatment (liraglutide placebo) - supplied by Novo Nordisk Ltd, UK. | |
| Reporting group title | Group 2 |
| Reporting group description: | |
| Group 2: Experimental group. Treatment with once daily subcutaneous injections 1.8 mg active liraglutide (Victoza) supplied by Novo Nordisk Ltd, UK | |

| Reporting group values | Group 1 | Group 2 | Total |
|---|---------|---------|-------|
| Number of subjects | 26 | 26 | 52 |
| Age categorical | | | |
| Units: Subjects | | | |
| Adults (18-64 years) | 24 | 25 | 49 |
| From 65-84 years | 2 | 1 | 3 |
| 85 years and over | 0 | 0 | 0 |
| Age continuous | | | |
| Age | | | |
| Units: years | | | |
| arithmetic mean | 52 | 50 | |
| standard deviation | ± 12 | ± 11 | - |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 13 | 8 | 21 |
| Male | 13 | 18 | 31 |
| Race | | | |
| Units: Subjects | | | |
| Asian (south Asian or oriental) | 1 | 1 | 2 |
| Black (African or caribbean) | 0 | 1 | 1 |
| Other (Including Mixed) | 2 | 1 | 3 |
| White | 23 | 23 | 46 |
| Smoking History | | | |
| Units: Subjects | | | |
| current smoker | 2 | 2 | 4 |
| ex-smoker | 13 | 8 | 21 |
| never smoked | 11 | 16 | 27 |
| Sex | | | |
| Units: Subjects | | | |
| Male | 18 | 13 | 31 |
| Female | 8 | 13 | 21 |
| Definite NASH | | | |
| Definite NASH | | | |
| Units: Subjects | | | |
| Positive | 26 | 26 | 52 |
| Kleiner fibrosis stages | | | |
| Kleiner fibrosis stages F0-F2 and F3-F4 | | | |

| | | | |
|--|-------|-------|----|
| Units: Subjects | | | |
| F0-F2 | 11 | 14 | 25 |
| F3-F4 | 15 | 12 | 27 |
| Comorbidity - Type II Diabetes | | | |
| Units: Subjects | | | |
| Yes | 8 | 9 | 17 |
| No | 18 | 17 | 35 |
| Comorbidity - Hyperlipidaemia | | | |
| Units: Subjects | | | |
| Yes | 7 | 9 | 16 |
| No | 19 | 17 | 36 |
| Comorbidity - Hypertension | | | |
| Units: Subjects | | | |
| Yes | 14 | 13 | 27 |
| No | 12 | 13 | 25 |
| Comorbidity - Cardiovascular disease | | | |
| Units: Subjects | | | |
| Yes | 3 | 0 | 3 |
| No | 23 | 26 | 49 |
| Comorbidity - Thyroid Disease | | | |
| Units: Subjects | | | |
| Yes | 4 | 3 | 7 |
| No | 22 | 23 | 45 |
| Concomitant Drug Use - Metformin | | | |
| Units: Subjects | | | |
| Yes | 8 | 9 | 17 |
| No | 18 | 17 | 35 |
| Concomitant Drug Use - Sulfonylurea | | | |
| Units: Subjects | | | |
| Yes | 1 | 1 | 2 |
| No | 25 | 25 | 50 |
| Concomitant Drug Use - Anti-lipidaemic | | | |
| Units: Subjects | | | |
| Yes | 7 | 10 | 17 |
| No | 19 | 16 | 35 |
| Concomitant Drug Use - Anti-hypertensive | | | |
| Units: Subjects | | | |
| Yes | 12 | 13 | 25 |
| No | 14 | 13 | 27 |
| Concomitant Drug Use - Anti-platelet | | | |
| Units: Subjects | | | |
| Yes | 5 | 5 | 10 |
| no | 21 | 21 | 42 |
| Glucose | | | |
| Glucose (mmol/L) | | | |
| Units: mmol/L | | | |
| arithmetic mean | 6.1 | 6.0 | |
| standard deviation | ± 1.5 | ± 1.7 | - |
| Insulin | | | |
| Insulin (pmol/L) | | | |

| | | | |
|---|--------|--------|---|
| Units: pmol/L | | | |
| arithmetic mean | 257 | 166 | |
| standard deviation | ± 289 | ± 80 | - |
| HOMA-IR | | | |
| HOMA-IR (mmol.IU.L) (glucose [mmol/L] × insulin[mmol × U/L]) | | | |
| Units: mmol.IU.L | | | |
| arithmetic mean | 9.6 | 6.7 | |
| standard deviation | ± 9.8 | ± 4.7 | - |
| HbA1c | | | |
| HbA1c mmol/mol | | | |
| Units: mmol/mol | | | |
| arithmetic mean | 42.4 | 6.0 | |
| standard deviation | ± 9.3 | ± 0.9 | - |
| HbA1c (%) | | | |
| HbA1c (%) | | | |
| Units: Percent % | | | |
| arithmetic mean | 6.0 | 5.9 | |
| standard deviation | ± 0.9 | ± 0.7 | - |
| NEFA | | | |
| NEFA | | | |
| Units: Micro mol / L | | | |
| arithmetic mean | 836 | 967 | |
| standard deviation | ± 368 | ± 535 | - |
| ADIPO-IR | | | |
| ADIPO-IR (mmol.IU.L) | | | |
| Units: mmol.IU.L | | | |
| arithmetic mean | 30.5 | 22.2 | |
| standard deviation | ± 42.7 | ± 12.7 | - |
| Weight (kg) | | | |
| Weight (kg) | | | |
| Units: kg | | | |
| arithmetic mean | 108 | 101 | |
| standard deviation | ± 18 | ± 18 | - |
| Body mass index | | | |
| Body mass index (Kg/m2) | | | |
| Units: Kg/m2 | | | |
| arithmetic mean | 37.7 | 34.2 | |
| standard deviation | ± 6.2 | ± 4.7 | - |
| Waist circumference | | | |
| Waist circumference (cm) | | | |
| Units: cm | | | |
| arithmetic mean | 120 | 110 | |
| standard deviation | ± 15 | ± 11 | - |
| Systolic blood pressure | | | |
| Systolic blood pressure (mmHg) | | | |
| Units: mmHg | | | |
| arithmetic mean | 133 | 130 | |
| standard deviation | ± 12 | ± 13 | - |
| Diastolic blood pressure | | | |
| Diastolic blood pressure (mmHg) | | | |
| Units: mmHg | | | |

| | | | |
|---|-------|-------|---|
| arithmetic mean | 78 | 79 | |
| standard deviation | ± 9 | ± 11 | - |
| Total cholesterol | | | |
| Total cholesterol (mmol/L) | | | |
| Units: mmol/L | | | |
| arithmetic mean | 5.0 | 4.5 | |
| standard deviation | ± 1.2 | ± 1.1 | - |
| High density lipoprotein | | | |
| High density lipoprotein (mmol/L) | | | |
| Units: mmol/L | | | |
| arithmetic mean | 1.3 | 1.1 | |
| standard deviation | ± 0.2 | ± 0.4 | - |
| Low density lipoprotein | | | |
| Low density lipoprotein (mmol/L) Low density lipoprotein (LDL) calculated using the Friedwald formula. LDL= Total Cholesterol -HDL- (Triglycerides / 2.1929). | | | |
| Units: mmol/L | | | |
| arithmetic mean | 2.9 | 2.6 | |
| standard deviation | ± 1.0 | ± 0.8 | - |
| Triglycerides | | | |
| Triglycerides (mmol/L) | | | |
| Units: mmol/L | | | |
| arithmetic mean | 1.8 | 1.9 | |
| standard deviation | ± 0.8 | ± 1.1 | - |
| Creatinine | | | |
| Creatinine (µmol/L) | | | |
| Units: micro mol/L | | | |
| arithmetic mean | 71 | 83 | |
| standard deviation | ± 15 | ± 20 | - |
| Alanine aminotransferase | | | |
| Alanine aminotransferase (IU/L) | | | |
| Units: IU/L | | | |
| arithmetic mean | 66 | 77 | |
| standard deviation | ± 42 | ± 34 | - |
| Aspartate aminotransferase | | | |
| Aspartate aminotransferase (IU/L) | | | |
| Units: IU/L | | | |
| arithmetic mean | 51 | 51 | |
| standard deviation | ± 27 | ± 22 | - |
| Gamma-glutamyl transferase | | | |
| Gamma-glutamyl transferase (IU/L) | | | |
| Units: IU/L | | | |
| arithmetic mean | 115 | 91 | |
| standard deviation | ± 174 | ± 69 | - |
| Alkaline phosphatase | | | |
| Alkaline phosphatase (IU/L) | | | |
| Units: IU/L | | | |
| arithmetic mean | 87 | 76 | |
| standard deviation | ± 41 | ± 25 | - |
| Total bilirubin | | | |
| Total bilirubin (µmol/L) | | | |
| Units: µmol/L | | | |

| | | | |
|---|-------|-------|---|
| arithmetic mean | 13 | 13 | |
| standard deviation | ± 7 | ± 5 | - |
| Albumin | | | |
| Albumin (g/L) | | | |
| Units: g/L | | | |
| arithmetic mean | 43 | 45 | |
| standard deviation | ± 5 | ± 6 | - |
| Cytokeratin-18 M30 | | | |
| Cytokeratin-18 M30 (IU/L) | | | |
| Units: IU/L | | | |
| arithmetic mean | 352 | 394 | |
| standard deviation | ± 370 | ± 304 | - |
| Enhanced Liver Fibrosis (ELF) test | | | |
| Enhanced Liver Fibrosis (ELF) test | | | |
| Units: Enhanced Liver Fibrosis (ELF) test | | | |
| arithmetic mean | 9.4 | 9.3 | |
| standard deviation | ± 1.3 | ± 0.9 | - |
| SF-36, physical component | | | |
| SF-36, physical component | | | |
| Quality of Life | | | |
| Units: Score | | | |
| arithmetic mean | 40 | 45 | |
| standard deviation | ± 13 | ± 11 | - |
| SF-36, mental component | | | |
| SF-36, mental component | | | |
| Quality of Life | | | |
| Units: Score | | | |
| arithmetic mean | 45 | 51 | |
| standard deviation | ± 14 | ± 10 | - |
| Dietary consumption Total calories | | | |
| Dietary consumption (Block FFQ) | | | |
| Total calories (Kcal) | | | |
| Units: Kcal | | | |
| arithmetic mean | 1926 | 1885 | |
| standard deviation | ± 677 | ± 700 | - |
| Dietary consumption Total protein | | | |
| Dietary consumption (Block FFQ) | | | |
| Total protein (g) | | | |
| Units: grams | | | |
| arithmetic mean | 70 | 72 | |
| standard deviation | ± 25 | ± 34 | - |
| Dietary consumption Total fat | | | |
| Dietary consumption (Block FFQ) | | | |
| Total fat (g) | | | |
| Units: grams | | | |
| arithmetic mean | 74 | 71 | |
| standard deviation | ± 35 | ± 30 | - |
| Dietary consumption Total carbohydrate | | | |
| Dietary consumption (Block FFQ) | | | |
| Total carbohydrate (g) | | | |
| Units: grams | | | |
| arithmetic mean | 248 | 240 | |
| standard deviation | ± 89 | ± 87 | - |
| Dietary consumption Caffeine | | | |

| | | | |
|--|-------|-------|---|
| Dietary consumption (Block FFQ) Caffeine (mg) | | | |
| Units: mg | | | |
| arithmetic mean | 26 | 21 | |
| standard deviation | ± 45 | ± 30 | - |
| Dietary consumption Alcohol | | | |
| Dietary consumption (Block FFQ) Alcohol (g) | | | |
| Units: grams | | | |
| arithmetic mean | 4.8 | 6.3 | |
| standard deviation | ± 8.4 | ± 8.3 | - |
| NAFLD activity score | | | |
| Liver histology Total NAFLD activity score (0-8) | | | |
| Units: Score | | | |
| arithmetic mean | 4.8 | 4.9 | |
| standard deviation | ± 0.9 | ± 0.9 | - |
| Hepatocyte ballooning score | | | |
| Liver histology Hepatocyte ballooning score (0-2) | | | |
| Units: Score | | | |
| arithmetic mean | 1.5 | 1.5 | |
| standard deviation | ± 0.4 | ± 0.5 | - |
| Steatosis score | | | |
| Liver histology Steatosis score (0-3) | | | |
| Units: Score | | | |
| arithmetic mean | 1.9 | 2.1 | |
| standard deviation | ± 0.7 | ± 0.7 | - |
| Lobular inflammation score | | | |
| Liver histology Lobular inflammation score (0-3) | | | |
| Units: Score | | | |
| arithmetic mean | 1.4 | 1.4 | |
| standard deviation | ± 0.4 | ± 0.3 | - |
| Kleiner fibrosis stage | | | |
| Liver histology Kleiner fibrosis stage (0-4) | | | |
| Units: Score | | | |
| arithmetic mean | 2.3 | 2.3 | |
| standard deviation | ± 1.3 | ± 0.9 | - |
| Liver biopsy length | | | |
| Liver biopsy length | | | |
| Units: mm | | | |
| arithmetic mean | 19.7 | 21.0 | |
| standard deviation | ± 5.7 | ± 7.6 | - |
| Number of portal tracts | | | |
| Liver Histology Number of portal tracts | | | |
| Units: Count | | | |
| arithmetic mean | 16.2 | 18.5 | |
| standard deviation | ± 5.3 | ± 7.1 | - |

End points

End points reporting groups

| | |
|---|--|
| Reporting group title | Group 1 |
| Reporting group description: Control group: Treatment with once daily subcutaneous injection of inactive treatment (liraglutide placebo) - supplied by Novo Nordisk Ltd, UK. | |
| Reporting group title | Group 2 |
| Reporting group description: Group 2: Experimental group. Treatment with once daily subcutaneous injections 1.8 mg active liraglutide (Victoza) supplied by Novo Nordisk Ltd, UK | |
| Reporting group title | Group 1 - Placebo |
| Reporting group description: Placebo | |
| Reporting group title | Group 2 - Liraglutide - Active Treatment Group |
| Reporting group description: Active- experimental | |
| Subject analysis set title | Evaluable Patient Set |
| Subject analysis set type | Modified intention-to-treat |
| Subject analysis set description: All randomised patients that were evaluable with biopsy at the 48 weeks endpoint irrespective of treatment received. | |
| Subject analysis set title | Safety patient cohort (ITT) |
| Subject analysis set type | Safety analysis |
| Subject analysis set description: All randomised patients as per intention to treat. | |

Primary: Histology: clearance of NASH and no worsening of fibrosis

| | |
|---|---|
| End point title | Histology: clearance of NASH and no worsening of fibrosis |
| End point description: Action number is the proportion of patients with an improvement in liver histology between biopsy at baseline and biopsy after 48 weeks of treatment: The definition of an improvement in liver histology requires both of the following; - Disappearance of NASH (defined as a disappearance of hepatocyte ballooning) AND No worsening of fibrosis. Liver biopsy results were reviewed by two independent pathologists that were blinded to the study group/ treatment. | |
| End point type | Primary |
| End point timeframe: Baseline (Screening within 6 months of randomisation) - End of treatment (within 14 days). A protocol defined treatment (completion of) is 48 weeks | |

| End point values | Group 1 - Placebo | Group 2 - Liraglutide - Active Treatment Group | | |
|-----------------------------|-------------------|--|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 22 | 23 | | |
| Units: number | 2 | 9 | | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | Histological |
| Comparison groups | Group 1 - Placebo v Group 2 - Liraglutide - Active Treatment Group |
| Number of subjects included in analysis | 45 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.019 |
| Method | Chi-squared |
| Parameter estimate | Risk ratio (RR) |
| Point estimate | 4.3 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1 |
| upper limit | 17.7 |
| Variability estimate | Standard error of the mean |

Secondary: Effect of treatment on individual histological features of Non-alcoholic steatohepatitis (NASH)

| | |
|--|---|
| End point title | Effect of treatment on individual histological features of Non-alcoholic steatohepatitis (NASH) |
| End point description: The liver biopsy's (baseline and end of treatment) were reviewed by two independent pathologists and the individual features of NASH including; 1. Steatosis 2. Hepatocyte inflammation and injury 3. Fibrosis Histological measures (change between baseline and end of treatment biopsy for individual patients) included; 1. Calculation of the mean changes in NAFLD activity score (NAS) between the two treatment groups. 2. Changes in the independent features of NAS; Steatosis, lobular inflammation and hepatocyte ballooning between the two treatment groups. 3. Changes in fibrosis stage according to Kleiner Non-Alcoholic Fatty Liver Disease (NAFLD) fibrosis score (F0-F4) between the two treatment groups. | |
| End point type | Secondary |
| End point timeframe: Baseline (within 6 months of randomisation date) and within 7 days of end of study treatment (maximum protocol defined treatment duration 48 weeks) | |

| End point values | Group 1 - Placebo | Group 2 - Liraglutide - Active Treatment Group | | |
|-------------------------------------|-------------------|--|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 22 | 23 | | |
| Units: Patient numbers / percentage | 22 | 23 | | |

| | |
|-----------------------------------|--|
| Attachments (see zip file) | Histology Data/1 EudraCT Histology.pdf |
|-----------------------------------|--|

Statistical analyses

| | |
|---|--|
| Statistical analysis title | Changes from baseline for NAS. |
| Statistical analysis description: Changes from baseline in histopathological parameters - Total NAFLD activity score | |
| Comparison groups | Group 1 - Placebo v Group 2 - Liraglutide - Active Treatment Group |
| Number of subjects included in analysis | 45 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.24 ^[1] |
| Method | Regression, Linear |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.5 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.3 |
| upper limit | 0.3 |

Notes:

[1] - From linear regression (equivalent to ANCOVA).

| | |
|---|--|
| Statistical analysis title | Patients with improvement in NAS |
| Statistical analysis description: Changes from baseline in histopathological parameters - Patients with improvement in NAS | |
| Comparison groups | Group 1 - Placebo v Group 2 - Liraglutide - Active Treatment Group |
| Number of subjects included in analysis | 45 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.46 |
| Method | Chi-squared |
| Parameter estimate | Risk ratio (RR) |
| Point estimate | 1.2 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.8 |
| upper limit | 1.7 |

| | |
|---|--|
| Statistical analysis title | Hepatocyte ballooning score - mean change |
| Statistical analysis description: | |
| Changes from baseline in histopathological parameters | |
| Comparison groups | Group 1 - Placebo v Group 2 - Liraglutide - Active Treatment Group |
| Number of subjects included in analysis | 45 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.15 |
| Method | Regression, Linear |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.3 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.7 |
| upper limit | 0.1 |

| | |
|---|--|
| Statistical analysis title | Patients with improved Hepatocyte ballooning |
| Statistical analysis description: | |
| Changes from baseline in histopathological parameters | |
| Hepatocyte ballooning score - N improved | |
| Patients with improvement | |
| Comparison groups | Group 1 - Placebo v Group 2 - Liraglutide - Active Treatment Group |
| Number of subjects included in analysis | 45 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.05 |
| Method | Chi-squared |
| Parameter estimate | Risk ratio (RR) |
| Point estimate | 1.9 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1 |
| upper limit | 3.8 |

| | |
|---|--|
| Statistical analysis title | Steatosis - Change in Score |
| Statistical analysis description: | |
| Changes from baseline in histopathological parameters | |
| Steatosis | |
| Change in score | |
| Comparison groups | Group 1 - Placebo v Group 2 - Liraglutide - Active Treatment Group |

| | |
|---|--------------------------------|
| Number of subjects included in analysis | 45 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.32 |
| Method | Regression, Linear |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.2 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.6 |
| upper limit | 0.2 |

| | |
|-----------------------------------|--|
| Statistical analysis title | Patients with improvement in Steatosis |
|-----------------------------------|--|

Statistical analysis description:

Changes from baseline in histopathological parameters

Steatosis

Patients with improvement

| | |
|---|--|
| Comparison groups | Group 1 - Placebo v Group 2 - Liraglutide - Active Treatment Group |
| Number of subjects included in analysis | 45 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.009 |
| Method | Chi-squared |
| Parameter estimate | Risk ratio (RR) |
| Point estimate | 1.8 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.1 |
| upper limit | 3 |

| | |
|---|--|
| Statistical analysis title | Lobular inflammation score - mean change |
| Comparison groups | Group 1 - Placebo v Group 2 - Liraglutide - Active Treatment Group |
| Number of subjects included in analysis | 45 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.97 |
| Method | Regression, Linear |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.01 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.3 |
| upper limit | 0.3 |

| | |
|--|--|
| Statistical analysis title | Patients with improvement in Lobular Inflammation |
| Statistical analysis description: Changes from baseline in histopathological parameters Lobular inflammation - Patients with improvement | |
| Comparison groups | Group 1 - Placebo v Group 2 - Liraglutide - Active Treatment Group |
| Number of subjects included in analysis | 45 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.65 |
| Method | Chi-squared |
| Parameter estimate | Risk ratio (RR) |
| Point estimate | 0.9 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.5 |
| upper limit | 1.6 |

| | |
|--|--|
| Statistical analysis title | Kleiner Fibrosis score - mean change |
| Statistical analysis description: Changes from baseline in histopathological parameters | |
| Comparison groups | Group 1 - Placebo v Group 2 - Liraglutide - Active Treatment Group |
| Number of subjects included in analysis | 45 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.11 |
| Method | Regression, Linear |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.4 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.8 |
| upper limit | 0.1 |

| | |
|-----------------------------------|--|
| Statistical analysis title | Patients with improvement in Kleiner Fibrosis |
| Comparison groups | Group 1 - Placebo v Group 2 - Liraglutide - Active Treatment Group |

| | |
|---|-----------------|
| Number of subjects included in analysis | 45 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.46 |
| Method | Fisher exact |
| Parameter estimate | Risk ratio (RR) |
| Point estimate | 1.9 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.5 |
| upper limit | 6.7 |

| | |
|-----------------------------------|---|
| Statistical analysis title | Patients with worsening in Kleiner Fibrosis |
|-----------------------------------|---|

Statistical analysis description:

Changes from baseline in histopathological parameters

Patients with worsening LIRAGLUTIDE - 2 (9%) PLACEBO - 8 (36%)

| | |
|---|--|
| Comparison groups | Group 1 - Placebo v Group 2 - Liraglutide - Active Treatment Group |
| Number of subjects included in analysis | 45 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.04 |
| Method | Fisher exact |
| Parameter estimate | Risk ratio (RR) |
| Point estimate | 0.2 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.1 |
| upper limit | 1 |

Secondary: Change to weight, BMI and waist: hip Circumference

| | |
|-----------------|--|
| End point title | Change to weight, BMI and waist: hip Circumference |
|-----------------|--|

End point description:

Each participants weight (kg), height (cm), waist and hip circumferences were measured at visits 1-8 (except visit 2) in order to calculate each individual patients body mass index (BMI) (Kg/m²) and waist: hip circumference.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Data recorded during the clinical trial at multiple time points between baseline (visit 1) and 3 months post end of treatment visit.

| End point values | Group 1 - Placebo | Group 2 - Liraglutide - Active Treatment Group | | |
|-------------------------------|-------------------|--|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 22 | 23 | | |
| Units: Numbers and percentage | 22 | 23 | | |

| | |
|-----------------------------------|--|
| Attachments (see zip file) | Fig 3a Abs Weight.pdf Fig 2a Weight.pdf Physical Data/1 EudraCT Physical.pdf |
|-----------------------------------|--|

Statistical analyses

| | |
|---|--|
| Statistical analysis title | Changes from baseline for Weight |
| Statistical analysis description: Absolute weight (kg) Lira change -5.3 (4.7) Placebo change -0.6 (4.4) | |
| Comparison groups | Group 1 - Placebo v Group 2 - Liraglutide - Active Treatment Group |
| Number of subjects included in analysis | 45 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.003 ^[2] |
| Method | Regression, Linear |
| Parameter estimate | Mean difference (net) |
| Point estimate | -4.39 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -7.19 |
| upper limit | -1.59 |

Notes:

[2] - *p values and adjusted treatment changes determined by linear regression analysis regressing change on the baseline characteristic score and treatment

| | |
|---|--|
| Statistical analysis title | Changes from baseline for BMI |
| Comparison groups | Group 1 - Placebo v Group 2 - Liraglutide - Active Treatment Group |
| Number of subjects included in analysis | 45 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.005 ^[3] |
| Method | Regression, Linear |
| Parameter estimate | Mean difference (net) |
| Point estimate | -1.59 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.66 |
| upper limit | -0.51 |

Notes:

[3] - *p values and adjusted treatment changes determined by linear regression analysis regressing change on the baseline characteristic score and treatment

| | |
|---|--|
| Statistical analysis title | Changes from baseline for Waist circumference |
| Statistical analysis description: Waist circumference (cm) | |
| Comparison groups | Group 1 - Placebo v Group 2 - Liraglutide - Active Treatment Group |
| Number of subjects included in analysis | 45 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.29 ^[4] |
| Method | Regression, Linear |
| Parameter estimate | Mean difference (net) |
| Point estimate | -2.54 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -7.32 |
| upper limit | 2.25 |

Notes:

[4] - *p values and adjusted treatment changes determined by linear regression analysis regressing change on the baseline characteristic score and treatment.

Secondary: Quality of Life (SF-36) / AUDIT

| | |
|--|---------------------------------|
| End point title | Quality of Life (SF-36) / AUDIT |
| End point description: The SF36 (version 2.0) was used /requested at three protocol defined time points (Visit 1, 7 and 8). | |
| End point type | Secondary |
| End point timeframe: Data recorded during the clinical trial at multiple time points between baseline (visit 1) and 3 months post end of treatment visit. | |

| End point values | Group 1 - Placebo | Group 2 - Liraglutide - Active Treatment Group | | |
|--------------------------------------|-------------------|--|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 22 | 23 | | |
| Units: SF-36 score | | | | |
| arithmetic mean (standard deviation) | -0.5 (± 8.0) | 1.9 (± 5.1) | | |

| | |
|-----------------------------------|---|
| Attachments (see zip file) | Questionnaires/1 EudraCT Questionnaires.pdf |
|-----------------------------------|---|

Statistical analyses

| | |
|--|--|
| Statistical analysis title | Quality of Life Physical Component |
| Statistical analysis description: Quality of life (SF-36v2) Mean (SD) change from baseline to 48 weeks Physical component | |
| Comparison groups | Group 1 - Placebo v Group 2 - Liraglutide - Active Treatment Group |
| Number of subjects included in analysis | 45 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.04 |
| Method | Regression, Linear |
| Parameter estimate | Mean difference (net) |
| Point estimate | 4.05 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.2 |
| upper limit | 7.9 |

| | |
|--|--|
| Statistical analysis title | Quality of life Mental component |
| Statistical analysis description: Quality of life (SF-36v2) Mean (SD) change from baseline to 48 weeks Physical component | |
| Comparison groups | Group 1 - Placebo v Group 2 - Liraglutide - Active Treatment Group |
| Number of subjects included in analysis | 45 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.62 |
| Method | Regression, Linear |
| Parameter estimate | Mean difference (net) |
| Point estimate | 1.5 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -4.64 |
| upper limit | 7.65 |

Secondary: A reduction in non-invasive inflammatory and fibrosis markers

| | |
|-----------------|---|
| End point title | A reduction in non-invasive inflammatory and fibrosis markers |
|-----------------|---|

End point description:

Changes in Liver function measured by the use of non invasive biomarker (Fibroscan) and multiple Blood Tests including; Liver function Tests (LFTs), and Cytokeratin-18. Glycaemic Control measurements relating to A reduction in global (hepatic, adipose and muscle) insulin resistance and A reduction in hepatic de-novo lipogenesis (DNL)

Reporting details the Mean (SD) from baseline to 48weeks

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline to end of Treatment / Study follow up

| End point values | Group 1 - Placebo | Group 2 - Liraglutide - Active Treatment Group | | |
|--------------------------------------|-------------------|--|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 22 | 23 | | |
| Units: Numerical | | | | |
| arithmetic mean (standard deviation) | | | | |
| Bilirubin | -1.1 (± 3.1) | -1.7 (± 3.1) | | |
| Alkaline Phosphatase | -1.2 (± 19.1) | -5.1 (± 11.7) | | |
| Alanine Transferase | -10.2 (± 35.8) | -26.6 (± 34.4) | | |
| Aspartate Transferase | -8.6 (± 28.3) | -15.8 (± 21.8) | | |
| CytoKeratin-18 (CK) | -92 (± 327) | -185 (± 295) | | |
| HbA1c | 0.0 (± 8.7) | -5.7 (± 6.9) | | |
| Glucose | 0.72 (± 2.3) | -1.0 (± 1.5) | | |
| HOMA-IR | 0.70 (± 9.49) | -1.8 (± 3.7) | | |
| Triglycerides | 0.18 (± 1.29) | -0.02 (± 0.64) | | |
| Total Cholesterol | -0.13 (± 0.91) | 0.01 (± 0.60) | | |
| HDL | -0.04 (± 0.13) | 0.07 (± 0.19) | | |
| LDL | -0.1 (± 0.9) | -0.1 (± 0.7) | | |

| | |
|----------------------------|---|
| Attachments (see zip file) | Clinical Data/1 EudraCT Clinical Data.pdf |
|----------------------------|---|

Statistical analyses

| | |
|----------------------------|---------|
| Statistical analysis title | Glucose |
|----------------------------|---------|

Statistical analysis description:

Mean (95% CI) changes from baseline

| | |
|-------------------|--|
| Comparison groups | Group 1 - Placebo v Group 2 - Liraglutide - Active Treatment Group |
|-------------------|--|

| | |
|---|--------------------------------|
| Number of subjects included in analysis | 45 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.005 |
| Method | Regression, Linear |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -1.67 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.81 |
| upper limit | -0.53 |

| | |
|--|--|
| Statistical analysis title | HOMA-IR |
| Statistical analysis description: Mean (95% CI) changes from baseline | |
| Comparison groups | Group 1 - Placebo v Group 2 - Liraglutide - Active Treatment Group |
| Number of subjects included in analysis | 45 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.23 |
| Method | Regression, Linear |
| Parameter estimate | Mean difference (net) |
| Point estimate | -2.74 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -7.24 |
| upper limit | 1.76 |

| | |
|---|--|
| Statistical analysis title | Glycated haemoglobin A1c |
| Statistical analysis description: Mean (95% CI) changes from baseline (liraglutide vs placebo) | |
| Comparison groups | Group 1 - Placebo v Group 2 - Liraglutide - Active Treatment Group |
| Number of subjects included in analysis | 45 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.03 |
| Method | Regression, Linear |
| Parameter estimate | Mean difference (net) |
| Point estimate | -5.18 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -9.91 |
| upper limit | -0.44 |

| | |
|--|--|
| Statistical analysis title | Total Cholesterol |
| Statistical analysis description: | |
| Mean (95% CI) changes from baseline (liraglutide vs placebo) | |
| Comparison groups | Group 1 - Placebo v Group 2 - Liraglutide - Active Treatment Group |
| Number of subjects included in analysis | 45 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.79 |
| Method | Regression, Linear |
| Parameter estimate | Mean difference (net) |
| Point estimate | 0.066 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.427 |
| upper limit | 0.56 |

| | |
|--|--|
| Statistical analysis title | HDL |
| Statistical analysis description: | |
| Mean (95% CI) changes from baseline (liraglutide vs placebo) | |
| Comparison groups | Group 1 - Placebo v Group 2 - Liraglutide - Active Treatment Group |
| Number of subjects included in analysis | 45 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.01 |
| Method | Regression, Linear |
| Parameter estimate | Mean difference (net) |
| Point estimate | 0.134 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.029 |
| upper limit | 0.238 |

| | |
|-----------------------------------|-----|
| Statistical analysis title | LDL |
|-----------------------------------|-----|

Statistical analysis description:

Mean (95% CI) changes from baseline (liraglutide vs placebo) - LDL (mmol/L)

| | |
|---|--|
| Comparison groups | Group 1 - Placebo v Group 2 - Liraglutide - Active Treatment Group |
| Number of subjects included in analysis | 45 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.61 |
| Method | Regression, Linear |
| Parameter estimate | Mean difference (net) |
| Point estimate | -0.126 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.622 |
| upper limit | 0.371 |

Statistical analysis title

Triglycerides

Statistical analysis description:

Mean (95% CI) changes from baseline (liraglutide vs placebo) - Triglycerides (mmol/L)

| | |
|---|--|
| Comparison groups | Group 1 - Placebo v Group 2 - Liraglutide - Active Treatment Group |
| Number of subjects included in analysis | 45 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.53 |
| Method | Regression, Linear |
| Parameter estimate | Mean difference (net) |
| Point estimate | -0.197 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.834 |
| upper limit | 0.439 |

Statistical analysis title

Alanine aminotransferase

Statistical analysis description:

Mean (95% CI) changes from baseline (liraglutide vs placebo) - Alanine aminotransferase (U/L) - ALT

| | |
|---|--|
| Comparison groups | Group 1 - Placebo v Group 2 - Liraglutide - Active Treatment Group |
| Number of subjects included in analysis | 45 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.16 |
| Method | Regression, Linear |
| Parameter estimate | Mean difference (net) |
| Point estimate | -10.7 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -25.9 |
| upper limit | 4.5 |

| | |
|---|--|
| Statistical analysis title | Aspartate aminotransferase |
| Statistical analysis description: | |
| Mean (95% CI) changes from baseline (liraglutide vs placebo) - Aspartate aminotransferase (U/L) AST | |
| Comparison groups | Group 1 - Placebo v Group 2 - Liraglutide - Active Treatment Group |
| Number of subjects included in analysis | 45 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.29 |
| Method | Regression, Linear |
| Parameter estimate | Mean difference (net) |
| Point estimate | -6.7 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -19.3 |
| upper limit | 5.9 |

| | |
|---|--|
| Statistical analysis title | γ-glutamyl transferase (U/L) |
| Statistical analysis description: | |
| Mean (95% CI) changes from baseline (liraglutide vs placebo) - Gamma-glutamyl transferase (U/L) - GGT | |
| Comparison groups | Group 1 - Placebo v Group 2 - Liraglutide - Active Treatment Group |
| Number of subjects included in analysis | 45 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.01 |
| Method | Regression, Linear |
| Parameter estimate | Mean difference (net) |
| Point estimate | -22.8 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -40.4 |
| upper limit | -5.2 |

| | |
|-----------------------------------|----------------------|
| Statistical analysis title | Alkaline phosphatase |
|-----------------------------------|----------------------|

| | |
|---|--|
| Statistical analysis description: | |
| Mean (95% CI) changes from baseline (liraglutide vs placebo) - Alkaline phosphatase (U/L) | |
| Comparison groups | Group 1 - Placebo v Group 2 - Liraglutide - Active Treatment Group |
| Number of subjects included in analysis | 45 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.22 |
| Method | Regression, Linear |
| Parameter estimate | Mean difference (net) |
| Point estimate | -5.46 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -14.36 |
| upper limit | 3.43 |

| | |
|---|--|
| Statistical analysis title | Bilirubin |
| Statistical analysis description: | |
| Mean (95% CI) changes from baseline (liraglutide vs placebo) - Total bilirubin (µmol/L) | |
| Comparison groups | Group 1 - Placebo v Group 2 - Liraglutide - Active Treatment Group |
| Number of subjects included in analysis | 45 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.51 |
| Method | Regression, Linear |
| Parameter estimate | Mean difference (net) |
| Point estimate | -0.63 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.52 |
| upper limit | 1.26 |

| | |
|--|--|
| Statistical analysis title | CK-18 |
| Statistical analysis description: | |
| Mean (95% CI) changes from baseline (liraglutide vs placebo) - Caspase-cleaved cytokeratin-18 fragment M30 (U/L) | |
| Comparison groups | Group 1 - Placebo v Group 2 - Liraglutide - Active Treatment Group |
| Number of subjects included in analysis | 45 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.1 |
| Method | Regression, Linear |
| Parameter estimate | Mean difference (net) |
| Point estimate | -86 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -188 |
| upper limit | 16 |

Secondary: Non Serious Adverse Events

| | |
|-----------------|----------------------------|
| End point title | Non Serious Adverse Events |
|-----------------|----------------------------|

End point description:

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

AEs reported over the course of the trial will be attached as a pdf to this end point analysis.

| | | | | |
|-----------------------------|-----------------------------|--|--|--|
| End point values | Safety patient cohort (ITT) | | | |
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 52 | | | |
| Units: Patients | 52 | | | |

| | |
|-----------------------------------|---|
| Attachments (see zip file) | Adverse Events/AE listing for EUDRACT.pdf |
|-----------------------------------|---|

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information^[1]

Timeframe for reporting adverse events:

Date of consent to end of study visit (3 months post end of treatment) for non-serious adverse events.
Date of consent to 30 days post end of study treatment (48 weeks) or 30 days post last administration of IMP for serious adverse events

| | |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

Dictionary used

| | |
|--------------------|-------|
| Dictionary name | CTCAE |
| Dictionary version | 4 |

Reporting groups

| | |
|-----------------------|------------------|
| Reporting group title | Group 1: Placebo |
|-----------------------|------------------|

Reporting group description:

Control group. Treatment with once-daily subcutaneous injection of inactive treatment (liraglutide placebo) (Supplied by Novo Nordisk Ltd, UK)

| | |
|-----------------------|-----------------|
| Reporting group title | Group 2: Active |
|-----------------------|-----------------|

Reporting group description:

Experimental group. Treatment with once-daily subcutaneous injections 1.8mg active liraglutide (Victoza ®) (Supplied by Novo Nordisk Ltd, UK)

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.

Justification: Results are posted in outcome section as validation error prevented uploading despite correct information- had to set number of patients not affected by non serious AE as `0` to post result as unable to over-ride validation warning to post results- group 1 is 24 and group 2 is 23.

| Serious adverse events | Group 1: Placebo | Group 2: Active | |
|---|---|-----------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 2 / 26 (7.69%) | 2 / 26 (7.69%) | |
| number of deaths (all causes) | 0 | 0 | |
| number of deaths resulting from adverse events | 0 | 0 | |
| Investigations | | | |
| Calcitonin stimulation test | Additional description: Calcitonin levels found to be abnormal | | |
| subjects affected / exposed | 1 / 26 (3.85%) | 0 / 26 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac disorders | | | |
| Conduct disorder | Additional description: ECG showed completed Heart Block and patient subsequently fitted with ventricular pacemaker. Occurred prior to any treatment being given. Ref: HE2013/0010/01 | | |
| subjects affected / exposed | 1 / 26 (3.85%) | 0 / 26 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nervous system disorders | | | |
| Headache | Additional description: Patient admitted with headache and associated nausea and dizziness. MRI and CT scan of head showed no abnormalities SAE ref: HE2013/0049/01 | | |

| | | | |
|---|--|----------------|--|
| subjects affected / exposed | 0 / 26 (0.00%) | 1 / 26 (3.85%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatobiliary disorders | | | |
| Granulomatous liver disease | Additional description: End of trial biopsy showed incidental finding of multiple granulomas. Patient was found to have active tuberculosis and treated with 6 months of antibiotics ref: HE2013/0012/01 | | |
| subjects affected / exposed | 0 / 26 (0.00%) | 1 / 26 (3.85%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metabolism and nutrition disorders | | | |
| Hypoglycaemia | Additional description: Patient diagnosed with REACTIVE HYPOGLYCAEMIA. REF: HE2013/0010/02 | | |
| subjects affected / exposed | 1 / 26 (3.85%) | 0 / 26 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

Frequency threshold for reporting non-serious adverse events: 0 %

| Non-serious adverse events | Group 1: Placebo | Group 2: Active | |
|---|------------------|-----------------|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 0 / 26 (0.00%) | 0 / 26 (0.00%) | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|-------------------|--|
| 01 July 2010 | <p>Amendment 2.0 The following statements were added to the exclusion criteria (p38 & p39):</p> <ul style="list-style-type: none"> • Patients with Multiple Endocrine Neoplasia Syndrome 2 (MEN2) • Family history of medullary thyroid cancer <p>Reason: These additional exclusion criteria are in keeping with the current recommended contraindications of Liraglutide (Victoza®) use in patients.</p> <p>Non-Substantial Amendments to the Protocol</p> <p>Throughout the protocol a number of non substantial amendments were made, specifically the contact details (p66) of Novo Nordisk Ltd offices have been updated. The central contact point between the sponsor (The University of Birmingham) and the Drug Manufacturer and Holder of the IMP MA (Novo Nordisk). In addition the current national ethical and regulatory approval status of study has been updated in the protocol sponsor section as well as some additional information in the finance section (p75) of the protocol concerning the supply of pen-injection needles for use on the study.</p> <ol style="list-style-type: none"> 1. Changes to IMP Labelling 2. Change to Patient Card: Inclusion of DUN Numbers (Prescribed study drug number) |
| 20 November 2010 | <p>Amendment 3.0: Change to exclusion criteria:</p> <ul style="list-style-type: none"> - No upper cut-off for BMI - removal of exclusion of patients that have had a significant change in dose of Angiotensin converting enzymes and (ACE) inhibitors and/or Angiotensin Receptor Blockers (ARBs) from exclusion criteria and inclusion of Multi-vitamins / vitamin E (containing > 200% recommended daily amount; >30mg/day). -Addition of a new participating site. |
| 20 January 2011 | <p>Amendment 4.0</p> <ul style="list-style-type: none"> - addition of new participating site - New wording added to protocol in relation to the requirement for sites to report pregnancies to study office. - New wording added to protocol in relation to the time period for reporting adverse events |
| 28 April 2011 | <p>Amendment 5.0 Change to clinical trial protocol</p> <ol style="list-style-type: none"> 1. Trial Site addition of Hull Royal Infirmary 2. Change to Target dates for trial completion. 3. Amendment to visit schedule - Amendment to visit 8, with regards to 12 weeks post visit 7 rather 24 weeks |
| 01 September 2011 | <p>Amendment 6.0: Addition of new participating centre and update to study protocol (protocol version 7.0) - site addition only.</p> |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

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| The information / data contained in this report is constrained /limited by the reporting structure of this report- for additional information and content please review the published articles and contact the corresponding author: Prof Philip Newsome. |
|---|

Notes:

Online references

<http://www.ncbi.nlm.nih.gov/pubmed/24189085>

<http://www.ncbi.nlm.nih.gov/pubmed/26608256>

<http://www.ncbi.nlm.nih.gov/pubmed/26394161>

<http://www.ncbi.nlm.nih.gov/pubmed/23163663>