

**Clinical trial results:****The effects of purified n-3 fatty acids on serum biomarkers and cardiovascular risk markers in a randomized placebo controlled trial in patients with non alcoholic fatty liver disease****Summary**

| | |
|--------------------------|------------------|
| EudraCT number | 2008-003766-26 |
| Trial protocol | GB |
| Global end of trial date | 29 November 2018 |

Results information

| | |
|-----------------------------------|---|
| Result version number | v1 (current) |
| This version publication date | 24 January 2019 |
| First version publication date | 24 January 2019 |
| Summary attachment (see zip file) | Effects of Purified Eicosapentaenoic and Docosahexaenoic Acids in the Nonalcoholic Fatty Liver Disease: Results from the WELCOME Study (Effects of Purified Eicosapentaenoic and Docosahexaenoic Acids in Nonalcoholic Fatty Liver Disease Results From the WELCOM Study - Scorletti et al. Hepatology.pdf) Design and rationale of the WELCOME trial: A randomised placebo controlled study to test the efficacy of purified long chain omega-3 fatty treatment in non-alcoholic fatty liver disease (Design and rationale of the WELCOME trial - Contemporary Clinical Trials.pdf) |

Trial information**Trial identification**

| | |
|-----------------------|----------|
| Sponsor protocol code | 25-12-59 |
|-----------------------|----------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT00760513 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|--|
| Sponsor organisation name | University Hospital Southampton NHS Foundation Trust |
| Sponsor organisation address | Tremona Road, Southampton, United Kingdom, |
| Public contact | Dr Mikayala King, University Hospital Southampton NHS Foundation Trust, mikayala.king@uhs.nhs.uk |
| Scientific contact | Lucinda England, University of Southampton , l.c.england@soton.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 | 29 November 2018 |
| Is this the analysis of the primary completion data? | No |

| | |
|----------------------------------|------------------|
| Global end of trial reached? | Yes |
| Global end of trial date | 29 November 2018 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

The aim of our study is to phenotype 100 people with NAFLD, either biopsy-proven or confirmed by non-invasive imaging in a high-risk cohort (i.e. diabetic and/or features of the metabolic syndrome), and randomize subjects to treatment with purified n-3 fatty acids (OMACOR) 4 g / day or to placebo for 15-18 months.

The primary end-points of the study are: a) to assess change in serum biomarkers with treatment b) to measure changes in liver fat and validate changes in biomarkers with changes in liver fat

Protection of trial subjects:

Liver biopsy is not without hazard, with the main complication being bleeding which requires intervention in around 1:1000 cases. The study has therefore opted to recruit volunteers with biopsy-proven NAFLD who have already undergone liver biopsy for diagnostic purposes or fatty liver diagnosed through non-invasive imaging e.g. liver ultrasound/CT/MRI who also have either diabetes or features of metabolic syndrome.

Background therapy: -

Evidence for comparator: -

| | |
|---|-----------------|
| Actual start date of recruitment | 12 January 2010 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | No |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|---------------------|
| Country: Number of subjects enrolled | United Kingdom: 103 |
| Worldwide total number of subjects | 103 |
| EEA total number of subjects | 103 |

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) | 93 |
| From 65 to 84 years | 10 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

First Patient Recruited took place on 12/01/2010, Last Patient Recruited was on 08/09/2011. Recruitment took place at University Hospital Southampton NHS FT as a single site. Other local collaborators responsible for the care of patients with NAFLD provided potential patients with patient information sheets however consent took place at UHS.

Pre-assignment

Screening details:

The study team identified a cohort of patients with non-alcoholic fatty liver disease diagnosed on either radiological or biopsy criteria for NAFLD with exclusion of other causes of chronic liver disease.

Period 1

| | |
|------------------------------|--------------------------------|
| Period 1 title | Overall Trial (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |
| Roles blinded | Subject, Investigator |

Blinding implementation details:

Volunteers were randomised via a computerised randomisation by a research Pharmacist at University Hospital NHS Foundation Trust

Arms

| | |
|--|----------------------------|
| Are arms mutually exclusive? | Yes |
| Arm title | Active Comparator - OMACOR |
| Arm description: - | |
| Arm type | Active comparator |
| Investigational medicinal product name | OMACOR |
| Investigational medicinal product code | |
| Other name | Lovaza |
| Pharmaceutical forms | Capsule |
| Routes of administration | Oral use |

Dosage and administration details:

4 grams per day for minimum 15 months and maximum 18 months

| | |
|--|---------------------------------|
| Arm title | Placebo comparator - Dummy pill |
| Arm description: - | |
| Arm type | Placebo |
| Investigational medicinal product name | Placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Capsule |
| Routes of administration | Oral use |

Dosage and administration details:

4 grams daily orally

| Number of subjects in period 1 | Active Comparator - OMACOR | Placebo comparator - Dummy pill |
|---------------------------------------|-------------------------------|------------------------------------|
| Started | 51 | 52 |
| Completed | 47 | 48 |
| Not completed | 4 | 4 |
| Consent withdrawn by subject | 4 | 4 |

Baseline characteristics

Reporting groups

| | |
|--------------------------------|---------------------------------|
| Reporting group title | Active Comparator - OMACOR |
| Reporting group description: - | |
| Reporting group title | Placebo comparator - Dummy pill |
| Reporting group description: - | |

| Reporting group values | Active Comparator - OMACOR | Placebo comparator - Dummy pill | Total |
|---|----------------------------|---------------------------------|-------|
| Number of subjects | 51 | 52 | 103 |
| Age categorical Units: Subjects | | | |
| Adults (18-64 years) | 47 | 46 | 93 |
| From 65-84 years | 4 | 6 | 10 |
| Age continuous Units: years | | | |
| log mean | 48.6 | 54 | |
| standard deviation | ± 11.1 | ± 9.6 | - |
| Gender categorical Units: Subjects | | | |
| Female | 26 | 17 | 43 |
| Male | 25 | 35 | 60 |
| Region of Enrollment Units: Subjects | | | |
| United Kingdom | 51 | 52 | 103 |

End points

End points reporting groups

| | |
|--------------------------------|---------------------------------|
| Reporting group title | Active Comparator - OMACOR |
| Reporting group description: - | |
| Reporting group title | Placebo comparator - Dummy pill |
| Reporting group description: - | |

Primary: Change of Liver Fat Percentage

| | |
|------------------------|--------------------------------|
| End point title | Change of Liver Fat Percentage |
| End point description: | |
| End point type | Primary |
| End point timeframe: | |
| 18 months | |

| End point values | Active Comparator - OMACOR | Placebo comparator - Dummy pill | | |
|--------------------------------|----------------------------|---------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 46 | 45 | | |
| Units: Percentage of Liver Fat | | | | |
| log mean (standard deviation) | -7.9 (± 17.4) | -4.6 (± 9.2) | | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | Statistical Analysis 1 |
| Comparison groups | Active Comparator - OMACOR v Placebo comparator - Dummy pill |
| Number of subjects included in analysis | 91 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.05 |
| Method | Regression, Linear |
| Parameter estimate | Mean difference (net) |
| Point estimate | -3.64 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -8 |
| upper limit | 0.8 |
| Variability estimate | Standard deviation |

Primary: Change in Liver Fibrosis Score

| | |
|-----------------|--------------------------------|
| End point title | Change in Liver Fibrosis Score |
|-----------------|--------------------------------|

End point description:

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

18 months

| End point values | Active Comparator - OMACOR | Placebo comparator - Dummy pill | | |
|-------------------------------|----------------------------|---------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 46 | 45 | | |
| Units: Unit on Scale | | | | |
| log mean (standard deviation) | 0.3 (± 0.6) | 0.2 (± 0.6) | | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | Statistical Analysis 1 |
| Comparison groups | Placebo comparator - Dummy pill v Active Comparator - OMACOR |
| Number of subjects included in analysis | 91 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.05 |
| Method | Regression, Linear |
| Parameter estimate | Mean difference (net) |
| Point estimate | 0.14 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.26 |
| upper limit | 0.33 |
| Variability estimate | Standard deviation |

Primary: Change in NAFLD Fibrosis Score

| | |
|-----------------|--------------------------------|
| End point title | Change in NAFLD Fibrosis Score |
|-----------------|--------------------------------|

End point description:

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

18 months

| End point values | Active Comparator - OMACOR | Placebo comparator - Dummy pill | | |
|-------------------------------|----------------------------------|---------------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 46 | 45 | | |
| Units: Unit on Scale | | | | |
| log mean (standard deviation) | 0.8 (\pm 0.9) | 0.8 (\pm 0.7) | | |

Statistical analyses

| Statistical analysis title | Statistical Analysis 1 |
|---|--|
| Comparison groups | Active Comparator - OMACOR v Placebo comparator - Dummy pill |
| Number of subjects included in analysis | 91 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.05 |
| Method | Regression, Linear |
| Parameter estimate | Mean difference (net) |
| Point estimate | 0.01 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.3 |
| upper limit | 0.3 |
| Variability estimate | Standard deviation |

Adverse events

Adverse events information

Timeframe for reporting adverse events:

18 months

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

Dictionary used

| | |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

| | |
|--------------------|------|
| Dictionary version | 10.0 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|--|
| Reporting group title | Omega 3 Fatty Acid (OMACOR) Active Arm |
|-----------------------|--|

Reporting group description: -

| | |
|-----------------------|------------------------|
| Reporting group title | Dummy Pill Placebo Arm |
|-----------------------|------------------------|

Reporting group description: -

| Serious adverse events | Omega 3 Fatty Acid (OMACOR) Active Arm | Dummy Pill Placebo Arm | |
|--|--|------------------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 4 / 51 (7.84%) | 8 / 52 (15.38%) | |
| number of deaths (all causes) | 0 | 0 | |
| number of deaths resulting from adverse events | 0 | 0 | |
| Cardiac disorders | | | |
| Chest Pain radiating to the neck with tingling to left arm | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 1 / 52 (1.92%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Surgical and medical procedures | | | |
| Laparoscopy and appendectomy | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 1 / 52 (1.92%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Tonsillectomy | | | |
| subjects affected / exposed | 1 / 51 (1.96%) | 0 / 52 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Elective Hysterectomy | | | |

| | | | |
|---|----------------|----------------|--|
| subjects affected / exposed | 0 / 51 (0.00%) | 1 / 52 (1.92%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Laparoscopic adhesiolysis | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 1 / 52 (1.92%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Removal of myxoma | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 1 / 52 (1.92%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Seminoma | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 1 / 52 (1.92%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal disorders | | | |
| Anaemia and disorientation | | | |
| subjects affected / exposed | 1 / 51 (1.96%) | 0 / 52 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Acute Asthma Attack | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 1 / 52 (1.92%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Severe Chest Pain | | | |
| subjects affected / exposed | 1 / 51 (1.96%) | 0 / 52 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Skin and subcutaneous tissue disorders | | | |
| Cellulitis on Right Lateral Malleolus | | | |
| subjects affected / exposed | 1 / 51 (1.96%) | 0 / 52 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|----------------|----------------|--|
| Endocrine disorders | | | |
| Stabilisation of Diabetes | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 1 / 52 (1.92%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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

| Non-serious adverse events | Omega 3 Fatty Acid (OMACOR) Active Arm | Dummy Pill Placebo Arm | |
|---|--|------------------------|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 49 / 51 (96.08%) | 44 / 52 (84.62%) | |
| General disorders and administration site conditions | | | |
| Accidental Fall | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 2 / 52 (3.85%) | |
| occurrences (all) | 0 | 2 | |
| Achille's Heel and foot problems | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 2 / 52 (3.85%) | |
| occurrences (all) | 0 | 2 | |
| Anxiety and Depression | | | |
| subjects affected / exposed | 4 / 51 (7.84%) | 2 / 52 (3.85%) | |
| occurrences (all) | 4 | 2 | |
| Dental Disorders | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 2 / 52 (3.85%) | |
| occurrences (all) | 0 | 2 | |
| Fall and fracture | | | |
| subjects affected / exposed | 1 / 51 (1.96%) | 0 / 52 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Fluid retention and oedema | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 2 / 52 (3.85%) | |
| occurrences (all) | 0 | 2 | |
| Headache and dizziness | | | |
| subjects affected / exposed | 6 / 51 (11.76%) | 6 / 52 (11.54%) | |
| occurrences (all) | 6 | 6 | |
| Hypertension | | | |

| | | | |
|---|------------------------|---------------------|--|
| subjects affected / exposed occurrences (all) | 5 / 51 (9.80%) 5 | 1 / 52 (1.92%) 1 | |
| Insomnia subjects affected / exposed occurrences (all) | 1 / 51 (1.96%) 1 | 0 / 52 (0.00%) 0 | |
| Reproductive system and breast disorders Fertility problems subjects affected / exposed occurrences (all) | 1 / 51 (1.96%) 1 | 0 / 52 (0.00%) 0 | |
| Gynaecological Disorders subjects affected / exposed occurrences (all) | 2 / 51 (3.92%) 2 | 1 / 52 (1.92%) 1 | |
| Pregnancy subjects affected / exposed occurrences (all) | 1 / 51 (1.96%) 1 | 0 / 52 (0.00%) 0 | |
| Respiratory, thoracic and mediastinal disorders Asthma and breathing subjects affected / exposed occurrences (all) | 3 / 51 (5.88%) 3 | 0 / 52 (0.00%) 0 | |
| Flu, cough and sore throat subjects affected / exposed occurrences (all) | 13 / 51 (25.49%) 13 | 5 / 52 (9.62%) 5 | |
| Product issues Other drug overdose subjects affected / exposed occurrences (all) | 2 / 51 (3.92%) 2 | 0 / 52 (0.00%) 0 | |
| Other drug reaction subjects affected / exposed occurrences (all) | 5 / 51 (9.80%) 5 | 0 / 52 (0.00%) 0 | |
| Cardiac disorders Chest Pain and ECG alterations subjects affected / exposed occurrences (all) | 5 / 51 (9.80%) 5 | 5 / 52 (9.62%) 5 | |
| Nervous system disorders Neurological Disorders | | | |

| | | | |
|--|---|---|--|
| subjects affected / exposed occurrences (all) | 1 / 51 (1.96%) 1 | 0 / 52 (0.00%) 0 | |
| Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all) | 2 / 51 (3.92%) 2 | 0 / 52 (0.00%) 0 | |
| Ear and labyrinth disorders Otolaryngological Disorders subjects affected / exposed occurrences (all) | 10 / 51 (19.61%) 10 | 3 / 52 (5.77%) 3 | |
| Eye disorders Ophtalmological Disorders subjects affected / exposed occurrences (all) | 0 / 51 (0.00%) 0 | 6 / 52 (11.54%) 6 | |
| Gastrointestinal disorders Nausea and Vomiting subjects affected / exposed occurrences (all) Diarrhoea subjects affected / exposed occurrences (all) Gastrointestinal disorder subjects affected / exposed occurrences (all) Proctological Disorders subjects affected / exposed occurrences (all) | 3 / 51 (5.88%) 3 4 / 51 (7.84%) 4 6 / 51 (11.76%) 6 3 / 51 (5.88%) 3 | 4 / 52 (7.69%) 4 6 / 52 (11.54%) 6 5 / 52 (9.62%) 5 3 / 52 (5.77%) 3 | |
| Hepatobiliary disorders Hepatological Disorder subjects affected / exposed occurrences (all) Liver Biopsy subjects affected / exposed occurrences (all) | 0 / 51 (0.00%) 0 1 / 51 (1.96%) 1 | 1 / 52 (1.92%) 1 0 / 52 (0.00%) 0 | |
| Skin and subcutaneous tissue disorders Dermatological Disorders | | | |

| | | | |
|--|---|---|--|
| subjects affected / exposed occurrences (all) | 8 / 51 (15.69%) 8 | 9 / 52 (17.31%) 9 | |
| Renal and urinary disorders Urological Disorders subjects affected / exposed occurrences (all) | 5 / 51 (9.80%) 5 | 11 / 52 (21.15%) 11 | |
| Endocrine disorders Onset Diabetes subjects affected / exposed occurrences (all) | 2 / 51 (3.92%) 2 | 1 / 52 (1.92%) 1 | |
| Musculoskeletal and connective tissue disorders Back Pain and Sciatica subjects affected / exposed occurrences (all) Carpal Disorders subjects affected / exposed occurrences (all) Fibromyalgia subjects affected / exposed occurrences (all) Joint pain subjects affected / exposed occurrences (all) Knee Surgery subjects affected / exposed occurrences (all) Orthopedic Disorder subjects affected / exposed occurrences (all) | 3 / 51 (5.88%) 3 0 / 51 (0.00%) 0 1 / 51 (1.96%) 1 13 / 51 (25.49%) 13 2 / 51 (3.92%) 2 0 / 51 (0.00%) 0 | 2 / 52 (3.85%) 2 1 / 52 (1.92%) 1 0 / 52 (0.00%) 0 11 / 52 (21.15%) 11 0 / 52 (0.00%) 0 1 / 52 (1.92%) 1 | |
| Infections and infestations Chest Infection subjects affected / exposed occurrences (all) | 13 / 51 (25.49%) 13 | 4 / 52 (7.69%) 4 | |
| Metabolism and nutrition disorders Dyslipidaemia | | | |

| | | | |
|----------------------------------|----------------|----------------|--|
| subjects affected / exposed | 1 / 51 (1.96%) | 1 / 52 (1.92%) | |
| occurrences (all) | 1 | 1 | |
| Hyperglycaemia and hypoglycaemia | | | |
| subjects affected / exposed | 1 / 51 (1.96%) | 3 / 52 (5.77%) | |
| occurrences (all) | 1 | 3 | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

<http://www.ncbi.nlm.nih.gov/pubmed/25043514>

<http://www.ncbi.nlm.nih.gov/pubmed/24556343>