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 form 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 (± 0.9)	0.8 (± 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 Melleolus			
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	5 / 51 (9.80%)	1 / 52 (1.92%)	
occurrences (all)	5	1	
Insomnia			
subjects affected / exposed	1 / 51 (1.96%)	0 / 52 (0.00%)	
occurrences (all)	1	0	
Reproductive system and breast disorders			
Fertility problems			
subjects affected / exposed	1 / 51 (1.96%)	0 / 52 (0.00%)	
occurrences (all)	1	0	
Gynaecological Disorders			
subjects affected / exposed	2 / 51 (3.92%)	1 / 52 (1.92%)	
occurrences (all)	2	1	
Pregnancy			
subjects affected / exposed	1 / 51 (1.96%)	0 / 52 (0.00%)	
occurrences (all)	1	0	
Respiratory, thoracic and mediastinal disorders			
Asthma and breathing			
subjects affected / exposed	3 / 51 (5.88%)	0 / 52 (0.00%)	
occurrences (all)	3	0	
Flu, cough and sore throat			
subjects affected / exposed	13 / 51 (25.49%)	5 / 52 (9.62%)	
occurrences (all)	13	5	
Product issues			
Other drug overdose			
subjects affected / exposed	2 / 51 (3.92%)	0 / 52 (0.00%)	
occurrences (all)	2	0	
Other drug reaction			
subjects affected / exposed	5 / 51 (9.80%)	0 / 52 (0.00%)	
occurrences (all)	5	0	
Cardiac disorders			
Chest Pain and ECG alterations			
subjects affected / exposed	5 / 51 (9.80%)	5 / 52 (9.62%)	
occurrences (all)	5	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)	3 / 51 (5.88%) 3	4 / 52 (7.69%) 4	
Diarrhoea subjects affected / exposed occurrences (all)	4 / 51 (7.84%) 4	6 / 52 (11.54%) 6	
Gastrointestinal disorder subjects affected / exposed occurrences (all)	6 / 51 (11.76%) 6	5 / 52 (9.62%) 5	
Proctological Disorders subjects affected / exposed occurrences (all)	3 / 51 (5.88%) 3	3 / 52 (5.77%) 3	
Hepatobiliary disorders Hepatological Disorder subjects affected / exposed occurrences (all)	0 / 51 (0.00%) 0	1 / 52 (1.92%) 1	
Liver Biopsy subjects affected / exposed occurrences (all)	1 / 51 (1.96%) 1	0 / 52 (0.00%) 0	
Skin and subcutaneous tissue disorders Dermatological Disorders			

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