Clinical trial results:
A Double-Blind Randomized Placebo-Controlled, Parallel-Group 12 Week Study to Investigate the Effects of Epanova® Compared to Placebo and Compared to Fenofibrate on Liver Fat Content in Hypertriglyceridemic Overweight Subjects; EFFECT I

Summary

EudraCT number	2014-003637-26
Trial protocol	SE
Global end of trial date	18 August 2016

Results information

Result version number	v1 (current)
This version publication date	21 May 2017
First version publication date	21 May 2017

Trial information

Trial identification

Sponsor protocol code	D5881C00007

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	AstraZeneca
Sponsor organisation address	Pepparedsleden 1, Mölndal, Sweden, SE-431 83
Public contact	Stefan Carlsson, AstraZeneca, 46 317762017, Stefan.C.Carlsson@astrazeneca.com
Scientific contact	Stefan Carlsson, AstraZeneca, 46 317762017 x, Stefan.C.Carlsson@astrazeneca.com

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	18 August 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	26 May 2016
Global end of trial reached?	Yes
Global end of trial date	18 August 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary aim of this study was to evaluate the efficacy of Epanova as compared to placebo with respect to reduction in liver fat content (%) in obese or overweight patients with no diabetes, but with BMI >25, serum triglycerides ≥1.7 mM, and with fatty liver (>5.5% as measured with MRI).

Protection of trial subjects:

Treated in routine care.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 September 2015
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	Sweden: 78
Worldwide total number of subjects	78
EEA total number of subjects	78

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)	52
From 65 to 84 years	26
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This study was conducted in 4 centers in Sweden between 01 September 2015 and 26 May 2016.

Pre-assignment

Screening details:

The study duration was up to 15 weeks, consisting of an initial screening period lasting up to 2 weeks, a 12-week treatment period, and a follow-up telephone call within 1 week after the last dose of study drug. A total of 171 subjects were enrolled, and 78 subjects were randomized.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Carer, Data analyst, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Epanova

Arm description:

Epanova 4 g/day + placebo to Fenofibrate

Arm type	Experimental
Investigational medicinal product name	Epanova
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

4 x 1 g capsules once daily in the morning

Investigational medicinal product name	Placebo to Fenofibrate
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

200 mg capsule once daily in the morning

Arm title	Fenofibrate

Arm description:

Fenofibrate 200 mg/day + placebo to Epanova

Arm type	Active comparator
Investigational medicinal product name	Placebo to Epanova
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

4 x 1 g capsules once daily in the morning

Investigational medicinal product name	Fenofibrate
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:
200 mg capsule once daily in the morning

Arm title	Placebo

Arm description:
Placebo to Epanova +placebo to Fenofibrate

Arm type	Placebo
Investigational medicinal product name	Placebo to Fenofibrate
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:
200 mg capsule once daily in the morning

Investigational medicinal product name	Placebo to Epanova
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:
4 x 1 g capsules once daily in the morning

Number of subjects in period 1	Epanova	Fenofibrate	Placebo
Started	25	27	26
Completed	23	26	23
Not completed	2	1	3
Adverse event, non-fatal	1	-	2
Other - reason not specified	1	-	1
Study-specifc withdrawal criteria	-	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Epanova
Reporting group description: Epanova 4 g/day + placebo to Fenofibrate	
Reporting group title	Fenofibrate
Reporting group description: Fenofibrate 200 mg/day + placebo to Epanova	
Reporting group title	Placebo
Reporting group description: Placebo to Epanova +placebo to Fenofibrate	

Reporting group values	Epanova	Fenofibrate	Placebo
Number of subjects	25	27	26
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age <37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	19	17	16
From 65-84 years	6	10	10
85 years and over	0	0	0
Age Continuous | Units: Years			
arithmetic mean	60	61.7	60.8
standard deviation	± 7.79	± 7.78	± 7.85
Gender, Male/Female Units: Participants			
Female	9	12	12
Male	16	15	14
Age, Customized Units: Subjects			
<50	3	3	1
>=50 - <65	16	14	15
>=65	6	10	10

Reporting group values	Total		
Number of subjects	78		
Age categorical Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age <37 wks)	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)	52			
From 65-84 years	26			

End points

End points reporting groups

Reporting group title	Epanova
Reporting group description:	
Epanova 4 g/day + placebo to Fenofibrate	
Reporting group title	Fenofibrate
Reporting group description:	
Fenofibrate 200 mg/day + placebo to Epanova	
Reporting group title	Placebo
Reporting group description:	
Placebo to Epanova +placebo to Fenofibrate	
Subject analysis set title	Full
Subject analysis set type	Full analysis
Subject analysis set description:	
All randomized patients, regardless of whether they took trial medication or not.	
Subject analysis set title	Safety
Subject analysis set type	Safety analysis
Subject analysis set description:	
All patients who were randomized to 1 of the treatment groups, and received at least 1 dose of study medication.	
Subject analysis set title	Placebo
Subject analysis set type	Per protocol
Subject analysis set description:	
The subset of the Full Analysis Set who adhered to the clinical study protocol.	

Primary: Change from Baseline to Week 12 in % liver fat as assessed by MRI (Epanova versus placebo)

End point title	Change from Baseline to Week 12 in % liver fat as assessed by MRI (Epanova versus placebo)[1]
End point description:	
To evaluate the efficacy of Epanova compared to placebo with respect to reduction in liver fat content (%) at the end of 12 weeks of double-blinded treatment.	
End point type	Primary
End point timeframe:	
12 weeks	
Notes:	
[1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: For the secondary endpoint, only the Epanova and placebo arms are included in the analysis	

End point values	Epanova	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22	23		
Units: ratio of % liver fat				
geometric mean (confidence interval 95%)	0.98 (0.82 to 1.17)	1.04 (0.95 to 1.13)		

Statistical analyses

Statistical analysis title	Mixed effects model (comparison versus placebo)
Comparison groups	Epanova v Placebo
Number of subjects included in analysis	45
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.407
Method	Mixed models analysis
Parameter estimate	Geometric mean ratio for difference
Point estimate	0.92
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.76
upper limit	1.12

Secondary: Change from Baseline to Week 12 in % liver fat as assessed by MRI (Epanova versus Fenofibrate)

End point title	Change from Baseline to Week 12 in % liver fat as assessed by MRI (Epanova versus Fenofibrate)[2]

End point description:

To evaluate the efficacy of Epanova compared to Fenofibrate with respect to reduction in liver fat content (%) at the end of 12 weeks of double-blinded treatment.

End point type	Secondary

End point timeframe:

12 weeks

Notes:

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: For the primary endpoint, only the Epanova and Fenofibrate arms are included in the analysis.

End point values	Epanova	Fenofibrate		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22	26		
Units: ratio of % liver fat				
geometric mean (confidence interval 95%)	0.98 (0.82 to 1.17)	1.17 (0.99 to 1.37)		

Statistical analyses

Statistical analysis title	Mixed effects model (active treatment)
Comparison groups	Epanova v Fenofibrate

Number of subjects included in analysis	48
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.077
Method	Mixed models analysis
Parameter estimate	Geometric mean ratio for difference
Point estimate	0.84
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.7
upper limit	1.02

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Adverse events were collected from visit 2 (randomization) throughout the treatment period until Visit 4 (end of treatment).	
Assessment type	Systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	19.0
Reporting groups	
Reporting group title	Epanova
Reporting group description:	
Epanova 4 g/day + placebo to Fenofribrate	
Reporting group title	Fenofibrate
Reporting group description:	
Fenofibrate 200 mg/ day + placebo to Epanova	
Reporting group title	Placebo
Reporting group description:	
Placebo to Epanova + placebo to Fenofibrate	

Serious adverse events	Epanova	Fenofibrate	Placebo
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 25 (4.00%)	0 / 27 (0.00%)	0 / 26 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Infections and infestations			
Urosepsis			
subjects affected / exposed	1 / 25 (4.00%)	0 / 27 (0.00%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Epanova	Fenofibrate	Placebo
Total subjects affected by non-serious adverse events			
subjects affected / exposed	12 / 25 (48.00%)	8 / 27 (29.63%)	5 / 26 (19.23%)
General disorders and administration site conditions			
Fatigue			

subjects affected / exposed	0 / 25 (0.00%)	2 / 27 (7.41%)	1 / 26 (3.85%)
occurrences (all)	0	2	1
Pyrexia			
subjects affected / exposed	0 / 25 (0.00%)	2 / 27 (7.41%)	0 / 26 (0.00%)
occurrences (all)	0	2	0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	2 / 25 (8.00%)	1 / 27 (3.70%)	2 / 26 (7.69%)
occurrences (all)	2	1	2
Abdominal pain upper			
subjects affected / exposed	2 / 25 (8.00%)	0 / 27 (0.00%)	1 / 26 (3.85%)
occurrences (all)	2	0	1
Diarrhoea			
subjects affected / exposed	7 / 25 (28.00%)	2 / 27 (7.41%)	4 / 26 (15.38%)
occurrences (all)	7	2	4
Flatulence			
subjects affected / exposed	3 / 25 (12.00%)	1 / 27 (3.70%)	1 / 26 (3.85%)
occurrences (all)	3	1	1
Nausea			
subjects affected / exposed	3 / 25 (12.00%)	0 / 27 (0.00%)	0 / 26 (0.00%)
occurrences (all)	3	0	0
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	2 / 25 (8.00%)	2 / 27 (7.41%)	1 / 26 (3.85%)
occurrences (all)	2	2	1

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
15 April 2015	Revision of exclusion critieria to capture the target population for the study.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported