Clinical trial results:
A Double-Blind, Randomized Placebo-Controlled, Parallel-Group, 12 Week Study to Investigate the Effects of Epanova® and Dapagliflozin on Liver Fat Content in Type 2 Diabetic Patients: Effect II

Summary

EudraCT number	2014-003638-26
Trial protocol	SE
Global end of trial date	29 February 2016

Results information

Result version number	v1 (current)
This version publication date	18 December 2016
First version publication date	18 December 2016

Trial information

Trial identification

Sponsor protocol code	D5883C00004

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, 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	29 February 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	11 December 2015
Global end of trial reached?	Yes
Global end of trial date	29 February 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 the combination of Epanova and dapagliflozin as compared to placebo with respect to reduction in liver fat content (%) at the end of 12 weeks of double-blind treatment in Type 2 diabetics with increased liver fat content as defined by >5.5% (assessed by MRI).

Protection of trial subjects:

Treated in routine care.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	20 January 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: 84
Worldwide total number of subjects	84
EEA total number of subjects	84

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)	28
From 65 to 84 years	56
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This study was conducted in 5 centers in Sweden between 20 January 2015 and 11 December 2015.

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 visit 1 week
after the last dose of study drug.

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	Investigator, Monitor, Carer, Data analyst, Assessor, Subject

Arms

Are arms mutually exclusive?	Yes
Arm title	Epanova + Dapagliflozin

Arm description:

Epanova 4 g/day + Dapagliflozin 10 mg/day

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	Dapagliflozin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

10 mg tablet once daily in the morning

Arm title	Dapagliflozin

Arm description:

Dapagliflozin 10 mg/day + placebo to Epanova

Arm type	Active comparator
Investigational medicinal product name	Dapagliflozin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

10 mg tablet 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 1g capsules once daily in the morning

Arm title	Epanova

Arm description:

Epanova 4 g/day + placebo to Dapagliflozin

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

Dosage and administration details:

10 mg tablet once daily in the morning

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

Arm title	Placebo

Arm description:

Placebo to Epanova and placebo to Dapagliflozin

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

Dosage and administration details:

10 mg tablet 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 1g capsules once daily in the morning

Number of subjects in period 1	Epanova + Dapagliflozin	Dapagliflozin	Epanova
Started	22	21	20
Completed	20	20	15
Not completed	2	1	5
Consent withdrawn by subject	1	-	1
Adverse event, non-fatal	1	1	2
Couldn't swallow IP; noncompliance	-	-	2

Number of subjects in period 1	Placebo
Started	21
Completed	20
Not completed	1
Consent withdrawn by subject	1
Adverse event, non-fatal	-
Couldn't swallow IP; noncompliance	-

Baseline characteristics

Reporting groups	
Reporting group title	Epanova + Dapagliflozin
Reporting group description:	
Epanova 4 g/day + Dapagliflozin 10 mg/day	
Reporting group title	Dapagliflozin
Reporting group description:	
Dapagliflozin 10 mg/day + placebo to Epanova	
Reporting group title	Epanova
Reporting group description:	
Epanova 4 g/day + placebo to Dapagliflozin	
Reporting group title	Placebo
Reporting group description:	
Placebo to Epanova and placebo to Dapagliflozin	

Reporting group values	Epanova + Dapagliflozin	Dapagliflozin	Epanova
Number of subjects	22	21	20
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)	9	7	6
From 65-84 years	13	14	14
85 years and over	0	0	0
Age Continuous | Units: years			
arithmetic mean	65	65	66.2
standard deviation	± 5.42	± 6.54	± 5.94
Gender, Male/Female Units: Participants			
Female	7	5	9
Male	15	16	11
Age, Customized Units: Subjects			
<50	0	1	0
>=50 - <65	9	6	6
>=65	13	14	14

Reporting group values	Placebo	Total	
Number of subjects	21	84	

Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	6	28	
From 65-84 years	15	56	
85 years and over	0	0	
Age Continuous | Units: years			
arithmetic mean	65.6		
standard deviation	± 6.1	-	
Gender, Male/Female Units: Participants			
Female	4	25	
Male	17	59	
Age, Customized Units: Subjects			
<50	0	1	
>=50 - <65	6	27	
>=65	15	56	

Subject analysis sets

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 in the Full Analysis Set who received at least 1 dose of study medication.

Subject analysis set title	Per protocol
Subject analysis set type	Per protocol

Subject analysis set description:

The subset of the Full Analysis Set who completed the 12-week double-blind treatment period without any important protocol deviations.

Reporting group values	Full	Safety	Per protocol
Number of subjects	84	84	68
Age categorical Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months)			

Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age Continuous | Units: years arithmetic mean standard deviation	 65 ± 5.42	 66.2 ± 5.94	 65.8 ± 5.88
Gender, Male/Female Units: Participants			
Female Male			
Age, Customized Units: Subjects			
<50 >=50 - <65 >=65			

End points

End points reporting groups

Reporting group title	Epanova + Dapagliflozin
Reporting group description:	
Epanova 4 g/day + Dapagliflozin 10 mg/day	
Reporting group title	Dapagliflozin
Reporting group description:	
Dapagliflozin 10 mg/day + placebo to Epanova	
Reporting group title	Epanova
Reporting group description:	
Epanova 4 g/day + placebo to Dapagliflozin	
Reporting group title	Placebo
Reporting group description:	
Placebo to Epanova and placebo to Dapagliflozin	
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 in the Full Analysis Set who received at least 1 dose of study medication.	
Subject analysis set title	Per protocol
Subject analysis set type	Per protocol
Subject analysis set description:	
The subset of the Full Analysis Set who completed the 12-week double-blind treatment period without any important protocol deviations.	

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

End point title	Change from Baseline to Week 12 in % liver fat as assessed by MRI (comparison versus placebo)[1]
End point description:	
To evaluate the efficacy of the combination therapy (Epanova + Dapagliflozin) when 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: not all arms
are evaluated for each endpoint, so for this study, the data is correct and the
warnings must remain

End point values	Epanova + Dapagliflozin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	19		
Units: ratio of % liver fat				
geometric mean (confidence interval 95%)	0.79 (0.69 to 0.9)	0.97 (0.9 to 1.04)		

Statistical analyses

Statistical analysis title	Mixed effects model (comparison versus placebo)
Comparison groups	Placebo v Epanova + Dapagliflozin
Number of subjects included in analysis	39
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.046 [2]
Method	Mixed models analysis
Parameter estimate	Geometric mean ratio for difference
Point estimate	0.83
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.7
upper limit	1

Notes:

[2] - Hypotheses tested using Dunnett's multiple testing procedure with a family-wise error rate of 5%, adjusting for 3 pairwise comparisons versus a single control (placebo).

Secondary: Change from Baseline to Week 12 in % liver fat (comparison between active treatment groups)

End point title	Change from Baseline to Week 12 in % liver fat (comparison between active treatment groups)[3]

End point description:

To evaluate the relative efficacy of the combination of Epanova and dapagliflozin versus Epanova alone and dapagliflozin alone with respect to reduction in % liver fat at the end of 12 weeks of double-blind treatment.

End point type	Secondary

End point timeframe:

12 weeks

Notes:

[3] - 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: not all arms
are evaluated for each endpoint, so for this study, the data is correct and the
warnings must remain

End point values	Epanova + Dapagliflozin	Dapagliflozin	Epanova	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	20	19	15	
Units: ratio of % liver fat				
geometric mean (confidence interval 95%)	0.79 (0.69 to 0.9)	0.87 (0.77 to 0.99)	0.85 (0.78 to 0.92)	

Statistical analyses

Statistical analysis title	Mixed effects model (active treatment)
Comparison groups	Epanova + Dapagliflozin v Dapagliflozin
Number of subjects included in analysis	39
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.502 [4]
Method	Mixed models analysis
Parameter estimate	Geometric mean ratio for difference
Point estimate	0.91
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.75
upper limit	1.11

Notes:

[4] - Conditional upon rejection of at least 1 of the 3 hypotheses for the primary analysis, secondary hypotheses are tested using Tukey's multiple testing procedure with a family-wise error rate of 5%, adjusting for 3 pairwise comparisons.

Statistical analysis title	Mixed effects model (active treatment)
Comparison groups	Epanova + Dapagliflozin v Epanova
Number of subjects included in analysis	35
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.562 [5]
Method	Mixed models analysis
Parameter estimate	Geometric mean ratio for difference
Point estimate	0.91
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.73
upper limit	1.13

Notes:

[5] - Conditional upon rejection of at least 1 of the hypotheses for the primary analysis, secondary hypotheses are tested using Tukey's multiple testing procedure with a family-wise error rate of 5%, adjusting for 3 pairwise comparisons.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were collected from visit 2 (randomization) throughout the treatment period until Visit 5 (end of treatment).

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.1

Reporting groups

Reporting group title	Epanova + Dapagliflozin

Reporting group description:

Epanova 4 g/day + Dapagliflozin 10 mg/day

Reporting group title	Placebo

Reporting group description:

Placebo to Epanova and placebo to Dapagliflozin

Reporting group title	Dapagliflozin

Reporting group description:

Dapagliflozin 10 mg/day + placebo to Epanova

Reporting group title	Epanova

Reporting group description:

Epanova 4 g/day + placebo to Dapagliflozin

Serious adverse events	Epanova + Dapagliflozin	Placebo	Dapagliflozin
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 22 (0.00%)	1 / 21 (4.76%)	1 / 21 (4.76%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Renal and urinary disorders			
Hydronephrosis			
subjects affected / exposed	0 / 22 (0.00%)	0 / 21 (0.00%)	1 / 21 (4.76%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Sepsis			
subjects affected / exposed	0 / 22 (0.00%)	1 / 21 (4.76%)	0 / 21 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Epanova		

Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 20 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Renal and urinary disorders			
Hydronephrosis			
subjects affected / exposed	0 / 20 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Sepsis			
subjects affected / exposed	0 / 20 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Epanova + Dapagliflozin	Placebo	Dapagliflozin
Total subjects affected by non-serious adverse events			
subjects affected / exposed	14 / 22 (63.64%)	7 / 21 (33.33%)	8 / 21 (38.10%)
Nervous system disorders			
Dizziness			
subjects affected / exposed	2 / 22 (9.09%)	1 / 21 (4.76%)	5 / 21 (23.81%)
occurrences (all)	2	1	5
Headache			
subjects affected / exposed	1 / 22 (4.55%)	2 / 21 (9.52%)	0 / 21 (0.00%)
occurrences (all)	1	2	0
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	3 / 22 (13.64%)	0 / 21 (0.00%)	0 / 21 (0.00%)
occurrences (all)	3	0	0
Constipation			
subjects affected / exposed	0 / 22 (0.00%)	1 / 21 (4.76%)	2 / 21 (9.52%)
occurrences (all)	0	1	2
Diarrhoea			

subjects affected / exposed	11 / 22 (50.00%)	0 / 21 (0.00%)	1 / 21 (4.76%)
occurrences (all)	12	0	1
Nausea			
subjects affected / exposed	2 / 22 (9.09%)	2 / 21 (9.52%)	0 / 21 (0.00%)
occurrences (all)	2	2	0
Renal and urinary disorders			
Pollakiuria			
subjects affected / exposed	2 / 22 (9.09%)	1 / 21 (4.76%)	2 / 21 (9.52%)
occurrences (all)	2	1	2
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	2 / 22 (9.09%)	1 / 21 (4.76%)	1 / 21 (4.76%)
occurrences (all)	2	2	1

Non-serious adverse events	Epanova		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	12 / 20 (60.00%)		
Nervous system disorders			
Dizziness			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Headache			
subjects affected / exposed	0 / 20 (0.00%)		
occurrences (all)	0		
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	2 / 20 (10.00%)		
occurrences (all)	2		
Constipation			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Diarrhoea			
subjects affected / exposed	7 / 20 (35.00%)		
occurrences (all)	7		
Nausea			
subjects affected / exposed	3 / 20 (15.00%)		
occurrences (all)	3		

Renal and urinary disorders Pollakiuria subjects affected / exposed occurrences (all)	 1 / 20 (5.00%) 1		
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all)	 2 / 20 (10.00%) 2		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
07 November 2014	Minor edits and corrections for clarity and accuracy.
23 March 2015	Revision of inclusion and exclusion critieria to capture the target population for the study.
25 June 2015	Reduction of sample size and revision of statistical analyses.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported