Clinical trial results:
A 12-Week, Randomized, Double-Blind, Olive Oil-Controlled Phase 3 Study to Assess the Efficacy and Safety of EPANOVA® in Subjects With Severe Hypertriglyceridemia (EVOLVE II)

Summary

EudraCT number	2013-004682-14
Trial protocol	HU CZ NL DK
Global end of trial date	23 December 2014

Results information

Result version number	v1 (current)
This version publication date	16 March 2016
First version publication date	16 March 2016

Trial information

Trial identification

Sponsor protocol code	D5880C00001

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	AstraZeneca AB
Sponsor organisation address	Södertälje, Södertälje, Sweden, SE-151 85
Public contact	Hong Yang, Study Statistician, AstraZeneca AB, +46 (0)317762397, hong.yang1@astrazeneca.com
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Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	
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	31 July 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	23 December 2014
Global end of trial reached?	Yes
Global end of trial date	23 December 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

This study investigated the efficacy and safety of Epanova in subjects with severe hypertriglyceridemia (ie, TG levels ≥500 mg/dL [5.65 mmol/L] and <2500 mg/dL [28.25 mmol/L]). However, in Canada, only subjects with TG ≥500 mg/dL (5.65 mmol/L) and <2000 mg/d(22.60 mmol/L) at screening were eligible for enrollment.

Protection of trial subjects:

ETHICS

1 Institutional Review Board
The Clinical Study Protocol and informed consent document were submitted to and approved by the duly constituted Institutional Review Board (IRB) or Independent Ethics Committee (IEC) for each center prior to initiation of the study. A copy of the letter of approval and the IRB/IEC membership roster were received by the Sponsor prior to any drug shipment. See Appendix 16.1.3 for a list of IRBs/IECs consulted for this study.

2 Ethical Conduct of the Study
The study was conducted in accordance with the Declaration of Helsinki and with all applicable laws and regulations of the locale and country where the study was conducted, and in compliance with Good Clinical Practice Guidelines.

3 Subject Information and Consent
The rationale of the study, procedural details, and investigational goals were explained to each subject, along with potential risks and benefits. Each subject was assured of his/her right to withdraw from the study at any time. Prior to the initiation of any study procedures, each subject signed and dated an approved informed consent form (Appendix 16.1.3). The original was kept on file by the Investigator with the subject's records, and a copy was given to each subject.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	16 December 2013
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 States: 44
Country: Number of subjects enrolled	Canada: 3
Country: Number of subjects enrolled	Czech Republic: 4
Country: Number of subjects enrolled	Denmark: 19
Country: Number of subjects enrolled	Hungary: 55
Country: Number of subjects enrolled	Netherlands: 2

Country: Number of subjects enrolled	Russian Federation: 35
Worldwide total number of subjects	162
EEA total number of subjects	80

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)	149
From 65 to 84 years	13
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The recruitment was planned at 43 sites, and in total, 162 were randomized in a 1:1 ratio to two treatment groups, Epanova (n=81) and Olive Oil (n=81). Randomization of subjects was stratified by two factors: 1. use of lipid-altering drugs (yes, no), and 2. Qualifying triglycerides values below or above 885 mg/dL.

Pre-assignment

Screening details:

Not applicable

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, Subject, Carer, Data analyst, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Epanova

Arm description:

2g once daily

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:

2g once daily (QD)

Arm title	Olive Oil

Arm description:

2g once daily (QD)

Arm type	Active comparator
Investigational medicinal product name	Olive Oil
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

2g once daily (QD)

Number of subjects in period 1	Epanova	Olive Oil
Started	81	81
Completed	80	76
Not completed	1	5
Consent withdrawn by subject	1	1
Adverse event, non-fatal	-	2
Protocol deviation	-	2

Baseline characteristics

Reporting groups	
Reporting group title	Epanova
Reporting group description:	
2g once daily	
Reporting group title	Olive Oil
Reporting group description:	
2g once daily (QD)	

Reporting group values	Epanova	Olive Oil	Total
Number of subjects	81	81	162
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)	74	75	149
From 65-84 years	7	6	13
85 years and over	0	0	0
Age Continuous | Units: Years			
arithmetic mean	50.3	50	
standard deviation	± 10.6	± 10.88	-
Gender, Male/Female Units: Participants			
Female	16	19	35
Male	65	62	127
Lipid-altering drug use Units: Subjects			
Yes	36	37	73
No	45	44	89
At least 1 qualifying TG category > 885 mg/dL Units: Subjects			
No	28	29	57
Yes	53	52	105

End points

End points reporting groups	
Reporting group title	Epanova
Reporting group description:	
2g once daily	
Reporting group title	Olive Oil
Reporting group description:	
2g once daily (QD)	

Primary: Percent Change in Triglyceride (mg/dL) for all Subjects in the Full Analysis Set (FAS)	
End point title	Percent Change in Triglyceride (mg/dL) for all Subjects in the Full Analysis Set (FAS)
End point description:	
This primary endpoint was tested in parallel together with the first of the secondary endpoints, each at 0.025 Type I error rate.	
End point type	Primary
End point timeframe:	
From Baseline to Week 12 Endpoint	

End point values	Epanova	Olive Oil		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	81	81		
Units: Percentage of Change (%)				
median (inter-quartile range (Q1-Q3))	-28.1 (-42.1 to -5.5)	-10.2 (-36.4 to 23)		

Statistical analyses

Statistical analysis title	Treatment Comparison
Statistical analysis description:	
Treatment comparison on percent change in Triglyceride from baseline to Week 12 endpoint of Epanova 2 g QD compared to olive oil 2 g QD for all subjects in the FAS	
Comparison groups	Epanova v Olive Oil
Number of subjects included in analysis	162
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	= 0.017
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Median difference (final values)
Point estimate	-14.2

Confidence interval	
level	95 %
sides	2-sided
lower limit	-26.2
upper limit	-2.8

Notes:

[1] - 1. Main analysis with missing values imputed using probabilities of missing estimated from logistic regression.2. The estimated median difference and its 95% CI were based on Hodges Lehmann procedure.

Secondary: 1. Percent Change in Triglyceride (mg/dL) for Subjects in the FAS with at Least 1 Qualifying TG >885 mg/dL and <2500 mg/dL

End point title	1. Percent Change in Triglyceride (mg/dL) for Subjects in the FAS with at Least 1 Qualifying TG >885 mg/dL and <2500 mg/dL

End point description:

This first secondary endpoint was tested in parallel together with the primary endpoint, each at 0.025 Type I error rate.

End point type	Secondary

End point timeframe:

From Baseline to Week 12 Endpoint

End point values	Epanova	Olive Oil		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	53	52		
Units: Percentage of Change (%)				
median (inter-quartile range (Q1-Q3))	-37.5 (-46.1 to -18.1)	-9.3 (-36.3 to 27)		

Statistical analyses

Statistical analysis title	Treatment Comparison

Statistical analysis description:

Treatment comparison on percent change in Triglyceride from baseline to Week 12 endpoint of Epanova 2 g QD compared to olive oil 2 g QD for Subjects in the FAS with at Least 1 Qualifying TG >885 mg/dL and <2500 mg/dL

Comparison groups	Epanova v Olive Oil
Number of subjects included in analysis	105
Analysis specification	Pre-specified
Analysis type	superiority[2]
P-value	= 0.0008
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Median difference (final values)
Point estimate	-26.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-40.5
upper limit	-11.5

Notes:

[2] - 1. Missing values were imputed using probabilities of missing estimated from logistic regression.2. The estimated median difference and its 95% CI were based on Hodges Lehmann procedure.

Secondary: 2. Percent Change in Non-High-Density Lipoprotein Cholesterol (mg/dL) for all Subjects in the Full Analysis Set (FAS)

End point title	2. Percent Change in Non-High-Density Lipoprotein Cholesterol (mg/dL) for all Subjects in the Full Analysis Set (FAS)

End point description:

This secondary endpoint, together with the 3rd. and 4th secondary ones, was treated as the core secondary, and the p value from the hypothesis test on its treatment comparison was adjusted by using Hommel's procedure.

End point type	Secondary

End point timeframe:

From Baseline to Week 12 Endpoint

End point values	Epanova	Olive Oil		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	81	81		
Units: Percentage of Change (%)				
median (inter-quartile range (Q1-Q3))	-8.8 (-15.7 to -1.4)	0.4 (-13.5 to 14.2)		

Statistical analyses

Statistical analysis title	Treatment Comparison

Statistical analysis description:

Treatment comparison on percent change in non-high-density lipoprotein cholesterol (mg/dL) from baseline to Week 12 endpoint of Epanova 2 g QD compared to olive oil 2 g QD for subjects in the FAS

Comparison groups	Epanova v Olive Oil
Number of subjects included in analysis	162
Analysis specification	Pre-specified
Analysis type	superiority[3]
P-value	= 0.018 [4]
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Median difference (final values)
Point estimate	-9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-14.8
upper limit	-2.8

Notes:

[3] - 1. Missing values were imputed using probabilities of missing estimated from logistic regression.2. The estimated median difference and its 95% CI were based on Hodges Lehmann procedure.
[4] - Adjusted by using Hommel's procedure

Secondary: 3. Percent Change in High-Density Lipoprotein Cholesterol (mg/dL) for all Subjects in the Full Analysis Set (FAS)

End point title	3. Percent Change in High-Density Lipoprotein Cholesterol (mg/dL) for all Subjects in the Full Analysis Set (FAS)

End point description:

1. Missing values were imputed using probabilities of missing estimated from logistic regression.2. The estimated median difference and its 95% CI were based on Hodges Lehmann procedure.

End point type	Secondary

End point timeframe:

From Baseline to Week 12 Endpoint

End point values	Epanova	Olive Oil		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	81	81		
Units: Percentage of Change (%)				
median (inter-quartile range (Q1-Q3))	3.4 (-5.1 to 12.5)	3.1 (-6.3 to 10.9)		

Statistical analyses

Statistical analysis title	Treatment Comparison

Statistical analysis description:

Treatment comparison on percent change in high-density lipoprotein cholesterol (mg/dL) from baseline to Week 12 endpoint of Epanova 2 g QD compared to olive oil 2 g QD for subjects in the FAS

Comparison groups	Epanova v Olive Oil
Number of subjects included in analysis	162
Analysis specification	Pre-specified
Analysis type	superiority[5]
P-value	= 0.7117 [6]
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Median difference (final values)
Point estimate	-0.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.5
upper limit	4.9

Notes:

[5] - The estimated median difference and its 95% CI were based on Hodges Lehmann procedure.

[6] - Adjusted by using Hommel's procedure

Secondary: 4. Percent Change in triglyceride (mg/dL) for subjects in the FAS with biochemically defined Fredrickson Type V (triglyceride/very-low-density lipoprotein cholesterol ≥6)

End point title	4. Percent Change in triglyceride (mg/dL) for subjects in the FAS with biochemically defined Fredrickson Type V (triglyceride/very-low-density lipoprotein cholesterol ≥6)

End point description:

1. Missing values were imputed using probabilities of missing estimated from logistic regression.2. The estimated median difference and its 95% CI were based on Hodges Lehmann procedure.

End point type	Secondary

End point timeframe:

From Baseline to Week 12 Endpoint

End point values	Epanova	Olive Oil		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	55	57		
Units: Percentage of Change (%)				
median (inter-quartile range (Q1-Q3))	-24.7 (-43.3 to -2.8)	-12.4 (-38.8 to 14.2)		

Statistical analyses

Statistical analysis title	Treatment Comparison

Statistical analysis description:

Treatment comparison on percent change in triglyceride (mg/dL) from baseline to Week 12 endpoint of Epanova 2 g QD compared to olive oil 2 g QD for subjects in the FAS with biochemically defined Fredrickson Type V (triglyceride/very-low-density lipoprotein cholesterol ≥6)

Comparison groups	Epanova v Olive Oil
Number of subjects included in analysis	112
Analysis specification	Pre-specified
Analysis type	superiority[7]
P-value	= 0.3034 [8]
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Median difference (final values)
Point estimate	-10.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-23.9
upper limit	3.5

Notes:

[7] - 1. Missing values were imputed using probabilities of missing estimated from logistic regression.2. The estimated median difference and its 95% CI were based on Hodges Lehmann procedure.

[8] - Adjusted by using Hommel's procedure

Adverse events

Adverse events information	
Timeframe for reporting adverse events: From Baseline to End of Trial	
Assessment type	Systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	16.1
Reporting groups	
Reporting group title	Olive Oil
Reporting group description: 2g once daily (QD)	
Reporting group title	Epanova
Reporting group description: 2g once daily (QD)	

Serious adverse events	Olive Oil	Epanova	
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 81 (2.47%)	1 / 81 (1.23%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Injury, poisoning and procedural complications			
Clavicle fracture			
subjects affected / exposed	1 / 81 (1.23%)	0 / 81 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Rectal haemorrhage			
subjects affected / exposed	1 / 81 (1.23%)	0 / 81 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			
subjects affected / exposed	0 / 81 (0.00%)	1 / 81 (1.23%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Olive Oil	Epanova	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	28 / 81 (34.57%)	29 / 81 (35.80%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
All neoplasms benign, malignant and unspecified (incl cysts and polyps)			
subjects affected / exposed	1 / 81 (1.23%)	1 / 81 (1.23%)	
occurrences (all)	1	1	
Lipoma			
subjects affected / exposed	1 / 81 (1.23%)	1 / 81 (1.23%)	
occurrences (all)	1	1	
Vascular disorders			
All vascular disorders			
subjects affected / exposed	1 / 81 (1.23%)	3 / 81 (3.70%)	
occurrences (all)	1	3	
Hypertension			
subjects affected / exposed	0 / 81 (0.00%)	3 / 81 (3.70%)	
occurrences (all)	0	3	
Flushing			
subjects affected / exposed	1 / 81 (1.23%)	0 / 81 (0.00%)	
occurrences (all)	1	0	
General disorders and administration site conditions			
All general disorders and administration site conditions			
subjects affected / exposed	2 / 81 (2.47%)	3 / 81 (3.70%)	
occurrences (all)	3	3	
Fatigue			
subjects affected / exposed	1 / 81 (1.23%)	2 / 81 (2.47%)	
occurrences (all)	1	2	
Chills			
subjects affected / exposed	0 / 81 (0.00%)	1 / 81 (1.23%)	
occurrences (all)	0	1	
Feeling hot			

subjects affected / exposed	1 / 81 (1.23%)	0 / 81 (0.00%)	
occurrences (all)	1	0	
Oedema peripheral			
subjects affected / exposed	1 / 81 (1.23%)	0 / 81 (0.00%)	
occurrences (all)	1	0	
Respiratory, thoracic and mediastinal disorders			
All respiratory, thoracic and mediastinal disorders			
subjects affected / exposed	2 / 81 (2.47%)	3 / 81 (3.70%)	
occurrences (all)	2	4	
Nasal congestion			
subjects affected / exposed	0 / 81 (0.00%)	1 / 81 (1.23%)	
occurrences (all)	0	1	
Oropharyngeal pain			
subjects affected / exposed	2 / 81 (2.47%)	1 / 81 (1.23%)	
occurrences (all)	2	1	
Rhinitis allergi			
subjects affected / exposed	0 / 81 (0.00%)	1 / 81 (1.23%)	
occurrences (all)	0	1	
Upper respiratory tract congestion			
subjects affected / exposed	0 / 81 (0.00%)	1 / 81 (1.23%)	
occurrences (all)	0	1	
Psychiatric disorders			
All psychiatric disorders			
subjects affected / exposed	1 / 81 (1.23%)	1 / 81 (1.23%)	
occurrences (all)	1	1	
Depression			
subjects affected / exposed	0 / 81 (0.00%)	1 / 81 (1.23%)	
occurrences (all)	0	1	
Anxiety			
subjects affected / exposed	1 / 81 (1.23%)	0 / 81 (0.00%)	
occurrences (all)	1	0	
Investigations			
All investigations			
subjects affected / exposed	3 / 81 (3.70%)	4 / 81 (4.94%)	
occurrences (all)	4	5	
Alanine aminotransferase increased			

subjects affected / exposed	1 / 81 (1.23%)	1 / 81 (1.23%)	
occurrences (all)	1	1	
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 81 (0.00%)	1 / 81 (1.23%)	
occurrences (all)	0	1	
Blood creatinine increased			
subjects affected / exposed	0 / 81 (0.00%)	1 / 81 (1.23%)	
occurrences (all)	0	1	
Blood glucose increased			
subjects affected / exposed	1 / 81 (1.23%)	1 / 81 (1.23%)	
occurrences (all)	1	1	
Gastric pH decreased			
subjects affected / exposed	0 / 81 (0.00%)	1 / 81 (1.23%)	
occurrences (all)	0	1	
Blood creatine phosphokinase increased			
subjects affected / exposed	2 / 81 (2.47%)	0 / 81 (0.00%)	
occurrences (all)	2	0	
Injury, poisoning and procedural complications			
All injury, poisoning and procedural complications			
subjects affected / exposed	2 / 81 (2.47%)	0 / 81 (0.00%)	
occurrences (all)	2	0	
Clavicle fracture			
subjects affected / exposed	1 / 81 (1.23%)	0 / 81 (0.00%)	
occurrences (all)	1	0	
Tooth fracture			
subjects affected / exposed	1 / 81 (1.23%)	0 / 81 (0.00%)	
occurrences (all)	1	0	
Cardiac disorders			
All cardiac disorders			
subjects affected / exposed	1 / 81 (1.23%)	1 / 81 (1.23%)	
occurrences (all)	2	1	
Coronary artery disease			
subjects affected / exposed	0 / 81 (0.00%)	1 / 81 (1.23%)	
occurrences (all)	0	1	

Angina pectoris			
subjects affected / exposed	1 / 81 (1.23%)	0 / 81 (0.00%)	
occurrences (all)	1	0	
Palpitations			
subjects affected / exposed	1 / 81 (1.23%)	0 / 81 (0.00%)	
occurrences (all)	1	0	
Nervous system disorders			
All nervous system disorders			
subjects affected / exposed	3 / 81 (3.70%)	5 / 81 (6.17%)	
occurrences (all)	6	5	
Dysgeusia			
subjects affected / exposed	0 / 81 (0.00%)	2 / 81 (2.47%)	
occurrences (all)	0	2	
Dizziness			
subjects affected / exposed	2 / 81 (2.47%)	1 / 81 (1.23%)	
occurrences (all)	3	1	
Headache			
subjects affected / exposed	1 / 81 (1.23%)	1 / 81 (1.23%)	
occurrences (all)	3	1	
Hypoaesthesia			
subjects affected / exposed	0 / 81 (0.00%)	1 / 81 (1.23%)	
occurrences (all)	0	1	
Paraesthesia			
subjects affected / exposed	1 / 81 (1.23%)	0 / 81 (0.00%)	
occurrences (all)	1	0	
Syncope			
subjects affected / exposed	1 / 81 (1.23%)	0 / 81 (0.00%)	
occurrences (all)	1	0	
Ear and labyrinth disorders			
All ear and labyrinth disorders			
subjects affected / exposed	2 / 81 (2.47%)	0 / 81 (0.00%)	
occurrences (all)	2	0	
Vertigo			
subjects affected / exposed	1 / 81 (1.23%)	0 / 81 (0.00%)	
occurrences (all)	1	0	
Vertigo positional			

subjects affected / exposed	1 / 81 (1.23%)	0 / 81 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	5 / 81 (6.17%)	5 / 81 (6.17%)	
occurrences (all)	6	5	
Eructation			
subjects affected / exposed	0 / 81 (0.00%)	3 / 81 (3.70%)	
occurrences (all)	0	3	
Constipation			
subjects affected / exposed	0 / 81 (0.00%)	2 / 81 (2.47%)	
occurrences (all)	0	2	
Dyspepsia			
subjects affected / exposed	1 / 81 (1.23%)	1 / 81 (1.23%)	
occurrences (all)	1	1	
Flatulence			
subjects affected / exposed	0 / 81 (0.00%)	1 / 81 (1.23%)	
occurrences (all)	0	1	
Food poisoning			
subjects affected / exposed	0 / 81 (0.00%)	1 / 81 (1.23%)	
occurrences (all)	0	1	
Nausea			
subjects affected / exposed	2 / 81 (2.47%)	1 / 81 (1.23%)	
occurrences (all)	2	1	
Pancreatitis			
subjects affected / exposed	0 / 81 (0.00%)	1 / 81 (1.23%)	
occurrences (all)	0	1	
Toothache			
subjects affected / exposed	0 / 81 (0.00%)	1 / 81 (1.23%)	
occurrences (all)	0	1	
Vomiting			
subjects affected / exposed	1 / 81 (1.23%)	1 / 81 (1.23%)	
occurrences (all)	1	1	
Abdominal distension			
subjects affected / exposed	1 / 81 (1.23%)	0 / 81 (0.00%)	
occurrences (all)	1	0	

Abdominal pain			
subjects affected / exposed	1 / 81 (1.23%)	0 / 81 (0.00%)	
occurrences (all)	2	0	
Haemorrhoids			
subjects affected / exposed	1 / 81 (1.23%)	0 / 81 (0.00%)	
occurrences (all)	1	0	
Rectal haemorrhage			
subjects affected / exposed	1 / 81 (1.23%)	0 / 81 (0.00%)	
occurrences (all)	1	0	
All gastrointestinal disorders			
subjects affected / exposed	7 / 81 (8.64%)	12 / 81 (14.81%)	
occurrences (all)	15	17	
Hepatobiliary disorders			
All hepatobiliary disorders			
subjects affected / exposed	0 / 81 (0.00%)	1 / 81 (1.23%)	
occurrences (all)	0	1	
Cholelithiasis			
subjects affected / exposed	0 / 81 (0.00%)	1 / 81 (1.23%)	
occurrences (all)	0	1	
Skin and subcutaneous tissue disorders			
All skin and subcutaneous tissue disorders			
subjects affected / exposed	0 / 81 (0.00%)	1 / 81 (1.23%)	
occurrences (all)	0	1	
Acne			
subjects affected / exposed	0 / 81 (0.00%)	1 / 81 (1.23%)	
occurrences (all)	0	1	
Renal and urinary disorders			
All renal and urinary disorders			
subjects affected / exposed	1 / 81 (1.23%)	0 / 81 (0.00%)	
occurrences (all)	1	0	
Renal impairment			
subjects affected / exposed	1 / 81 (1.23%)	0 / 81 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal and connective tissue disorders			
All musculoskeletal and connective tissue disorders			

subjects affected / exposed	5 / 81 (6.17%)	0 / 81 (0.00%)	
occurrences (all)	6	0	
Arthralgia			
subjects affected / exposed	1 / 81 (1.23%)	0 / 81 (0.00%)	
occurrences (all)	1	0	
Back pain			
subjects affected / exposed	1 / 81 (1.23%)	0 / 81 (0.00%)	
occurrences (all)	1	0	
Gouty arthritis			
subjects affected / exposed	1 / 81 (1.23%)	0 / 81 (0.00%)	
occurrences (all)	1	0	
Intervertebral disc protrusion			
subjects affected / exposed	1 / 81 (1.23%)	0 / 81 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal chest pain			
subjects affected / exposed	1 / 81 (1.23%)	0 / 81 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal pain			
subjects affected / exposed	1 / 81 (1.23%)	0 / 81 (0.00%)	
occurrences (all)	1	0	
Infections and infestations			
All infections and infestations			
subjects affected / exposed	6 / 81 (7.41%)	10 / 81 (12.35%)	
occurrences (all)	7	11	
Nasopharyngitis			
subjects affected / exposed	1 / 81 (1.23%)	3 / 81 (3.70%)	
occurrences (all)	1	3	
Bronchitis			
subjects affected / exposed	1 / 81 (1.23%)	1 / 81 (1.23%)	
occurrences (all)	1	1	
Erysipelas			
subjects affected / exposed	0 / 81 (0.00%)	1 / 81 (1.23%)	
occurrences (all)	0	1	
Gastroenteritis viral			
subjects affected / exposed	0 / 81 (0.00%)	1 / 81 (1.23%)	
occurrences (all)	0	1	

Influenza			
subjects affected / exposed	0 / 81 (0.00%)	1 / 81 (1.23%)	
occurrences (all)	0	1	
Respiratory tract infection viral			
subjects affected / exposed	0 / 81 (0.00%)	1 / 81 (1.23%)	
occurrences (all)	0	2	
Sialadenitis			
subjects affected / exposed	0 / 81 (0.00%)	1 / 81 (1.23%)	
occurrences (all)	0	1	
Urinary tract infection			
subjects affected / exposed	3 / 81 (3.70%)	1 / 81 (1.23%)	
occurrences (all)	3	1	
Upper respiratory tract infection			
subjects affected / exposed	2 / 81 (2.47%)	0 / 81 (0.00%)	
occurrences (all)	2	0	
Metabolism and nutrition disorders			
All metabolism and nutrition disorders			
subjects affected / exposed	5 / 81 (6.17%)	1 / 81 (1.23%)	
occurrences (all)	5	1	
Gout			
subjects affected / exposed	0 / 81 (0.00%)	1 / 81 (1.23%)	
occurrences (all)	0	1	
Decreased appetite			
subjects affected / exposed	1 / 81 (1.23%)	0 / 81 (0.00%)	
occurrences (all)	1	0	
Diabetes mellitus inadequate control			
subjects affected / exposed	1 / 81 (1.23%)	0 / 81 (0.00%)	
occurrences (all)	1	0	
Hypertriglyceridaemia			
subjects affected / exposed	2 / 81 (2.47%)	0 / 81 (0.00%)	
occurrences (all)	2	0	
Type 2 diabetes mellitus			
subjects affected / exposed	1 / 81 (1.23%)	0 / 81 (0.00%)	
occurrences (all)	1	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
08 November 2013	Amendment 1 (Protocol V2.0)
13 November 2013	Amendment 2 (Protocol V3.0)
23 December 2013	Amendment 3 (Protocol V4.0)
23 June 2014	Amendment 3.1 (Protocol V4.1)

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported