Clinical trial results:
A Phase III Randomized, Controlled, Superiority Study Evaluating EVARREST™ Fibrin Sealant Patch Versus Standard of Care Treatment in Controlling Parenchymal Bleeding During Hepatic Surgery

Summary

EudraCT number	2013-002535-24
Trial protocol	GB
Global end of trial date	22 September 2014

Results information

Result version number	v1 (current)
This version publication date	26 March 2016
First version publication date	26 March 2016

Trial information

Trial identification

Sponsor protocol code	BIOS-13-005

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Ethicon, a Johnson & Johnson company
Sponsor organisation address	Route 22 West, Somerville, United States, NJ 08876-0151
Public contact	Clinical Development, Johnson & Johnson Medical Ltd., +44 1506594675, vjevans@its.jnj.com
Scientific contact	Clinical Development, Johnson & Johnson Medical Ltd., +44 1506594675, vjevans@its.jnj.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	15 October 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	22 September 2014
Global end of trial reached?	Yes
Global end of trial date	22 September 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the safety and hemostatic effectiveness of EVARREST Fibrin Sealant Patch versus standard of care treatment (SoC) in controlling parenchymal bleeding during hepatic surgery.

Protection of trial subjects:

A DMC was established. The DMC was to be convened if a stopping rule for safety was met, however no such stopping rule requiring DMC review was met for this trial. In addition a Clinical Adjudication Committee was appointed to adjudicate adverse events or serious adverse events that were potentially related to target bleeding site bleeding or thrombotic events.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	29 October 2013
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 30
Country: Number of subjects enrolled	United States: 36
Country: Number of subjects enrolled	Australia: 23
Country: Number of subjects enrolled	New Zealand: 13
Worldwide total number of subjects	102
EEA total number of subjects	30

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)	54

From 65 to 84 years	47
85 years and over	1

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Potentially eligible patients were reviewed and enrolled following the consent process. Screening involved a full history, physical examination, determination of full blood count, LFT's, coagulation studies and if appropriate, pregnancy test and occurred within 21 days of the surgical procedure.

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	EVARREST

Arm description:

EVARREST

Arm type	Experimental
Investigational medicinal product name	EVARREST
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Sealant matrix
Routes of administration	Topical use

Dosage and administration details:

Up to 4 units (10.2 x 10.2cm / 4x4 in) of EVARREST were permitted to be left in place at treatment sites per subjects randomized to treatment with EVARREST. After placement of EVARREST, firm manual compression sufficient to stem all bleeding was applied continuously and maintained until 4 minutes post randomization.

Arm title	Standard of care

Arm description:

Standard of care

Arm type	Standard of care

No investigational medicinal product assigned in this arm

Number of subjects in period 1	EVARREST	Standard of care
Started	50	52
Completed	48	49
Not completed	2	3
Adverse event, serious fatal	1	1
Consent withdrawn by subject	-	1
Lost to follow-up	1	1

Baseline characteristics

Reporting groups	
Reporting group title	EVARREST
Reporting group description: EVARREST	
Reporting group title	Standard of care
Reporting group description: Standard of care	

Reporting group values	EVARREST	Standard of care	Total
Number of subjects	50	52	102
Age categorical Units: Subjects			
Adults 18-<50 years	11	5	16
Adults 50-<65 years	15	23	38
Adults 65-<75 years	17	15	32
Adults >=75	7	9	16
Gender categorical Units: Subjects			
Female	20	20	40
Male	30	32	62

End points

End points reporting groups

Reporting group title	EVARREST
Reporting group description: EVARREST	
Reporting group title	Standard of care
Reporting group description: Standard of care	
Subject analysis set title	Safety
Subject analysis set type	Safety analysis
Subject analysis set description: Safety analysis set	
Subject analysis set title	Intent to treat (ITT)
Subject analysis set type	Intention-to-treat
Subject analysis set description: Intent to treat	
Subject analysis set title	Per Protocol
Subject analysis set type	Per protocol
Subject analysis set description: Per protocol	

Primary: Hemostasis at 4 mins and maintenance to wound closure

End point title	Hemostasis at 4 mins and maintenance to wound closure
End point description:	
End point type	Primary
End point timeframe: 4-minutes after randomization	

End point values	EVARREST	Standard of care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	50	52		
Units: Percentage of successes	96	46		

Statistical analyses

Statistical analysis title	Primary efficacy endpoint
Comparison groups	EVARREST v Standard of care

Number of subjects included in analysis	102
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Chi-squared

Secondary: Hemostasis at 10 mins and maintenance to wound closure

End point title	Hemostasis at 10 mins and maintenance to wound closure

End point description:

End point type	Secondary

End point timeframe:

Hemostatic success at 10 minutes post randomization

End point values	EVARREST	Standard of care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	50	52		
Units: Percentage of successes	98	81		

Statistical analyses

Statistical analysis title	Secondary endpoint analysis
Comparison groups	EVARREST v Standard of care
Number of subjects included in analysis	102
Analysis specification	Pre-specified
Analysis type	other[1]
P-value	= 0.1243 [2]
Method	Logistic model

Notes:

[1] - Secondary endpoint analysis - therefore no formal hypothesis testing

[2] - In the ITT analysis the p-value was 0.1243 and did not show statistical significance, however in the PP analysis a statistical difference in favour of EVARREST compared to SOC was achieved (P=0.0126)

Secondary: Absolute time to hemostasis

End point title	Absolute time to hemostasis

End point description:

End point type	Secondary

End point timeframe:

Absolute time to hemostasis (mins)

End point values	EVARREST	Standard of care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	50	51[3]		
Units: Minutes				
median (full range (min-max))	4 (4 to 15.9)	4.7 (1.7 to 33)		

Notes:

[3] - One missing result

Statistical analyses

Statistical analysis title	Secondary endpoint analysis
Comparison groups	EVARREST v Standard of care
Number of subjects included in analysis	101
Analysis specification	Pre-specified
Analysis type	other[4]
P-value	< 0.0001
Method	Wilcoxon rank-sum

Notes:

[4] - Secondary endpoint analysis - no formal hypothesis testing

Adverse events

Adverse events information

Timeframe for reporting adverse events:

AE's were collected from the point of randomization during the surgical procedure, throughout the hospital admission, and until completion of the 60-day follow-up visit.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	16.0

Reporting groups

Reporting group title	EVARREST
Reporting group description: -	
Reporting group title	Standard of care

Reporting group description: -

Serious adverse events	EVARREST	Standard of care	
Total subjects affected by serious adverse events			
subjects affected / exposed	12 / 50 (24.00%)	16 / 52 (30.77%)	
number of deaths (all causes)	1	1	
number of deaths resulting from adverse events	0	0	
Injury, poisoning and procedural complications			
Chemical peritonitis			
subjects affected / exposed	1 / 50 (2.00%)	0 / 52 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Incisional hernia			
subjects affected / exposed	0 / 50 (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	
Post procedural bile leak			
subjects affected / exposed	2 / 50 (4.00%)	0 / 52 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postoperative ileus			

subjects affected / exposed	0 / 50 (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	
Wound decomposition			
subjects affected / exposed	0 / 50 (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	
Vascular disorders			
Orthostatic hypertension			
subjects affected / exposed	1 / 50 (2.00%)	0 / 52 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	0 / 50 (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	
Bradycardia			
subjects affected / exposed	0 / 50 (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	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 50 (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			
Ascites			
subjects affected / exposed	0 / 50 (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	
Constipation			

subjects affected / exposed	0 / 50 (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	
Diarrhoea			
subjects affected / exposed	0 / 50 (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	
Ileus			
subjects affected / exposed	1 / 50 (2.00%)	0 / 52 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal perforation			
subjects affected / exposed	1 / 50 (2.00%)	0 / 52 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Localised intraabdominal fluid collection			
subjects affected / exposed	0 / 50 (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	
Small intestinal obstruction			
subjects affected / exposed	1 / 50 (2.00%)	0 / 52 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stomatitis			
subjects affected / exposed	0 / 50 (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	
Hepatobiliary disorders			
Hepatic failure			
subjects affected / exposed	1 / 50 (2.00%)	0 / 52 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Respiratory, thoracic and mediastinal disorders			

Hypoxia			
subjects affected / exposed	1 / 50 (2.00%)	0 / 52 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax			
subjects affected / exposed	0 / 50 (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	
Respiratory failure			
subjects affected / exposed	0 / 50 (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	
Psychiatric disorders			
Delirium			
subjects affected / exposed	0 / 50 (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	
Renal and urinary disorders			
Renal failure	Additional description: This event term of renal failure includes those coded to renal failure, renal failure acute and renal failure chronic.		
subjects affected / exposed	2 / 50 (4.00%)	3 / 52 (5.77%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	
Infections and infestations			
Abdominal abscess			
subjects affected / exposed	1 / 50 (2.00%)	0 / 52 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile colitis			
subjects affected / exposed	0 / 50 (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	
Gastroenteritis			

subjects affected / exposed	1 / 50 (2.00%)	0 / 52 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematoma infection			
subjects affected / exposed	2 / 50 (4.00%)	0 / 52 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Liver abscess			
subjects affected / exposed	0 / 50 (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	
Pneumonia			
subjects affected / exposed	2 / 50 (4.00%)	1 / 52 (1.92%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	0 / 50 (0.00%)	2 / 52 (3.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subdiaphragmatic abscess			
subjects affected / exposed	0 / 50 (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	
Urinary tract infection			
subjects affected / exposed	0 / 50 (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	
Urosepsis			
subjects affected / exposed	0 / 50 (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	
Metabolism and nutrition disorders			
Hypomagnesaemia			

subjects affected / exposed	1 / 50 (2.00%)	0 / 52 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	EVARREST	Standard of care	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	45 / 50 (90.00%)	50 / 52 (96.15%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	6 / 50 (12.00%)	5 / 52 (9.62%)	
occurrences (all)	6	5	
Hypotension			
subjects affected / exposed	14 / 50 (28.00%)	18 / 52 (34.62%)	
occurrences (all)	16	19	
General disorders and administration site conditions			
Oedema			
subjects affected / exposed	4 / 50 (8.00%)	1 / 52 (1.92%)	
occurrences (all)	4	1	
Oedema peripheral			
subjects affected / exposed	5 / 50 (10.00%)	3 / 52 (5.77%)	
occurrences (all)	6	3	
Pain			
subjects affected / exposed	3 / 50 (6.00%)	1 / 52 (1.92%)	
occurrences (all)	4	1	
Pyrexia			
subjects affected / exposed	13 / 50 (26.00%)	11 / 52 (21.15%)	
occurrences (all)	14	13	
Respiratory, thoracic and mediastinal disorders			
Atelectasis			
subjects affected / exposed	3 / 50 (6.00%)	9 / 52 (17.31%)	
occurrences (all)	3	9	
Dyspnoea			

subjects affected / exposed	3 / 50 (6.00%)	2 / 52 (3.85%)	
occurrences (all)	3	2	
Hiccups			
subjects affected / exposed	3 / 50 (6.00%)	1 / 52 (1.92%)	
occurrences (all)	3	1	
Hypoxia			
subjects affected / exposed	2 / 50 (4.00%)	4 / 52 (7.69%)	
occurrences (all)	2	5	
Pleural effusion			
subjects affected / exposed	5 / 50 (10.00%)	3 / 52 (5.77%)	
occurrences (all)	5	4	
Psychiatric disorders			
Confusional state			
subjects affected / exposed	3 / 50 (6.00%)	6 / 52 (11.54%)	
occurrences (all)	3	7	
Hallucination			
subjects affected / exposed	3 / 50 (6.00%)	1 / 52 (1.92%)	
occurrences (all)	3	1	
Insomnia			
subjects affected / exposed	5 / 50 (10.00%)	1 / 52 (1.92%)	
occurrences (all)	6	1	
Investigations			
Blood lactic acid increased			
subjects affected / exposed	4 / 50 (8.00%)	6 / 52 (11.54%)	
occurrences (all)	4	6	
International normalised ratio increased			
subjects affected / exposed	4 / 50 (8.00%)	2 / 52 (3.85%)	
occurrences (all)	4	2	
Urine output decreased			
subjects affected / exposed	4 / 50 (8.00%)	3 / 52 (5.77%)	
occurrences (all)	4	4	
Injury, poisoning and procedural complications			
Post procedural bile leak			
subjects affected / exposed	2 / 50 (4.00%)	3 / 52 (5.77%)	
occurrences (all)	2	3	
Postoperative ileus			

subjects affected / exposed	3 / 50 (6.00%)	4 / 52 (7.69%)	
occurrences (all)	3	4	
Procedural pain			
subjects affected / exposed	5 / 50 (10.00%)	10 / 52 (19.23%)	
occurrences (all)	5	11	
Wound secretion			
subjects affected / exposed	3 / 50 (6.00%)	4 / 52 (7.69%)	
occurrences (all)	3	4	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	2 / 50 (4.00%)	4 / 52 (7.69%)	
occurrences (all)	2	5	
Bradycardia			
subjects affected / exposed	1 / 50 (2.00%)	3 / 52 (5.77%)	
occurrences (all)	1	3	
Tachycardia			
subjects affected / exposed	4 / 50 (8.00%)	11 / 52 (21.15%)	
occurrences (all)	4	11	
Nervous system disorders			
Dizziness			
subjects affected / exposed	6 / 50 (12.00%)	6 / 52 (11.54%)	
occurrences (all)	6	7	
Lethargy			
subjects affected / exposed	1 / 50 (2.00%)	3 / 52 (5.77%)	
occurrences (all)	1	3	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	4 / 50 (8.00%)	5 / 52 (9.62%)	
occurrences (all)	4	5	
Leukocytosis			
subjects affected / exposed	3 / 50 (6.00%)	2 / 52 (3.85%)	
occurrences (all)	3	2	
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	2 / 50 (4.00%)	3 / 52 (5.77%)	
occurrences (all)	3	3	
Abdominal pain			

subjects affected / exposed	5 / 50 (10.00%)	7 / 52 (13.46%)	
occurrences (all)	5	10	
Abdominal pain upper			
subjects affected / exposed	4 / 50 (8.00%)	1 / 52 (1.92%)	
occurrences (all)	4	1	
Ascites			
subjects affected / exposed	5 / 50 (10.00%)	3 / 52 (5.77%)	
occurrences (all)	5	3	
Constipation			
subjects affected / exposed	14 / 50 (28.00%)	22 / 52 (42.31%)	
occurrences (all)	19	25	
Diarrhoea			
subjects affected / exposed	3 / 50 (6.00%)	7 / 52 (13.46%)	
occurrences (all)	3	7	
Nausea			
subjects affected / exposed	25 / 50 (50.00%)	23 / 52 (44.23%)	
occurrences (all)	30	30	
Small intestinal obstruction			
subjects affected / exposed	3 / 50 (6.00%)	0 / 52 (0.00%)	
occurrences (all)	3	0	
Vomiting			
subjects affected / exposed	13 / 50 (26.00%)	14 / 52 (26.92%)	
occurrences (all)	15	16	
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	6 / 50 (12.00%)	7 / 52 (13.46%)	
occurrences (all)	6	7	
Renal and urinary disorders			
Urinary retention			
subjects affected / exposed	2 / 50 (4.00%)	3 / 52 (5.77%)	
occurrences (all)	2	3	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	2 / 50 (4.00%)	4 / 52 (7.69%)	
occurrences (all)	2	4	
Musculoskeletal pain			

subjects affected / exposed	8 / 50 (16.00%)	5 / 52 (9.62%)	
occurrences (all)	8	5	
Infections and infestations			
Pneumonia			
subjects affected / exposed	3 / 50 (6.00%)	3 / 52 (5.77%)	
occurrences (all)	3	3	
Urinary tract infection			
subjects affected / exposed	2 / 50 (4.00%)	5 / 52 (9.62%)	
occurrences (all)	3	5	
Wound infection			
subjects affected / exposed	1 / 50 (2.00%)	3 / 52 (5.77%)	
occurrences (all)	1	3	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	1 / 50 (2.00%)	3 / 52 (5.77%)	
occurrences (all)	1	3	
Hyperglycaemia			
subjects affected / exposed	0 / 50 (0.00%)	3 / 52 (5.77%)	
occurrences (all)	0	3	
Hyperkalaemia			
subjects affected / exposed	2 / 50 (4.00%)	4 / 52 (7.69%)	
occurrences (all)	2	4	
Hypokalaemia			
subjects affected / exposed	12 / 50 (24.00%)	11 / 52 (21.15%)	
occurrences (all)	13	11	
Hypomagnesaemia			
subjects affected / exposed	12 / 50 (24.00%)	12 / 52 (23.08%)	
occurrences (all)	14	13	
Hypophosphataemia			
subjects affected / exposed	11 / 50 (22.00%)	11 / 52 (21.15%)	
occurrences (all)	12	11	
Malnutrition			
subjects affected / exposed	3 / 50 (6.00%)	0 / 52 (0.00%)	
occurrences (all)	3	0	
Vitamin D deficiency			

subjects affected / exposed occurrences (all)	3 / 50 (6.00%) 3	1 / 52 (1.92%) 1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
15 February 2014	Addition of DMC and CEC details to the protocol along with other various clarifications and improvements to grammar.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported