Clinical trial results:
A Phase III Randomized, Controlled, Superiority Study Evaluating the Fibrin Pad Versus Standard of Care Treatment in Controlling Parenchymal Bleeding During Elective Hepatic Surgery

Summary

EudraCT number	2010-019427-58
Trial protocol	DE GB NL
Global end of trial date	17 October 2011

Results information

Result version number	v1 (current)
This version publication date	05 August 2016
First version publication date	05 August 2016

Trial information

Trial identification

Sponsor protocol code	400-10-001

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01166243
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Ethicon Inc.,a Johnston & Johnson co.
Sponsor organisation address	Route 22 West , Somerville, United States,
Public contact	Jonathan Batiller, Ethicon Inc., a Johnston & Johnson co., +1 9082182492, jbatill2@its.jnj.com
Scientific contact	Jonathan Batiller, Ethicon Inc., a Johnston & Johnson co., +1 9082182492, jbatill2@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	25 October 2011
Is this the analysis of the primary completion data?	Yes
Primary completion date	17 October 2011
Global end of trial reached?	Yes
Global end of trial date	17 October 2011
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 Fibrin Pad(FP) versus Standard of Care (SOC)treatment in controlling parenchymal bleeding during hepatic surgery.

Protection of trial subjects:

The protocol and consent form were provided to the appropriate Ethics Committee for approval.

Background therapy:

Not applicable

Evidence for comparator:

The control group was to be treated with the surgeon’s Standard of Care (SoC) methods. Standard of Care is a composite of techniques/methods typically used by the surgeon to control parenchymal bleeding after conventional methods (e.g. suture, ligature, cautery) are ineffective or impractical. For this study, SoC was to be initiated with continuous firm manual compression with or without gauze or sponge and with or without a topical absorbable hemostat (TAH).

Actual start date of recruitment	14 June 2010
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	Netherlands: 2
Country: Number of subjects enrolled	United Kingdom: 27
Country: Number of subjects enrolled	Germany: 25
Country: Number of subjects enrolled	Australia: 34
Country: Number of subjects enrolled	New Zealand: 16
Worldwide total number of subjects	104
EEA total number of subjects	54

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	0

months)	
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	50
From 65 to 84 years	54
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The first subject was recruited on the 14 June 2010 and the last subject was 25 August 2011

Pre-assignment

Screening details:

Subjects were screened within 21 days prior to surgery. Prior to any study related procedures, subjects were fully informed of all aspects of the study and asked to sign a consent form. A ‘run-in’ phase in which the first eligible subject for each investigator without prior clinical experience with the FP was not randomized and were treated with FP

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	FIBRIN PAD

Arm description:

FP is a sterile bio-absorbable combination product consisting of two constituent parts— a flexible matrix and a coating of two biological components. The matrix consists of polyglactin 910 (PG910) filaments needle punched into a backing fabric of Oxidized Regenerated Cellulose (ORC). The biological components are Human Thrombin and Human Fibrinogen.

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

Dosage and administration details:

FP is a sterile bio-absorbable combination product consisting of two constituent parts— a flexible matrix and a coating of two biological components. The matrix consists of polyglactin 910 (PG910) filaments needle punched into a backing fabric of Oxidized Regenerated Cellulose (ORC). The biological components are Human Thrombin and Human Fibrinogen. FP was supplied in units of 10.2 x 10.2 cm (4 x 4 inches). The TBS required to be adequately covered with a single unit of FP, with an overlap 1-2 cm beyond the margins of the wound. If required, FP could be cut to fit the size of the bleeding site. If breakthrough bleeding occurred at the TBS during the 4-minute treatment period, the surgeon was permitted to retreat with FP. If bleeding was due to insufficient coverage of the TBS, the additional units were to be applied so that they overlapped the previously applied product.If bleeding was due to incomplete adherence to the tissue, the previous unit was removed and replaced with a new unit

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[1]	FIBRIN PAD	Standard of care
Started	40	44
Completed	39	42
Not completed	1	2
Consent withdrawn by subject	-	1
Lost to follow-up	1	1

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: There were 20 subjects included in the run-in phase so these patients were included in the safety anaylsis set not in the ITT.

Baseline characteristics

Reporting groups	
Reporting group title	FIBRIN PAD
Reporting group description:	
FP is a sterile bio-absorbable combination product consisting of two constituent parts— a flexible matrix and a coating of two biological components. The matrix consists of polyglactin 910 (PG910) filaments needle punched into a backing fabric of Oxidized Regenerated Cellulose (ORC). The biological components are Human Thrombin and Human Fibrinogen.	
Reporting group title	Standard of care
Reporting group description:	
Standard of care	

Reporting group values	FIBRIN PAD	Standard of care	Total
Number of subjects	40	44	84
Age categorical Units: Subjects			
18-<50 years	6	7	13
50-<65 years	12	14	26
65-<75 years	13	13	26
>=75 years	9	10	19
Gender categorical Units: Subjects			
Female	16	20	36
Male	24	24	48

End points

End points reporting groups

Reporting group title	FIBRIN PAD
Reporting group description:	
FP is a sterile bio-absorbable combination product consisting of two constituent parts— a flexible matrix and a coating of two biological components. The matrix consists of polyglactin 910 (PG910) filaments needle punched into a backing fabric of Oxidized Regenerated Cellulose (ORC). The biological components are Human Thrombin and Human Fibrinogen.	
Reporting group title	Standard of care
Reporting group description:	
Standard of care	

Primary: hemostasis at 4-minutes at TBS and with no re-bleeding requiring treatment prior to wound closure

End point title	hemostasis at 4-minutes at TBS and with no re-bleeding requiring treatment prior to wound closure
End point description:	
Proportion of subjects achieving hemostasis at the TBS at 4-minutes following randomization and with no re-bleeding requiring treatment at the TBS anytime prior to initiation of wound closure (latest point in time where FP is visible to confirmhemostasis). Hemostasis is defined as no detectable bleeding at the TBS.	
End point type	Primary
End point timeframe:	
haemostasis at 4 minutes	

End point values	FIBRIN PAD	Standard of care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	40	44		
Units: haemostasis at 4 minutes				
Hemostasis achieved at 4 min	33	13		

Statistical analyses

Statistical analysis title	Primary efficacy endpoint
Statistical analysis description:	
The proportion of subjects achieving hemostatic success at 4 minutes after randomization with no re-bleeding requiring treatment prior to initiation of wound closure. Hemostasis is defined as no detectable bleeding at the TBS. The triangular test for a binary response variable was utilized (PEST 4.4 software) with a two-sided alpha 0.05 and power 0.90. Subjects were randomized with a 1:1 allocation ratio, FP to SoC. The assumed success rate in the control arm was 50%, and FP was 75%.	
Comparison groups	FIBRIN PAD v Standard of care

Number of subjects included in analysis	84
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Chi-squared

Secondary: Proportion of subjects achieving hemostatic success at 10 minutes following randomization

End point title	Proportion of subjects achieving hemostatic success at 10 minutes following randomization

End point description:

Proportion of subjects achieving hemostatic success at 10 minutes following randomization (defined as achievement of hemostasis at 10 minutes and no further bleeding requiring re-treatment prior to wound closure)

End point type	Secondary

End point timeframe:

10 minutes following randomization

End point values	FIBRIN PAD	Standard of care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	40	44		
Units: Achievement of hemostasis	38	30		

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute time to hemostasis

End point title	Absolute time to hemostasis

End point description:

Absolute time to hemostasis (defined as the absolute time to achieve hemostasis at or after 4 minutes from randomization)

End point type	Secondary

End point timeframe:

Absolute time to achieve hemostasis at or after 4 minutes from randomization

End point values	FIBRIN PAD	Standard of care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	40	44		
Units: minutes				
median (confidence interval 95%)	4 (4 to 4)	9.7 (4 to 10)		

Statistical analyses

Statistical analysis title	Secondary endpoint analysis
Comparison groups	FIBRIN PAD v Standard of care
Number of subjects included in analysis	84
Analysis specification	Pre-specified
Analysis type	other[1]
P-value	< 0.0001
Method	Wilcoxon Rank -Sum Test

Notes:

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

Secondary: Proportion of subjects who, after the initial hemostatic success at 4 minutes, have breakthrough bleeding requiring treatment

End point title	Proportion of subjects who, after the initial hemostatic success at 4 minutes, have breakthrough bleeding requiring treatment

End point description:

The proportion of subjects who, after the initial hemostatic success at 4 minutes, have breakthrough bleeding requiring treatment

End point type	Secondary

End point timeframe:

Proportion of subjects who, after the initial hemostatic success at 4 minutes, have breakthrough bleeding requiring treatment

End point values	FIBRIN PAD	Standard of care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	38	44		
Units: Breakthrough bleeding requiring treatmen	1	1		

Statistical analyses

Statistical analysis title	secondary endpoint analysis
Comparison groups	Standard of care v FIBRIN PAD

Number of subjects included in analysis	82
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 1
Method	logistic model
Parameter estimate	Log odds ratio
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.994
upper limit	2.994

Secondary: The proportion of subjects who, after the initial establishment of hemostasis (after 4 minutes), had breakthrough bleeding requiring treatment

End point title	The proportion of subjects who, after the initial establishment of hemostasis (after 4 minutes), had breakthrough bleeding requiring treatment

End point description:

The proportion of subjects who, after the initial establishment of hemostasis (after 4 minutes), had breakthrough bleeding requiring treatment

End point type	Secondary

End point timeframe:

The proportion of subjects who, after the initial establishment of hemostasis (after 4 minutes), had breakthrough bleeding requiring treatment

End point values	FIBRIN PAD	Standard of care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	40	44		
Units: breakthrough bleeding requiring treatmen	4	27		

Statistical analyses

Statistical analysis title	Secondary endpoint analysis
Comparison groups	FIBRIN PAD v Standard of care
Number of subjects included in analysis	84
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	logistic model
Parameter estimate	Log odds ratio
Point estimate	-1.82

Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.947
upper limit	-0.692

Adverse events

Adverse events information

Timeframe for reporting adverse events:

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

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	11.0

Reporting groups

Reporting group title	FIBRIN PAD

Reporting group description:

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Reporting group title	Standard of care

Reporting group description:

Standard of care

Serious adverse events	FIBRIN PAD	Standard of care	
Total subjects affected by serious adverse events			
subjects affected / exposed	16 / 59 (27.12%)	10 / 45 (22.22%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Injury, poisoning and procedural complications			
Post procedural bile leak			
subjects affected / exposed	1 / 59 (1.69%)	2 / 45 (4.44%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural haemorrhage			
subjects affected / exposed	1 / 59 (1.69%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal haematoma			
subjects affected / exposed	1 / 59 (1.69%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound dehiscence			

subjects affected / exposed	1 / 59 (1.69%)	1 / 45 (2.22%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Vena cava thrombosis			
subjects affected / exposed	0 / 59 (0.00%)	1 / 45 (2.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	1 / 59 (1.69%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	1 / 59 (1.69%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	1 / 59 (1.69%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular tachycardia			
subjects affected / exposed	2 / 59 (3.39%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Disease progression			
subjects affected / exposed	2 / 59 (3.39%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-cardiac chest pain			
subjects affected / exposed	1 / 59 (1.69%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 59 (0.00%)	1 / 45 (2.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain upper			
subjects affected / exposed	0 / 59 (0.00%)	1 / 45 (2.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intra-abdominal haemorrhage			
subjects affected / exposed	2 / 59 (3.39%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestine perforation			
subjects affected / exposed	0 / 59 (0.00%)	1 / 45 (2.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Localised intraabdominal fluid collection			
subjects affected / exposed	2 / 59 (3.39%)	3 / 45 (6.67%)	
occurrences causally related to treatment / all	1 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	1 / 59 (1.69%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal obstruction			
subjects affected / exposed	0 / 59 (0.00%)	1 / 45 (2.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	1 / 59 (1.69%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Hepatobiliary disorders			
Biloma			
subjects affected / exposed	1 / 59 (1.69%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic failure			
subjects affected / exposed	0 / 59 (0.00%)	1 / 45 (2.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Jaundice			
subjects affected / exposed	1 / 59 (1.69%)	0 / 45 (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			
Pleural effusion			
subjects affected / exposed	1 / 59 (1.69%)	1 / 45 (2.22%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	1 / 59 (1.69%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	1 / 59 (1.69%)	0 / 45 (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	FIBRIN PAD	Standard of care	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	56 / 59 (94.92%)	43 / 45 (95.56%)	
Vascular disorders			

Hypertension			
subjects affected / exposed	6 / 59 (10.17%)	10 / 45 (22.22%)	
occurrences (all)	10	11	
Hypotension			
subjects affected / exposed	21 / 59 (35.59%)	17 / 45 (37.78%)	
occurrences (all)	25	22	
General disorders and administration site conditions			
Oedema peripheral			
subjects affected / exposed	4 / 59 (6.78%)	9 / 45 (20.00%)	
occurrences (all)	4	10	
Pain			
subjects affected / exposed	15 / 59 (25.42%)	18 / 45 (40.00%)	
occurrences (all)	23	24	
Pyrexia			
subjects affected / exposed	15 / 59 (25.42%)	12 / 45 (26.67%)	
occurrences (all)	18	19	
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	3 / 59 (5.08%)	1 / 45 (2.22%)	
occurrences (all)	3	1	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	4 / 59 (6.78%)	2 / 45 (4.44%)	
occurrences (all)	4	2	
Hypoxia			
subjects affected / exposed	3 / 59 (5.08%)	1 / 45 (2.22%)	
occurrences (all)	3	1	
Pleural effusion			
subjects affected / exposed	7 / 59 (11.86%)	8 / 45 (17.78%)	
occurrences (all)	7	8	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	8 / 59 (13.56%)	3 / 45 (6.67%)	
occurrences (all)	9	3	
Confusional state			

subjects affected / exposed	3 / 59 (5.08%)	5 / 45 (11.11%)	
occurrences (all)	3	6	
Delirium			
subjects affected / exposed	2 / 59 (3.39%)	3 / 45 (6.67%)	
occurrences (all)	2	3	
Hallucination			
subjects affected / exposed	3 / 59 (5.08%)	5 / 45 (11.11%)	
occurrences (all)	4	5	
Insomnia			
subjects affected / exposed	9 / 59 (15.25%)	7 / 45 (15.56%)	
occurrences (all)	10	8	
Investigations			
Liver function test abnormal			
subjects affected / exposed	3 / 59 (5.08%)	0 / 45 (0.00%)	
occurrences (all)	3	0	
Prothrombin time prolonged			
subjects affected / exposed	3 / 59 (5.08%)	1 / 45 (2.22%)	
occurrences (all)	3	1	
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	0 / 59 (0.00%)	4 / 45 (8.89%)	
occurrences (all)	0	5	
Post procedural bile leak			
subjects affected / exposed	3 / 59 (5.08%)	4 / 45 (8.89%)	
occurrences (all)	3	4	
Procedural pain			
subjects affected / exposed	12 / 59 (20.34%)	7 / 45 (15.56%)	
occurrences (all)	18	9	
Wound dehiscence			
subjects affected / exposed	3 / 59 (5.08%)	3 / 45 (6.67%)	
occurrences (all)	3	3	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	2 / 59 (3.39%)	3 / 45 (6.67%)	
occurrences (all)	2	3	
Sinus tachycardia			

subjects affected / exposed	3 / 59 (5.08%)	2 / 45 (4.44%)	
occurrences (all)	3	3	
Tachycardia			
subjects affected / exposed	6 / 59 (10.17%)	5 / 45 (11.11%)	
occurrences (all)	9	6	
Nervous system disorders			
Dizziness			
subjects affected / exposed	9 / 59 (15.25%)	7 / 45 (15.56%)	
occurrences (all)	10	9	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	14 / 59 (23.73%)	11 / 45 (24.44%)	
occurrences (all)	14	11	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	3 / 59 (5.08%)	4 / 45 (8.89%)	
occurrences (all)	3	4	
Constipation			
subjects affected / exposed	22 / 59 (37.29%)	20 / 45 (44.44%)	
occurrences (all)	24	23	
Diarrhoea			
subjects affected / exposed	3 / 59 (5.08%)	2 / 45 (4.44%)	
occurrences (all)	5	2	
Dyspepsia			
subjects affected / exposed	3 / 59 (5.08%)	0 / 45 (0.00%)	
occurrences (all)	3	0	
Flatulence			
subjects affected / exposed	1 / 59 (1.69%)	3 / 45 (6.67%)	
occurrences (all)	1	3	
Gastrooesophageal reflux disease			
subjects affected / exposed	3 / 59 (5.08%)	1 / 45 (2.22%)	
occurrences (all)	3	1	
Localised intraabdominal fluid collection			
subjects affected / exposed	2 / 59 (3.39%)	6 / 45 (13.33%)	
occurrences (all)	2	6	
Nausea			

subjects affected / exposed	31 / 59 (52.54%)	28 / 45 (62.22%)	
occurrences (all)	42	34	
Vomiting			
subjects affected / exposed	20 / 59 (33.90%)	14 / 45 (31.11%)	
occurrences (all)	24	20	
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	4 / 59 (6.78%)	3 / 45 (6.67%)	
occurrences (all)	4	3	
Renal and urinary disorders			
Incontinence			
subjects affected / exposed	0 / 59 (0.00%)	5 / 45 (11.11%)	
occurrences (all)	0	6	
Urinary retention			
subjects affected / exposed	2 / 59 (3.39%)	3 / 45 (6.67%)	
occurrences (all)	2	3	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	8 / 59 (13.56%)	7 / 45 (15.56%)	
occurrences (all)	8	8	
Back pain			
subjects affected / exposed	3 / 59 (5.08%)	3 / 45 (6.67%)	
occurrences (all)	3	3	
Pain in extremity			
subjects affected / exposed	0 / 59 (0.00%)	3 / 45 (6.67%)	
occurrences (all)	0	4	
Infections and infestations			
Oral candidiasis			
subjects affected / exposed	2 / 59 (3.39%)	3 / 45 (6.67%)	
occurrences (all)	2	3	
Pneumonia			
subjects affected / exposed	3 / 59 (5.08%)	2 / 45 (4.44%)	
occurrences (all)	3	2	
Metabolism and nutrition disorders			
Hyperglycaemia			

subjects affected / exposed	1 / 59 (1.69%)	5 / 45 (11.11%)	
occurrences (all)	1	5	
Hypoglycaemia			
subjects affected / exposed	3 / 59 (5.08%)	0 / 45 (0.00%)	
occurrences (all)	3	0	
Hypokalaemia			
subjects affected / exposed	14 / 59 (23.73%)	11 / 45 (24.44%)	
occurrences (all)	15	13	
Hypomagnesaemia			
subjects affected / exposed	9 / 59 (15.25%)	3 / 45 (6.67%)	
occurrences (all)	10	4	
Hyponatraemia			
subjects affected / exposed	3 / 59 (5.08%)	3 / 45 (6.67%)	
occurrences (all)	3	3	
Hypophosphataemia			
subjects affected / exposed	3 / 59 (5.08%)	4 / 45 (8.89%)	
occurrences (all)	3	4	

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