Clinical trial results:
Prospective, Randomised, Controlled Phase 2 Study Investigating the Haemostatic Efficacy and Safety of Fibrinogen Concentrate (Octafibrin) and Cryoprecipitate as Fibrinogen Supplementation Sources in Patients Undergoing Cytoreductive Surgery for Pseudomyxoma Peritonei.

Summary

EudraCT number	2016-003749-27
Trial protocol	GB
Global end of trial date	20 July 2018

Results information

Result version number	v1 (current)
This version publication date	02 August 2019
First version publication date	02 August 2019

Trial information

Trial identification

Sponsor protocol code	FORMA-05

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Octapharma AG
Sponsor organisation address	Seidenstrasse 2, Lachen, Switzerland, CH-8853
Public contact	Sigurd Knaub, Octapharma AG, +41 (0)55 451 21 41, sigurd.knaub@octapharma.com
Scientific contact	Sigurd Knaub, Octapharma AG, +41 (0)55 451 21 41, sigurd.knaub@octapharma.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	19 December 2018
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	20 July 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study is to compare the overall (i.e. intra- and postoperative) haemostatic efficacy (ability to stop bleeding) of Octafibrin, a human blood-derived protein with that of cryoprecipitate in bleeding patients developing acquired fibrinogen deficiency during removal of tumour growth from the abdomen (cytoreductive surgery) for Pseudomyxoma Peritonei (PMP).

Protection of trial subjects:

This trial was conducted in accordance to the principles of ICH- GCP, ensuring that the rights, safety and well-being of patients are protected and in consistency with the Declaration of Helsinki.
Inclusion and exclusion criteria were carefully defined in order to protect subjects from contraindications, interactions with other medication and risk factors associated with the investigational medicinal product.
Throughout the study safety was assessed, such as collecting information (e.g., frequency, severity, causality) on adverse events (AEs), treatment-emergent adverse events (TEAEs), serious AEs (SAEs) and adverse drug reactions (ADRs). In addition, monitoring of vital signs, routine clinical laboratory assessment including of coagulation parameters and viral safety testing were performed.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	13 March 2017
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: 45
Worldwide total number of subjects	45
EEA total number of subjects	45

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)	31
From 65 to 84 years	14
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Patients undergoing cytoreductive surgery for Pseudomyxoma peritonei with need of Fibrinogen supplementation were screened according to predefined in- and exclusion criteria.

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	Octafibirn

Arm description: -

Arm type	Experimental
Investigational medicinal product name	Octafibrin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

Octafibrin was administered by IV injection, using an established IV route. The first dose of Octafibrin (4 g) was pre-emptively administered based on clinical judgement for fibrinogen supplementation made at the 'bleeding risk assessment' time point, which took place approximately 60–90 minutes after the beginning of surgery, before 2 L of blood had been lost.
Further Octafibrin administration intraoperatively was based on the FIBTEM test of the ROTEM® analysis. A FIBTEM A20 of 12 mm or less triggered the administration of 4 g Octafibrin. Any administration of Octafibrin during the first 24 hours postoperatively was based on clinical judgement of need for further haemostatic support and guided by the FIBTEM test of the ROTEM® analysis. A FIBTEM A20 of 12 mm or less triggered the administration of 2 g Octafibrin.

Arm title	Cryoprecipitate

Arm description: -

Arm type	Active comparator
Investigational medicinal product name	Cryoprecipitate
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Cryoprecipitate was used as comparator and administered by IV injection, using an established IV route. A single unit contained a mean of approximately 400–460 mg fibrinogen. First dose of cryoprecipitate (2 pools of 5 units each) was pre-emptively administered based on clinical judgement for fibrinogen supplementation made at the 'bleeding risk assessment' time point, which took place approximately 60–90 minutes after the beginning of surgery, before 2 L of blood had been lost. Further cryoprecipitate administration intraoperatively was based on the FIBTEM test of the ROTEM® analysis. A FIBTEM A20 of 12 mm or less triggered the administration of 2 cryoprecipitate pools of 5 units each. Any administration of cryoprecipitate during the first 24 hours postoperatively was based on clinical judgement of need for further haemostatic support and guided by the FIBTEM test of the ROTEM® analysis. A FIBTEM A20 of 12 mm or less triggered the administration of 1 cryoprecipitate pool of 5 units.

Number of subjects in period 1	Octafibirn	Cryoprecipitate
Started	22	23
Completed	22	22
Not completed	0	1
Adverse event, non-fatal	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Overall Trial

Reporting group description: -

Reporting group values	Overall Trial	Total	
Number of subjects	45	45	
Age categorical Units: Subjects			
Age continuous Units: years median full range (min-max)	 61 34 to 76	 -	
Gender categorical Units: Subjects			
Female	25	25	
Male	20	20	

End points

End points reporting groups

Reporting group title	Octafibirn
Reporting group description: -	
Reporting group title	Cryoprecipitate
Reporting group description: -	
Subject analysis set title	Difference in overall haemostatic success
Subject analysis set type	Full analysis
Subject analysis set description: Test for non-inferiority between treatment groups (Octafibrin - Cryoprecipitate)	
Subject analysis set title	N (ratings)
Subject analysis set type	Full analysis
Subject analysis set description: Number of ratings Octafibrin	
Subject analysis set title	% (ratings)
Subject analysis set type	Full analysis
Subject analysis set description: % ratings Octafibrin	
Subject analysis set title	N (ratings)
Subject analysis set type	Full analysis
Subject analysis set description: Number of ratings Cryoprecipitate	
Subject analysis set title	% (ratings)
Subject analysis set type	Full analysis
Subject analysis set description: Percentage of ratings Cryoprecipitate	
Subject analysis set title	N (total)
Subject analysis set type	Full analysis
Subject analysis set description: Total number of ratings	
Subject analysis set title	% (total)
Subject analysis set type	Full analysis
Subject analysis set description: Percentage of total ratings	

Primary: Frequency of the Overall Haemostatic Success Adjudicated by the IDMEAC (PP-population)

End point title	Frequency of the Overall Haemostatic Success Adjudicated by the IDMEAC (PP-population)[1]

End point description:

The primary efficacy endpoint was the overall haemostatic efficacy rating as assessed by the IDMEAC. Haemostatic efficacy was rated as 'excellent,' 'good,' 'moderate,' or 'none'.
Ratings of 'excellent' and 'good' were considered 'haemostatic success', whereas ratings of 'moderate' and 'none' were considered 'haemostatic failure'.
In the primary analysis population (PP set), 100% (95% CI 83.89–100.0%) of 21 patients in the Octafibrin group and 100% (95% CI 84.56–100.0%) of the 22 patients in the cryoprecipitate group were adjudicated as having achieved 'treatment success.

End point type	Primary

End point timeframe:

Overall haemostatic efficacy was determined using a predefined composite assessment algorithm based on the intraoperative and postoperative efficacy assessments and was adjudicated in a treatment-blinded manner by the IDMEAC.

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Due to the pathological situation (both success probabilities being equal to 1) no statistical inference on difference in proportions can be performed.

End point values	Octafibirn	Cryoprecipitate		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	21	22		
Units: Rating as Success				
number (not applicable)				
Success Rating (N)	21	22		
Success Rate (%)	100	100		
95%-Pearson Clopper interval lower	83.89	84.56		
95%-Pearson Clopper interval upper	100	100		

Statistical analyses

No statistical analyses for this end point

Primary: Non-inferiority between treatment groups on the overall haemostatic success adjudicated by the IDMEAC (PP-population)

End point title	Non-inferiority between treatment groups on the overall haemostatic success adjudicated by the IDMEAC (PP-population)[2]

End point description:

End point type	Primary

End point timeframe:

Treatment success assesed intraoperatively and postoperatively.

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Due to the pathological situation (both success probabilities being equal to 1) the statistical test was performed by adding/subtracting a small epsilon (0.00001) to the subject count per treatment group. Non-inferiority margin = 0.2

End point values	Difference in overall haemostatic success			
Subject group type	Subject analysis set			
Number of subjects analysed	43			
Units: Difference				
number (not applicable)				
Difference in overall haemostatic success	0.0000			
Lower 95% confidence limit	-0.1671			
Upper 95% confidence limit	0.1671			
p-value for the Farrington-Manning test	0.0095			

Statistical analyses

No statistical analyses for this end point

Secondary: Intraoperative haemostatic efficacy assessed by surgeon and anaesthesiologist (Octafibrin)

End point title	Intraoperative haemostatic efficacy assessed by surgeon and anaesthesiologist (Octafibrin)

End point description:

Intraoperative haemostatic efficacy as assessed at end of surgery using an objective 4-point haemostatic efficacy scale

p-value for the Cochran-Mantel-Haenszel test as comparison between both treatment groups on the distribution of intraoperative haemostatic efficacy: 0.3319.

End point type	Secondary

End point timeframe:

Intraoperative

End point values	N (ratings)	% (ratings)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	21	21		
Units: Rating				
number (not applicable)				
Excellent	13	61.90		
Good	7	33.33		
Moderate	1	4.76		
Total	21	100		

Statistical analyses

No statistical analyses for this end point

Secondary: Intraoperative haemostatic efficacy assessed by surgeon and anaesthesiologist (Cryoprecipitate)

End point title	Intraoperative haemostatic efficacy assessed by surgeon and anaesthesiologist (Cryoprecipitate)

End point description:

Intraoperative haemostatic efficacy as assessed at end of surgery using an objective 4-point haemostatic efficacy scale.

p-value for the Cochran-Mantel-Haenszel test as comparison between both treatment groups on the distribution of intraoperative haemostatic efficacy: 0.3319.

End point type	Secondary

End point timeframe:
Intraoperative

End point values	N (ratings)	% (ratings)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	22	22		
Units: Rating				
number (not applicable)				
Excellent	12	54.55		
Good	6	27.27		
Moderate	4	18.18		
Total	22	100		

Statistical analyses

No statistical analyses for this end point

Secondary: Intraoperative haemostatic efficacy assessed by surgeon and anaesthesiologist (Total)

End point title	Intraoperative haemostatic efficacy assessed by surgeon and anaesthesiologist (Total)

End point description:
Intraoperative haemostatic efficacy assessed by surgeon and anaesthesiologist.

p-value for the Cochran-Mantel-Haenszel test as comparison between both treatment groups on the distribution of intraoperative haemostatic efficacy: 0.3319.

End point type	Secondary

End point timeframe:
Intraoperative

End point values	N (total)	% (total)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	43	43		
Units: Rating				
number (not applicable)				
Excellent	25	58.14		
Good	13	30.23		
Moderate	5	11.63		
Total	43	100		

Statistical analyses

No statistical analyses for this end point

Secondary: Postoperative haemostatic efficacy ratings assessed by haematologist (Octafibrin)

End point title	Postoperative haemostatic efficacy ratings assessed by haematologist (Octafibrin)

End point description:

Due to the pathological situation (both treatment groups with excellent assessments being equal to 1) no statistical inference on distribution of postoperative hemostatic efficacy can be performed.

End point type	Secondary

End point timeframe:

Post operative

End point values	N (ratings)	% (ratings)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	21	21		
Units: Rating				
number (not applicable)				
Exellent	21	100		
Total	21	100		

Statistical analyses

No statistical analyses for this end point

Secondary: Postoperative haemostatic efficacy ratings assessed by haematologist (Cryoprecipitate)

End point title	Postoperative haemostatic efficacy ratings assessed by haematologist (Cryoprecipitate)

End point description:

Due to the pathological situation (both treatment groups with excellent assessments being equal to 1) no statistical inference on distribution of postoperative hemostatic efficacy can be performed

End point type	Secondary

End point timeframe:

Post-operative

End point values	N (ratings)	% (ratings)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	22	22		
Units: Rating				
number (not applicable)				
Excellent	22	100		
Total	22	100		

Statistical analyses

No statistical analyses for this end point

Secondary: Postoperative haemostatic efficacy ratings assessed by haematologist (Total)

End point title	Postoperative haemostatic efficacy ratings assessed by haematologist (Total)

End point description:

Due to the pathological situation (both treatment groups with excellent assessments being equal to 1) no statistical inference on distribution of postoperative hemostatic efficacy can be performed.

End point type	Secondary

End point timeframe:

Post-operative

End point values	N (total)	% (total)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	43	43		
Units: Rating				
number (not applicable)				
Excellent	43	100		
Total	43	100		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Throughout the whole study starting from the pre-operative assessment until end of the study assessment 21 days after surgery or end of hospitalization which ever came first.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.0

Reporting groups

Reporting group title	Octafibrin
Reporting group description: -	
Reporting group title	Cryoprecipitate

Reporting group description: -

Serious adverse events	Octafibrin	Cryoprecipitate	
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 22 (22.73%)	13 / 23 (56.52%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Injury, poisoning and procedural complications			
Gastrointestinal stoma complication			
subjects affected / exposed	1 / 22 (4.55%)	0 / 23 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal anastomotic leak			
subjects affected / exposed	0 / 22 (0.00%)	1 / 23 (4.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatic leak			
subjects affected / exposed	0 / 22 (0.00%)	1 / 23 (4.35%)	
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	0 / 22 (0.00%)	1 / 23 (4.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Haemodynamic instability			
subjects affected / exposed	1 / 22 (4.55%)	0 / 23 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Deep vein thrombosis			
subjects affected / exposed	0 / 22 (0.00%)	2 / 23 (8.70%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	1 / 22 (4.55%)	1 / 23 (4.35%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tachycardia			
subjects affected / exposed	1 / 22 (4.55%)	0 / 23 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Parenteral nutrition			
subjects affected / exposed	1 / 22 (4.55%)	0 / 23 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	0 / 22 (0.00%)	1 / 23 (4.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus			

subjects affected / exposed	0 / 22 (0.00%)	1 / 23 (4.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			
subjects affected / exposed	0 / 22 (0.00%)	1 / 23 (4.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	0 / 22 (0.00%)	5 / 23 (21.74%)	
occurrences causally related to treatment / all	0 / 0	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Pneumonia			
subjects affected / exposed	1 / 22 (4.55%)	2 / 23 (8.70%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound infection			
subjects affected / exposed	0 / 22 (0.00%)	1 / 23 (4.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Octafibrin	Cryoprecipitate	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	22 / 22 (100.00%)	23 / 23 (100.00%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	2 / 22 (9.09%)	1 / 23 (4.35%)	
occurrences (all)	2	1	
Hypotension			
subjects affected / exposed	6 / 22 (27.27%)	4 / 23 (17.39%)	
occurrences (all)	6	4	
Deep vein thrombosis			

subjects affected / exposed	0 / 22 (0.00%)	2 / 23 (8.70%)	
occurrences (all)	0	2	
General disorders and administration site conditions			
Chest discomfort			
subjects affected / exposed	1 / 22 (4.55%)	2 / 23 (8.70%)	
occurrences (all)	1	3	
Oedema			
subjects affected / exposed	2 / 22 (9.09%)	0 / 23 (0.00%)	
occurrences (all)	2	0	
Oedema peripheral			
subjects affected / exposed	6 / 22 (27.27%)	3 / 23 (13.04%)	
occurrences (all)	8	4	
Pain			
subjects affected / exposed	3 / 22 (13.64%)	5 / 23 (21.74%)	
occurrences (all)	4	5	
Peripheral swelling			
subjects affected / exposed	2 / 22 (9.09%)	0 / 23 (0.00%)	
occurrences (all)	2	0	
Pyrexia			
subjects affected / exposed	5 / 22 (22.73%)	8 / 23 (34.78%)	
occurrences (all)	5	8	
Respiratory, thoracic and mediastinal disorders			
Atelectasis			
subjects affected / exposed	7 / 22 (31.82%)	8 / 23 (34.78%)	
occurrences (all)	7	8	
Dyspnoea			
subjects affected / exposed	2 / 22 (9.09%)	3 / 23 (13.04%)	
occurrences (all)	2	3	
Lung consolidation			
subjects affected / exposed	2 / 22 (9.09%)	3 / 23 (13.04%)	
occurrences (all)	2	3	
Non-cardiac chest pain			
subjects affected / exposed	2 / 22 (9.09%)	1 / 23 (4.35%)	
occurrences (all)	2	1	
Oropharyngeal pain			

subjects affected / exposed	2 / 22 (9.09%)	0 / 23 (0.00%)	
occurrences (all)	2	0	
Pleural effusion			
subjects affected / exposed	11 / 22 (50.00%)	11 / 23 (47.83%)	
occurrences (all)	11	12	
Pleuritic pain			
subjects affected / exposed	2 / 22 (9.09%)	1 / 23 (4.35%)	
occurrences (all)	2	1	
Pneumothorax			
subjects affected / exposed	4 / 22 (18.18%)	9 / 23 (39.13%)	
occurrences (all)	5	9	
Pulmonary embolism			
subjects affected / exposed	0 / 22 (0.00%)	5 / 23 (21.74%)	
occurrences (all)	0	5	
Wheezing			
subjects affected / exposed	0 / 22 (0.00%)	2 / 23 (8.70%)	
occurrences (all)	0	2	
Psychiatric disorders			
Hallucination			
subjects affected / exposed	17 / 22 (77.27%)	17 / 23 (73.91%)	
occurrences (all)	17	17	
Insomnia			
subjects affected / exposed	2 / 22 (9.09%)	0 / 23 (0.00%)	
occurrences (all)	2	0	
Panic attack			
subjects affected / exposed	1 / 22 (4.55%)	2 / 23 (8.70%)	
occurrences (all)	1	2	
Investigations			
Haemoglobin decreased			
subjects affected / exposed	2 / 22 (9.09%)	2 / 23 (8.70%)	
occurrences (all)	2	2	
Injury, poisoning and procedural complications			
Gastrointestinal stoma complication			
subjects affected / exposed	2 / 22 (9.09%)	1 / 23 (4.35%)	
occurrences (all)	3	1	
Wound complication			

subjects affected / exposed	1 / 22 (4.55%)	3 / 23 (13.04%)	
occurrences (all)	1	4	
Wound dehiscence			
subjects affected / exposed	3 / 22 (13.64%)	3 / 23 (13.04%)	
occurrences (all)	3	3	
Wound secretion			
subjects affected / exposed	1 / 22 (4.55%)	2 / 23 (8.70%)	
occurrences (all)	1	2	
Pancreatic leak			
subjects affected / exposed	0 / 22 (0.00%)	2 / 23 (8.70%)	
occurrences (all)	0	2	
Cardiac disorders			
Sinus tachycardia			
subjects affected / exposed	2 / 22 (9.09%)	2 / 23 (8.70%)	
occurrences (all)	2	2	
Tachycardia			
subjects affected / exposed	12 / 22 (54.55%)	8 / 23 (34.78%)	
occurrences (all)	13	8	
Nervous system disorders			
Dizziness			
subjects affected / exposed	3 / 22 (13.64%)	3 / 23 (13.04%)	
occurrences (all)	3	3	
Hypoaesthesia			
subjects affected / exposed	2 / 22 (9.09%)	1 / 23 (4.35%)	
occurrences (all)	2	1	
Blood and lymphatic system disorders			
Thrombocytosis			
subjects affected / exposed	5 / 22 (22.73%)	8 / 23 (34.78%)	
occurrences (all)	5	8	
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	2 / 22 (9.09%)	1 / 23 (4.35%)	
occurrences (all)	2	1	
Abdominal pain			
subjects affected / exposed	2 / 22 (9.09%)	2 / 23 (8.70%)	
occurrences (all)	2	2	
Constipation			

subjects affected / exposed	7 / 22 (31.82%)	4 / 23 (17.39%)	
occurrences (all)	7	4	
Diarrhoea			
subjects affected / exposed	3 / 22 (13.64%)	3 / 23 (13.04%)	
occurrences (all)	3	3	
Ileus			
subjects affected / exposed	1 / 22 (4.55%)	2 / 23 (8.70%)	
occurrences (all)	1	2	
Intra-abdominal fluid collection			
subjects affected / exposed	2 / 22 (9.09%)	3 / 23 (13.04%)	
occurrences (all)	2	3	
Nausea			
subjects affected / exposed	12 / 22 (54.55%)	7 / 23 (30.43%)	
occurrences (all)	12	7	
Vomiting			
subjects affected / exposed	8 / 22 (36.36%)	10 / 23 (43.48%)	
occurrences (all)	8	10	
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 22 (0.00%)	2 / 23 (8.70%)	
occurrences (all)	0	2	
Retching			
subjects affected / exposed	0 / 22 (0.00%)	2 / 23 (8.70%)	
occurrences (all)	0	2	
Skin and subcutaneous tissue disorders			
Subcutaneous emphysema			
subjects affected / exposed	3 / 22 (13.64%)	3 / 23 (13.04%)	
occurrences (all)	3	3	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	3 / 22 (13.64%)	2 / 23 (8.70%)	
occurrences (all)	3	2	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	6 / 22 (27.27%)	1 / 23 (4.35%)	
occurrences (all)	6	1	
Infections and infestations			

Lower respiratory tract infection			
subjects affected / exposed	3 / 22 (13.64%)	3 / 23 (13.04%)	
occurrences (all)	3	3	
Oral candidiasis			
subjects affected / exposed	2 / 22 (9.09%)	1 / 23 (4.35%)	
occurrences (all)	2	1	
Pneumonia			
subjects affected / exposed	4 / 22 (18.18%)	3 / 23 (13.04%)	
occurrences (all)	4	3	
Urinary tract infection			
subjects affected / exposed	2 / 22 (9.09%)	2 / 23 (8.70%)	
occurrences (all)	2	2	
Wound infection			
subjects affected / exposed	1 / 22 (4.55%)	3 / 23 (13.04%)	
occurrences (all)	1	3	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
17 November 2016	Amendment 1 : Text changed upon request of MHRA: - text regarding relevant protocol deviations has been expanded. - text has been amended to clearly specify where in the Investigator's Brochure the Reference Safety Information and list of ADRs can be found - text has been amended to stipulate reporting of all SAEs within 24 hours of their occurrence, as per the clarification of UK Statutory Instrument 2004 No 1031 Part 5 in the EC guidance document 2011/C 172/01 (CT-3), Section 4.3, paragraph 29 - Text has been added to define the Sponsor's responsibility in reporting all SAEs at least possibly related to the study drug as suspected unexpected serious adverse reactions (SUSARs)
21 April 2017	Amendment 2: -Text stating tumour stage/grade as one of the planned pre-operative baseline assessments has been deleted as pre-operative assessment of tumor grade/stage will not be performed at baseline. - The text describing planned intraoperative assessments has been updated to include assessment of tumour stage/grade. -The text regarding blood sampling for coagulation parameters has been expanded to provide greater clarity. -The text defining what constitutes the end of surgery, at which point end-of-surgery assessments are to be made, has been revised to make it clearer. - Some sentences and typos have been corrected for clearer understanding.
21 November 2017	Amendment 3: An administrative interim analysis when approximately 50% of the planned patients have completed the study and adjudicated efficacy endpoint evaluation is available in these patients. has been added. This interim analysis is for administrative purposes only, no stopping rules based on statistical tests will be applied.
05 February 2018	Amendment 4: - The planned clinical end date has been updated to 2 quarter 2018

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported