Clinical trial results:
INtegratioN of trastuzumab, with or without pertuzumab, into periOperatiVe chemotherApy of HER-2 posiTIve stOmach caNcer: the INNOVATION-TRIAL

Summary

EudraCT number	2014-000722-38
Trial protocol	EE DE BE NO PT GB ES NL FR IT
Global end of trial date	30 September 2024

Results information

Result version number	v1 (current)
This version publication date	07 June 2026
First version publication date	07 June 2026

Trial information

Trial identification

Sponsor protocol code	1203-GITCG

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02205047
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	European Organisation for the Research and Treatment of Cancer
Sponsor organisation address	Avenue Emmanuel Mounier 83/11, Brussels, Belgium, 1200
Public contact	Regulatory Affairs Department, European Organisation for Research and Treatment of Cancer (EORTC), +32 27741586, regulatory@eortc.org
Scientific contact	Regulatory Affairs Department, European Organisation for Research and Treatment of Cancer (EORTC), +32 27741586, regulatory@eortc.org

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	06 June 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	06 June 2022
Global end of trial reached?	Yes
Global end of trial date	30 September 2024
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To increase the major pathological response rate (< 10% vital tumor cells) to neoadjuvant treatment by integrating both trastuzumab and pertuzumab or trastuzumab alone into perioperative chemotherapy for HER-2 positive, resectable gastric cancer.

Protection of trial subjects:

This study was conducted in agreement with either the Declaration of Helsinki (available on the World Medical Association web site (http://www.wma.net)) and/or the laws and regulations of the country, whichever provides the greatest protection of the patient.

The protocol had been written, and the study was conducted according to the ICH Harmonized Tripartite Guideline on Good Clinical Practice (ICH-GCP, available online at https://www.ema.europa.eu/documents/scientific-guideline/ich-e6-r1-guideline-good-clinical-practice_en.pdf).

Background therapy:

Adjuvant chemotherapy based on the latest ESMO guidelines.

Evidence for comparator: -

Actual start date of recruitment	13 November 2015
Long term follow-up planned	Yes
Long term follow-up rationale	Efficacy, Scientific research
Long term follow-up duration	6 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Belgium: 1
Country: Number of subjects enrolled	Estonia: 7
Country: Number of subjects enrolled	France: 28
Country: Number of subjects enrolled	Germany: 65
Country: Number of subjects enrolled	Italy: 22
Country: Number of subjects enrolled	Korea, Republic of: 16
Country: Number of subjects enrolled	Netherlands: 3
Country: Number of subjects enrolled	Norway: 1
Country: Number of subjects enrolled	Singapore: 1
Country: Number of subjects enrolled	Spain: 20
Country: Number of subjects enrolled	Switzerland: 4
Country: Number of subjects enrolled	United Kingdom: 4

Worldwide total number of subjects	172
EEA total number of subjects	147

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)	92
From 65 to 84 years	80
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A total of 621 patients were recruited from Belgium, Estonia, France, Germany, Israel, Italy, Korea, Netherlands, Norway, Portugal, Singapore, Spain, Switzerland and the United Kingdom between the 13/11/2015 and 27/12/2021.

Pre-assignment

Screening details:

A total of 621 patients were registered in the study and signed an informed consent for further testing of their HER2 status. This status was assessed locally and/or centrally. After assessment, 172 patients were found eligible.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Control Arm

Arm description:

Patients were treated with chemotherapy alone. In protocol v1.0, all patients were treated with cisplatin and capecitabine or 5-FU. The protocol was amended (v 4.0) on 19/10/2017 to mandate that patients were given FLOT, CapOX or mFOLFOX6 in European centers.

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

Dosage and administration details:

Capecitabine was administered for three cycles of 3 weeks before and after surgery. Capecitabine was given orally at a dose of 1000 mg/m2 twice daily on days 1 to 14 out of 21 days.

Investigational medicinal product name	Cisplatin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Infusion

Dosage and administration details:

Cisplatin was administered for three cycles of 3 weeks before and after surgery. Cisplatin was administered at the dose of 80 mg/m2 every three weeks by IV infusion.

Investigational medicinal product name	5-FU
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Infusion

Dosage and administration details:

5-FU was administered for three cycles of 3 weeks before and after surgery. 5-FU was given at a dose of 800 mg/m2/day by continuous infusion on days 1 to 5 every 21 days (for patients with contraindications for capecitabine) and is given after cisplatin.

Investigational medicinal product name	FLOT
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Infusion

Dosage and administration details:

FLOT was administered in cycles of 2 weeks for 4 cycles (= 8 weeks) on day 1, 15, 29 and 43 pre- and postoperatively.
Docetaxel 50 mg/m2 was given as 1 hour infusion, followed by Oxaliplatin 85 mg/m2 diluted with 250 to 500 ml of 5% glucose solution as a 2-hour infusion, leucovorin 200 mg/m2 over 2 hours and 5-FU 2600mg/m2 as a 24 hour-infusion, with oral dexamethasone for prevention of fluid retention and allergic reactions for example at a dose of 8 mg in the morning (8am) and evening (8pm) on the day before administration of FLOT, and a third dose together with antiemetic premedication on the day of chemotherapy administration.

Investigational medicinal product name	CapOx
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Infusion

Dosage and administration details:

CapOx was given for 3 cycles of 3 weeks (= 9 weeks) on day 1, 22 and 43 pre- and postoperatively. Oxaliplatin was given as a 2-hour intravenous infusion at a dose of 130 mg/m2 on day 1. Oxaliplatin needed to be diluted with 250 to 500 ml of 5% glucose solution, followed by capecitabine given orally at a dose of 1000 mg/m2 twice daily from the evening of day 1 to the morning of day 15 every 3 weeks.

Investigational medicinal product name	mFOLFOX6
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Infusion

Dosage and administration details:

mFOLFOX6 was given for 4 cycles of 2 weeks (=8 weeks) on day 1, 15, 29 and 43 pre- and postoperatively.
Oxaliplatin diluted with 250 to 500 ml of 5% glucose solution was given as a 2-hour intravenous infusion at a dose of 85mg/m2, followed by leucovorin 400 mg/m2 iv over 2 hours on day 1, and 5-FU 400mg/m2 iv bolus on day 1, then 1200 mg/m2/d x 2 days over 46-48 hours continuous infusion every 2 weeks.

Arm title	Experimental Arm 1

Arm description:

Experimental arm 1 consisted of perioperative chemotherapy plus trastuzumab. Trastuzumab was administered independently of the chemotherapy regimen at day 1 of each cycle, with an 8 mg/kg loading dose followed by 6 mg/kg every 3 weeks. Trastuzumab was given in combination with pre and postoperative chemotherapy for three 3 week cycles and was continued after completion of adjuvant chemotherapy as maintenance treatment. Antibody therapy was planned to continue up to a total of 17 cycles from the start of neoadjuvant treatment.

Arm type	Experimental
Investigational medicinal product name	Trastuzumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Infusion

Dosage and administration details:

Trastuzumab was administered at a 8 mg/kg loading dose, followed by 6 mg/kg every 3 weeks at day 1, independent of the chemotherapy regimen chosen for 3 cycles of 3 weeks before and after surgery and for up to 17 cycles from the start of neoadjuvant treatment.

Investigational medicinal product name	Capecitabine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet

Routes of administration	Oral use

Dosage and administration details:

Capecitabine was given orally at a dose of 1000 mg/m2 twice daily on days 1 to 14 out of 21 days. Capecitabine was administered for three cycles of 3 weeks before and after surgery.

Investigational medicinal product name	Cisplatin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Infusion

Dosage and administration details:

Cisplatin was administered for three cycles of 3 weeks before and after surgery. Cisplatin was administered at the dose of 80 mg/m2 every three weeks by IV infusion.

Investigational medicinal product name	5-FU
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Infusion

Dosage and administration details:

5-FU was administered for three cycles of 3 weeks before and after surgery. 5-FU was given at a dose of 800 mg/m2/day by continuous infusion on days 1 to 5 every 21 days (for patients with contraindications for capecitabine) and is given after cisplatin.

Investigational medicinal product name	FLOT
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Infusion

Dosage and administration details:

FLOT was administered in cycles of 2 weeks for 4 cycles (= 8 weeks) on day 1, 15, 29 and 43 pre- and postoperatively.
Docetaxel 50 mg/m2 was given as 1 hour infusion, followed by Oxaliplatin 85 mg/m2 diluted with 250 to 500 ml of 5% glucose solution as a 2-hour infusion, leucovorin 200 mg/m2 over 2 hours and 5-FU 2600mg/m2 as a 24 hour-infusion, with oral dexamethasone for prevention of fluid retention and allergic reactions for example at a dose of 8 mg in the morning (8am) and evening (8pm) on the day before administration of FLOT, and a third dose together with antiemetic premedication on the day of chemotherapy administration.

Investigational medicinal product name	CapOx
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Infusion

Dosage and administration details:

CapOx was given for 3 cycles of 3 weeks (= 9 weeks) on day 1, 22 and 43 pre- and postoperatively. Oxaliplatin was given as a 2-hour intravenous infusion at a dose of 130 mg/m2 on day 1. Oxaliplatin needed to be diluted with 250 to 500 ml of 5% glucose solution, followed by capecitabine given orally at a dose of 1000 mg/m2 twice daily from the evening of day 1 to the morning of day 15 every 3 weeks.

Investigational medicinal product name	mFOLFOX6
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Infusion

Dosage and administration details:

mFOLFOX6 was given for 4 cycles of 2 weeks (=8 weeks) on day 1, 15, 29 and 43 pre- and postoperatively.
Oxaliplatin diluted with 250 to 500 ml of 5% glucose solution was given as a 2-hour intravenous infusion at a dose of 85mg/m2, followed by leucovorin 400 mg/m2 iv over 2 hours on day 1, and 5-FU 400mg/m2 iv bolus on day 1, then 1200 mg/m2/d x 2 days over 46-48 hours continuous infusion every 2 weeks.

Arm title	Experimental Arm 2

Arm description:

Experimental arm 2 consisted of perioperative chemotherapy plus trastuzumab and pertuzumab, with pertuzumab administered at a fixed dose of 840 mg every 3 weeks on day 1, independent of the chemotherapy regimen chosen. Trastuzumab and pertuzumab were administered for three 3week cycles in combination with pre and postoperative chemotherapy, followed by maintenance antibody therapy. After completion of adjuvant chemotherapy, trastuzumab and pertuzumab were continued as maintenance treatment up to a total of 17 cycles from the start of neoadjuvant therapy.

Arm type	Experimental
Investigational medicinal product name	Pertuzumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Infusion

Dosage and administration details:

Pertuzumab was administered as an infusion at a dose of 840 mg every 3 weeks at day 1, for 3 cycles of 3 weeks before and after surgery and for up to 17 cycles from the start of neoadjuvant treatment.

Investigational medicinal product name	Trastuzumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Infusion

Dosage and administration details:

Trastuzumab was administered at a 8 mg/kg loading dose, followed by 6 mg/kg every 3 weeks at day 1, independent of the chemotherapy regimen chosen for 3 cycles of 3 weeks before and after surgery and for up to 17 cycles from the start of neoadjuvant treatment.

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

Dosage and administration details:

Capecitabine was administered for three cycles of 3 weeks before and after surgery. Capecitabine was given orally at a dose of 1000 mg/m2 twice daily on days 1 to 14 out of 21 days.

Investigational medicinal product name	Cisplatin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Infusion

Dosage and administration details:

Cisplatin was administered for three cycles of 3 weeks before and after surgery. Cisplatin was administered at the dose of 80 mg/m2 every three weeks by IV infusion.

Investigational medicinal product name	5-FU
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Infusion

Dosage and administration details:

5-FU was administered for three cycles of 3 weeks before and after surgery. 5-FU was given at a dose of 800 mg/m2/day by continuous infusion on days 1 to 5 every 21 days (for patients with contraindications for capecitabine) and is given after cisplatin.

Investigational medicinal product name	FLOT
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion

Routes of administration	Infusion

Dosage and administration details:

FLOT was administered in cycles of 2 weeks for 4 cycles (= 8 weeks) on day 1, 15, 29 and 43 pre- and postoperatively.
Docetaxel 50 mg/m2 was given as 1 hour infusion, followed by Oxaliplatin 85 mg/m2 diluted with 250 to 500 ml of 5% glucose solution as a 2-hour infusion, leucovorin 200 mg/m2 over 2 hours and 5-FU 2600mg/m2 as a 24 hour-infusion, with oral dexamethasone for prevention of fluid retention and allergic reactions for example at a dose of 8 mg in the morning (8am) and evening (8pm) on the day before administration of FLOT, and a third dose together with antiemetic premedication on the day of chemotherapy administration.

Investigational medicinal product name	CapOx
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Infusion

Dosage and administration details:

CapOx was given for 3 cycles of 3 weeks (= 9 weeks) on day 1, 22 and 43 pre- and postoperatively. Oxaliplatin was given as a 2-hour intravenous infusion at a dose of 130 mg/m2 on day 1. Oxaliplatin needed to be diluted with 250 to 500 ml of 5% glucose solution, followed by capecitabine given orally at a dose of 1000 mg/m2 twice daily from the evening of day 1 to the morning of day 15 every 3 weeks.

Investigational medicinal product name	mFOLFOX6
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Infusion

Dosage and administration details:

mFOLFOX6 was given for 4 cycles of 2 weeks (=8 weeks) on day 1, 15, 29 and 43 pre- and postoperatively.
Oxaliplatin diluted with 250 to 500 ml of 5% glucose solution was given as a 2-hour intravenous infusion at a dose of 85mg/m2, followed by leucovorin 400 mg/m2 iv over 2 hours on day 1, and 5-FU 400mg/m2 iv bolus on day 1, then 1200 mg/m2/d x 2 days over 46-48 hours continuous infusion every 2 weeks.

Number of subjects in period 1	Control Arm	Experimental Arm 1	Experimental Arm 2
Started	35	67	70
Completed	20	30	24
Not completed	15	37	46
Adverse event, serious fatal	-	2	2
Consent withdrawn by subject	1	4	7
Physician decision	1	4	6
Adverse event, non-fatal	6	12	20
Spondylodiscitis	1	-	-
Covid-19	1	-	-
Treatment never started due to GI bleeding	1	-	-
Poor clinical condition	1	1	-
Protocol deviation	1	5	4
Lack of efficacy	2	9	7

Baseline characteristics

Reporting groups	
Reporting group title	Control Arm
Reporting group description:	
Patients were treated with chemotherapy alone. In protocol v1.0, all patients were treated with cisplatin and capecitabine or 5-FU. The protocol was amended (v 4.0) on 19/10/2017 to mandate that patients were given FLOT, CapOX or mFOLFOX6 in European centers.	
Reporting group title	Experimental Arm 1
Reporting group description:	
Experimental arm 1 consisted of perioperative chemotherapy plus trastuzumab. Trastuzumab was administered independently of the chemotherapy regimen at day 1 of each cycle, with an 8 mg/kg loading dose followed by 6 mg/kg every 3 weeks. Trastuzumab was given in combination with pre and postoperative chemotherapy for three 3 week cycles and was continued after completion of adjuvant chemotherapy as maintenance treatment. Antibody therapy was planned to continue up to a total of 17 cycles from the start of neoadjuvant treatment.	
Reporting group title	Experimental Arm 2
Reporting group description:	
Experimental arm 2 consisted of perioperative chemotherapy plus trastuzumab and pertuzumab, with pertuzumab administered at a fixed dose of 840 mg every 3 weeks on day 1, independent of the chemotherapy regimen chosen. Trastuzumab and pertuzumab were administered for three 3week cycles in combination with pre and postoperative chemotherapy, followed by maintenance antibody therapy. After completion of adjuvant chemotherapy, trastuzumab and pertuzumab were continued as maintenance treatment up to a total of 17 cycles from the start of neoadjuvant therapy.	

Reporting group values	Control Arm	Experimental Arm 1	Experimental Arm 2
Number of subjects	35	67	70
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)	19	35	38
From 65-84 years	16	32	32
85 years and over	0	0	0
Age continuous Units: years			
median	63.0	63.0	64.0
inter-quartile range (Q1-Q3)	52.0 to 70.0	55.0 to 72.0	59.0 to 70.0
Gender categorical Units: Subjects			
Female	2	21	7
Male	33	46	63
Site of the tumor Units: Subjects			
Stomach	13	26	26
Esophagogastric junction	22	41	44
Histological subtype			

Units: Subjects			
Intestinal	25	46	50
Non-intestinal	10	21	20
Clinical UICC stage as defined by CT-scan and/or MRI and endosonography if applicable Units: Subjects			
Stage IB	2	4	3
Stage IIA	4	7	5
Stage IIB	6	11	14
Stage IIIA	11	22	31
Stage IIIB	4	13	5
Stage IIIC	7	10	11
Stage IV	1	0	1
Histological grade Units: Subjects			
GI	3	9	7
GII	23	35	36
GIII	7	17	13
Missing	2	6	14
T-Stage Units: Subjects			
cT1	0	1	2
cT2	8	10	10
cT3	16	42	46
cT4	0	1	2
cT1b	2	0	0
cTX	0	2	3
cT4a	7	10	5
cT4b	1	1	2
Missing	1	0	0
N-Stage Units: Subjects			
cN0	6	12	10
cN1	14	29	33
cN2	10	14	14
cN3	1	4	6
cN3a	0	2	1
cN3b	1	1	0
cNX	3	5	5
Missing	0	0	1
M-Stage Units: Subjects			
cM0	34	67	70
cM1	1	0	0

Reporting group values	Total		
Number of subjects	172		
Age categorical Units: Subjects			
In utero	0		

Preterm newborn infants (gestational age < 37 wks)	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)	92		
From 65-84 years	80		
85 years and over	0		
Age continuous			
Units: years			
median			
inter-quartile range (Q1-Q3)	-		
Gender categorical			
Units: Subjects			
Female	30		
Male	142		
Site of the tumor			
Units: Subjects			
Stomach	65		
Esophagogastric junction	107		
Histological subtype			
Units: Subjects			
Intestinal	121		
Non-intestinal	51		
Clinical UICC stage as defined by CT-scan and/or MRI and endosonography if applicable			
Units: Subjects			
Stage IB	9		
Stage IIA	16		
Stage IIB	31		
Stage IIIA	64		
Stage IIIB	22		
Stage IIIC	28		
Stage IV	2		
Histological grade			
Units: Subjects			
GI	19		
GII	94		
GIII	37		
Missing	22		
T-Stage			
Units: Subjects			
cT1	3		
cT2	28		
cT3	104		
cT4	3		
cT1b	2		
cTX	5		
cT4a	22		
cT4b	4		

Missing	1		
N-Stage Units: Subjects			
cN0	28		
cN1	76		
cN2	38		
cN3	11		
cN3a	3		
cN3b	2		
cNX	13		
Missing	1		
M-Stage Units: Subjects			
cM0	171		
cM1	1		

Subject analysis sets

Subject analysis set title	Per Protocol Population
Subject analysis set type	Per protocol

Subject analysis set description:

All patients who met the important eligibility criteria (as assessed during medical review) and have started their allocated treatment (at least one dose of the study drug(s) planned as pre-operative treatment).

Subject analysis set title	Safety Population
Subject analysis set type	Safety analysis

Subject analysis set description:

All patients who have started their allocated treatment (at least one dose of the study drug(s) planned as pre-operative treatment).

Subject analysis set title	Resected Population
Subject analysis set type	Sub-group analysis

Subject analysis set description:

All patients who met the important eligibility criteria (as assessed during medical review, have started the allocated pre-operative treatment, were operated and achieved an R0 or R1 resection.

Reporting group values	Per Protocol Population	Safety Population	Resected Population
Number of subjects	161	169	148
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)	86	80	91
From 65-84 years	75	65	78
85 years and over	0	0	0

Age continuous Units: years			
median	64.0		
inter-quartile range (Q1-Q3)	57.0 to 71.0		
Gender categorical Units: Subjects			
Female	30		
Male	131		
Site of the tumor Units: Subjects			
Stomach	61		
Esophagogastric junction	100		
Histological subtype Units: Subjects			
Intestinal	116		
Non-intestinal	45		
Clinical UICC stage as defined by CT-scan and/or MRI and endosonography if applicable Units: Subjects			
Stage IB	9		
Stage IIA	16		
Stage IIB	28		
Stage IIIA	60		
Stage IIIB	22		
Stage IIIC	26		
Stage IV			
Histological grade Units: Subjects			
GI	18		
GII	86		
GIII	35		
Missing	22		
T-Stage Units: Subjects			
cT1	3		
cT2	27		
cT3	99		
cT4	3		
cT1b	2		
cTX	3		
cT4a	19		
cT4b	4		
Missing	1		
N-Stage Units: Subjects			
cN0	27		
cN1	68		
cN2	38		
cN3	11		
cN3a	3		
cN3b	2		

cNX	11		
Missing	1		
M-Stage Units: Subjects			
cM0	161		
cM1	0		

End points

End points reporting groups

Reporting group title	Control Arm

Reporting group description:

Patients were treated with chemotherapy alone. In protocol v1.0, all patients were treated with cisplatin and capecitabine or 5-FU. The protocol was amended (v 4.0) on 19/10/2017 to mandate that patients were given FLOT, CapOX or mFOLFOX6 in European centers.

Reporting group title	Experimental Arm 1

Reporting group description:

Experimental arm 1 consisted of perioperative chemotherapy plus trastuzumab. Trastuzumab was administered independently of the chemotherapy regimen at day 1 of each cycle, with an 8 mg/kg loading dose followed by 6 mg/kg every 3 weeks. Trastuzumab was given in combination with pre and postoperative chemotherapy for three 3 week cycles and was continued after completion of adjuvant chemotherapy as maintenance treatment. Antibody therapy was planned to continue up to a total of 17 cycles from the start of neoadjuvant treatment.

Reporting group title	Experimental Arm 2

Reporting group description:

Experimental arm 2 consisted of perioperative chemotherapy plus trastuzumab and pertuzumab, with pertuzumab administered at a fixed dose of 840 mg every 3 weeks on day 1, independent of the chemotherapy regimen chosen. Trastuzumab and pertuzumab were administered for three 3week cycles in combination with pre and postoperative chemotherapy, followed by maintenance antibody therapy. After completion of adjuvant chemotherapy, trastuzumab and pertuzumab were continued as maintenance treatment up to a total of 17 cycles from the start of neoadjuvant therapy.

Subject analysis set title	Per Protocol Population
Subject analysis set type	Per protocol

Subject analysis set description:

All patients who met the important eligibility criteria (as assessed during medical review) and have started their allocated treatment (at least one dose of the study drug(s) planned as pre-operative treatment).

Subject analysis set title	Safety Population
Subject analysis set type	Safety analysis

Subject analysis set description:

All patients who have started their allocated treatment (at least one dose of the study drug(s) planned as pre-operative treatment).

Subject analysis set title	Resected Population
Subject analysis set type	Sub-group analysis

Subject analysis set description:

All patients who met the important eligibility criteria (as assessed during medical review, have started the allocated pre-operative treatment, were operated and achieved an R0 or R1 resection.

Primary: Major Pathological Response (mpR) rate

End point title	Major Pathological Response (mpR) rate

End point description:

Pathological response was assessed centrally using the Becker regression grading. Histopathologists were blinded to treatment allocation. Major pathological response is defined as major tumor regression (<10% vital residual tumor cells). The mpR rate is computed in each arm as the percentage of patients who had mpR after neoadjuvant treatment. Patients not resected were considered as not having major pathological response. MpR rate in each arm is calculated in the per protocol population with its exact 2-sided 95% confidence interval.

End point type	Primary

End point timeframe:

Pathological response is assessed after neoadjuvant therapy and surgery.

End point values	Control Arm	Experimental Arm 1	Experimental Arm 2	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	30[1]	54[2]	53[3]	
Units: % of patients with mpR				
number (confidence interval 95%)	23.3 (9.9 to 42.3)	37.0 (24.3 to 51.3)	26.4 (15.3 to 40.3)	

Notes:

[1] - For 3 patients operated in the Control Arm, sample was missing or judged of insufficient quality

[2] - For 10 patients operated in Experimental Arm 1, sample was missing or judged of insufficient quality

[3] - For 11 patients operated in Experimental Arm 2, sample was missing or judged of insufficient quality

Statistical analyses

Statistical analysis title	Primary Analysis: Exp Arm 1 vs Control arm

Statistical analysis description:

The primary analysis was done in the per protocol analysis. Difference in major Pathological Response Rate (% of patients with mpR) between experimental arm 1 (Chemo + Trastuzumab) and chemo only arm was tested at a one-sided 10% level of significance. The asymptotic one-sided 90% confidence interval was calculated. Results are expressed in %.

Comparison groups	Control Arm v Experimental Arm 1
Number of subjects included in analysis	84
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Risk difference (RD)
Point estimate	13.7
Confidence interval	
level	90 %
sides	1-sided
lower limit	0.7

Statistical analysis title	Primary Analysis: Exp Arm 2 vs Control arm

Statistical analysis description:

The primary analysis was done in the per protocol analysis. Difference in major Pathological Response Rate (% of patients with mpR) between experimental arm 2 (Chemo + Trastuzumab + Pertuzumab) and chemo only arm was tested at a one-sided 10% level of significance. The asymptotic one-sided 90% confidence interval was calculated. Results are expressed in %.

Comparison groups	Control Arm v Experimental Arm 2
Number of subjects included in analysis	83
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Risk difference (RD)
Point estimate	3.1

Confidence interval	
level	90 %
sides	1-sided
lower limit	-9.5

Secondary: R0 resection rate (%)

End point title	R0 resection rate (%)

End point description:

R0 resection is defined as the absence of residual tumor at the resection margins. The R0 resection rate is computed in each arm as the percentage of patients who had a R0 resection after neoadjuvant treatment. Patients who did not undergo surgery or did not have a resection are considered as no R0 resection. R0 resection rate in each arm is calculated in the per protocol population with its exact 2-sided 95% confidence interval.

End point type	Secondary

End point timeframe:

R0 resection is assessed after surgery.

End point values	Control Arm	Experimental Arm 1	Experimental Arm 2	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	32[4]	63[5]	64	
Units: % of patients with R0 resection				
number (confidence interval 95%)	87.5 (71.0 to 96.5)	90.5 (80.4 to 96.4)	85.9 (75.0 to 93.4)	

Notes:

[4] - 1 patient with unknow resection status in the Control Arm

[5] - 1 patient with unknow resection status in Experimental Arm 1

Statistical analyses

No statistical analyses for this end point

Secondary: Progression Free Survival (RECIST v1.1)

End point title	Progression Free Survival (RECIST v1.1)

End point description:

Progression free survival is defined as the time interval between randomization and the date of disease progression or death from any cause, whichever comes first. Patients alive with no disease progression are censored at the date of the last follow-up examination. The primary analysis of Progression-free survival was performed in the Per protocol population.

End point type	Secondary

End point timeframe:

Disease evaluation was performed at end of neoadjuvant treatment, every 6 months after surgery for the first 2 years and every 12 months for additional 4 years until progression, death, lost to follow-up or end of study.

End point values	Control Arm	Experimental Arm 1	Experimental Arm 2	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	33	64	64	
Units: PFS rate (%) at 3 years				
number (confidence interval 95%)	63.6 (44.9 to 77.5)	64.7 (51.5 to 75.2)	52.0 (38.8 to 63.8)	

Attachments (see zip file)	PFS_KM_PP/KM_PFS.png

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival

End point title	Overall Survival

End point description:

Overall survival is defined as the time interval between the date of randomization and the date of death from any cause. Patients who are still alive when last traced are censored at the date of last follow up. The primary analysis of Overall survival was performed in the Per protocol population.

End point type	Secondary

End point timeframe:

All patients were followed-up until death for 6 years following surgery or until lost to follow-up or end of study.

End point values	Control Arm	Experimental Arm 1	Experimental Arm 2	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	33	64	64	
Units: OS rate (%) at 3 years				
number (confidence interval 95%)	75.6 (57.1 to 87.0)	76.9 (64.1 to 85.6)	65.2 (51.3 to 76.1)	

Attachments (see zip file)	OS_KM_PP/KM_OS.png

Statistical analyses

No statistical analyses for this end point

Secondary: Recurrence Free Survival (from surgery)

End point title	Recurrence Free Survival (from surgery)

End point description:

Recurrence-free survival was defined in resected patients who achieved a R0 or R1 resection as the time interval from surgery to the date of first recurrence (local, regional or distant) or death, whichever comes first. Patients alive and recurrence free at the time of data analysis were censored at the date of the most recent follow-up. Recurrence-free survival was analyzed in the resected population.

End point type	Secondary

End point timeframe:

Post surgery, disease evaluation was performed every 6 months for the first 2 years and every 12 months for 4 additional years until recurrence, death, lost to follow-up or end of study.

End point values	Control Arm	Experimental Arm 1	Experimental Arm 2	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	28	62	58	
Units: RFS rate (%) at 3 years				
number (confidence interval 95%)	67.9 (47.3 to 81.8)	63.2 (49.7 to 74.1)	54.6 (40.5 to 66.8)	

Attachments (see zip file)	RFS_KM_RES/KM_RFS.png

Statistical analyses

Statistical analysis title	Experimental Arm 1 vs Control Arm

Statistical analysis description:

The primary analysis of the secondary endpoint RFS was conducted in the Resected Only population. A Cox regression model with treatment as covariate was used to provide an estimate of the treatment effect (hazard ratio) together its two-sided 95% confidence interval.

Comparison groups	Control Arm v Experimental Arm 1
Number of subjects included in analysis	90
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Hazard ratio (HR)
Point estimate	0.92
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.45
upper limit	1.9

Statistical analysis title	Experimental Arm 2 vs Control Arm

Statistical analysis description:

The primary analysis of the secondary endpoint RFS was conducted in the Resected Only population. A Cox regression model with treatment as covariate was used to provide an estimate of the treatment effect (hazard ratio) together its two-sided 95% confidence interval.

Comparison groups	Experimental Arm 2 v Control Arm

Number of subjects included in analysis	86
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Hazard ratio (HR)
Point estimate	1.24
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.61
upper limit	2.51

Secondary: Cumulative Incidence of Locoregional Failure

End point title	Cumulative Incidence of Locoregional Failure

End point description:

Locoregional failure is defined as local or regional recurrence/progression, a tumor that cannot be resected or R2 resection at surgery. Local recurrence/progression is defined as evidence/progression of tumor in the anastomotic area or as recurrence/progression in the locoregional lymph nodes. Death in absence of locoregional failure is considered as a competing risk in the estimation of the cumulative incidence of locoregional failure. Patients who have not had any such event at the time of data analysis are censored at the date of the most recent follow-up. Locoregional failure was analysed in the per protocol population.

End point type	Secondary

End point timeframe:

Disease evaluation was performed at end of neoadjuvant treatment, every 6 months after surgery for the first 2 years and every 12 months for additional 4 years until progression, death, lost to follow-up or end of study.

End point values	Control Arm	Experimental Arm 1	Experimental Arm 2	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	33	64	64	
Units: Cumulative incidence rate (%) at 3 years				
number (confidence interval 95%)	21.3 (9.2 to 36.8)	19.3 (10.6 to 30.0)	20.1 (11.0 to 31.1)	

Attachments (see zip file)	CUM_LRF_PP/CUM_LRF.png

Statistical analyses

No statistical analyses for this end point

Secondary: Cumulative Incidence of Distant Failure

End point title	Cumulative Incidence of Distant Failure

End point description:

Distant failure is defined as the appearance of distant metastases. Death in absence of distant failure will be considered as a competing risk in the estimation of the cumulative incidence of distant failure.

Patients who have not had any such event at the time of data analysis are censored at the date of the most recent follow-up. Distant failure was analysed in the per protocol population.

End point type	Secondary

End point timeframe:

Disease evaluation was performed at end of neoadjuvant treatment, every 6 months after surgery for the first 2 years and every 12 months for additional 4 years until progression, death, lost to follow-up or end of study.

End point values	Control Arm	Experimental Arm 1	Experimental Arm 2	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	33	64	64	
Units: Cumulative incidence rate (%) at 3 years				
number (confidence interval 95%)	33.3 (17.9 to 49.6)	25.7 (15.6 to 37.1)	28.3 (17.5 to 40.1)	

Attachments (see zip file)	CUM_DF_PP/CUM_DF.png

Statistical analyses

No statistical analyses for this end point

Secondary: Complete Pathological Response (cpR) rate (%)

End point title	Complete Pathological Response (cpR) rate (%)

End point description:

Pathological response was assessed centrally using the Becker regression grading. Histopathologists were blinded to treatment allocation. Complete pathological response (cpR) is defined as no residual invasive cancer detected of the resected primary tumor following neoadjuvant therapy. The cpR rate is computed in each arm as the percentage of patients who had cpR after neoadjuvant treatment. Patients not resected were considered as not having pathological complete response. CpR rate in each arm is calculated in the per protocol population with its exact 2-sided 95% confidence interval.

End point type	Secondary

End point timeframe:

Pathological response is assessed after neoadjuvant therapy and surgery.

End point values	Control Arm	Experimental Arm 1	Experimental Arm 2	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	30[6]	54[7]	53[8]	
Units: % of patients with cpR				
number (confidence interval 95%)	3.3 (0.1 to 17.2)	14.8 (6.6 to 27.1)	5.7 (1.2 to 15.7)	

Notes:

[6] - For 3 patients operated in the Control Arm, sample was missing or judged of insufficient quality

[7] - For 10 patients operated in Experimental Arm 1, sample was missing or judged of insufficient

quality

[8] - For 11 patients operated in Experimental Arm 2, sample was missing or judged of insufficient quality

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were collected starting from the registration of the patient until 28 days after the last dose of study treatment. SAEs are to be reported within 24 hours. All AEs and SAEs are to be followed until resolution or stabilisation.

Adverse event reporting additional description:

CRF for AEs contains pre-specified items + additional boxes for all "other" AEs. (AEs reported as "other" are not reported as not available from the list of SOC).
AEs are evaluated using CTC grading version 4.0, SAEs using MedDra version 25. Non-SAEs has not been collected specifically, all AEs will be reported in non-SAE section.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	25

Reporting groups

Reporting group title	Control Arm

Reporting group description:

Perioperative chemotherapy alone.

Reporting group title	Experimental Arm 2

Reporting group description:

Experimental arm 2 consisted of perioperative chemotherapy plus trastuzumab and pertuzumab.

Reporting group title	Experimental Arm 1

Reporting group description:

Experimental arm 1 consisted of perioperative chemotherapy plus trastuzumab.

Serious adverse events	Control Arm	Experimental Arm 2	Experimental Arm 1
Total subjects affected by serious adverse events			
subjects affected / exposed	13 / 34 (38.24%)	47 / 69 (68.12%)	35 / 66 (53.03%)
number of deaths (all causes)	12	25	19
number of deaths resulting from adverse events	0	2	2
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
TUMOUR HAEMORRHAGE			
alternative dictionary used: MedDRA 25			
subjects affected / exposed	0 / 34 (0.00%)	1 / 69 (1.45%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
METASTASES TO CENTRAL NERVOUS SYSTEM			
alternative dictionary used: MedDRA 25			

subjects affected / exposed	0 / 34 (0.00%)	1 / 69 (1.45%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
GASTROINTESTINAL STROMAL TUMOUR			
alternative dictionary used: MedDRA 25			
subjects affected / exposed	0 / 34 (0.00%)	0 / 69 (0.00%)	2 / 66 (3.03%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
HAEMATOMA			
alternative dictionary used: MedDRA 25			
subjects affected / exposed	0 / 34 (0.00%)	1 / 69 (1.45%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
LYMPHATIC FISTULA			
alternative dictionary used: MedDRA 25			
subjects affected / exposed	0 / 34 (0.00%)	0 / 69 (0.00%)	1 / 66 (1.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PERIPHERAL ARTERY THROMBOSIS			
alternative dictionary used: MedDRA 25			
subjects affected / exposed	0 / 34 (0.00%)	1 / 69 (1.45%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PERIPHERAL VEIN THROMBOSIS			
alternative dictionary used: MedDRA 25			
subjects affected / exposed	0 / 34 (0.00%)	0 / 69 (0.00%)	1 / 66 (1.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
ASTHENIA			
alternative dictionary used: MedDRA 25			

subjects affected / exposed	0 / 34 (0.00%)	0 / 69 (0.00%)	1 / 66 (1.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PYREXIA			
alternative dictionary used: MedDRA 25			
subjects affected / exposed	1 / 34 (2.94%)	1 / 69 (1.45%)	1 / 66 (1.52%)
occurrences causally related to treatment / all	0 / 1	0 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PERFORATION			
alternative dictionary used: MedDRA 25			
subjects affected / exposed	0 / 34 (0.00%)	1 / 69 (1.45%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
GENERAL PHYSICAL HEALTH DETERIORATION			
alternative dictionary used: MedDRA 25			
subjects affected / exposed	0 / 34 (0.00%)	0 / 69 (0.00%)	1 / 66 (1.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
DEHISCENCE			
alternative dictionary used: MedDRA 25			
subjects affected / exposed	0 / 34 (0.00%)	1 / 69 (1.45%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
MUCOSAL INFLAMMATION			
alternative dictionary used: MedDRA 25			
subjects affected / exposed	0 / 34 (0.00%)	3 / 69 (4.35%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	0 / 0	3 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 0
Respiratory, thoracic and mediastinal disorders			
PULMONARY EMBOLISM			
alternative dictionary used: MedDRA 25			

subjects affected / exposed	0 / 34 (0.00%)	1 / 69 (1.45%)	1 / 66 (1.52%)
occurrences causally related to treatment / all	0 / 0	0 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
RESPIRATORY FAILURE			
alternative dictionary used: MedDRA 25			
subjects affected / exposed	0 / 34 (0.00%)	1 / 69 (1.45%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PNEUMOTHORAX			
alternative dictionary used: MedDRA 25			
subjects affected / exposed	0 / 34 (0.00%)	2 / 69 (2.90%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ASPHYXIA			
alternative dictionary used: MedDRA 25			
subjects affected / exposed	0 / 34 (0.00%)	0 / 69 (0.00%)	1 / 66 (1.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ASPIRATION			
alternative dictionary used: MedDRA 25			
subjects affected / exposed	0 / 34 (0.00%)	1 / 69 (1.45%)	1 / 66 (1.52%)
occurrences causally related to treatment / all	0 / 0	0 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
BRONCHIAL FISTULA			
alternative dictionary used: MedDRA 25			
subjects affected / exposed	0 / 34 (0.00%)	1 / 69 (1.45%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
DYSPNOEA			
alternative dictionary used: MedDRA 25			
subjects affected / exposed	0 / 34 (0.00%)	0 / 69 (0.00%)	1 / 66 (1.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

INTERSTITIAL LUNG DISEASE			
alternative dictionary used: MedDRA 25			
subjects affected / exposed	0 / 34 (0.00%)	1 / 69 (1.45%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PLEURAL EFFUSION			
alternative dictionary used: MedDRA 25			
subjects affected / exposed	0 / 34 (0.00%)	2 / 69 (2.90%)	1 / 66 (1.52%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PNEUMONITIS			
alternative dictionary used: MedDRA 25			
subjects affected / exposed	1 / 34 (2.94%)	0 / 69 (0.00%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
WEIGHT DECREASED			
alternative dictionary used: MedDRA 25			
subjects affected / exposed	0 / 34 (0.00%)	2 / 69 (2.90%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
EJECTION FRACTION DECREASED			
alternative dictionary used: MedDRA 25			
subjects affected / exposed	0 / 34 (0.00%)	0 / 69 (0.00%)	2 / 66 (3.03%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
BLOOD CREATININE INCREASED			
alternative dictionary used: MedDRA 25			
subjects affected / exposed	0 / 34 (0.00%)	1 / 69 (1.45%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
BLOOD CHOLINESTERASE DECREASED			
alternative dictionary used: MedDRA 25			

subjects affected / exposed	0 / 34 (0.00%)	1 / 69 (1.45%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
INCISIONAL HERNIA			
alternative dictionary used: MedDRA 25			
subjects affected / exposed	0 / 34 (0.00%)	0 / 69 (0.00%)	1 / 66 (1.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
VASCULAR PSEUDOANEURYSM			
alternative dictionary used: MedDRA 25			
subjects affected / exposed	0 / 34 (0.00%)	1 / 69 (1.45%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
GASTROINTESTINAL ANASTOMOTIC COMPLICATION			
alternative dictionary used: MedDRA 25			
subjects affected / exposed	0 / 34 (0.00%)	0 / 69 (0.00%)	1 / 66 (1.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
FAILURE TO ANASTOMOSE			
alternative dictionary used: MedDRA 25			
subjects affected / exposed	0 / 34 (0.00%)	1 / 69 (1.45%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
EXTRADURAL HAEMATOMA			
alternative dictionary used: MedDRA 25			
subjects affected / exposed	0 / 34 (0.00%)	1 / 69 (1.45%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CRANIOFACIAL FRACTURE			
alternative dictionary used: MedDRA 25			

subjects affected / exposed	1 / 34 (2.94%)	0 / 69 (0.00%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ANASTOMOTIC LEAK			
alternative dictionary used: MedDRA 25			
subjects affected / exposed	0 / 34 (0.00%)	2 / 69 (2.90%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ANASTOMOTIC FISTULA			
alternative dictionary used: MedDRA 25			
subjects affected / exposed	0 / 34 (0.00%)	1 / 69 (1.45%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ANASTOMOTIC COMPLICATION			
alternative dictionary used: MedDRA 25			
subjects affected / exposed	1 / 34 (2.94%)	0 / 69 (0.00%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
INFUSION RELATED REACTION			
alternative dictionary used: MedDRA 25			
subjects affected / exposed	0 / 34 (0.00%)	1 / 69 (1.45%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
LIMB INJURY			
alternative dictionary used: MedDRA 25			
subjects affected / exposed	0 / 34 (0.00%)	1 / 69 (1.45%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
POST PROCEDURAL COMPLICATION			
alternative dictionary used: MedDRA 25			
subjects affected / exposed	0 / 34 (0.00%)	1 / 69 (1.45%)	1 / 66 (1.52%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

POST PROCEDURAL FISTULA			
alternative dictionary used: MedDRA 25			
subjects affected / exposed	0 / 34 (0.00%)	1 / 69 (1.45%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
POST PROCEDURAL HAEMORRHAGE			
alternative dictionary used: MedDRA 25			
subjects affected / exposed	1 / 34 (2.94%)	0 / 69 (0.00%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
STOMA SITE EXTRAVASATION			
alternative dictionary used: MedDRA 25			
subjects affected / exposed	1 / 34 (2.94%)	0 / 69 (0.00%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
GASTROINTESTINAL ANASTOMOTIC LEAK			
alternative dictionary used: MedDRA 25			
subjects affected / exposed	1 / 34 (2.94%)	2 / 69 (2.90%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	1 / 1	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
WOUND DEHISCENCE			
alternative dictionary used: MedDRA 25			
subjects affected / exposed	0 / 34 (0.00%)	0 / 69 (0.00%)	1 / 66 (1.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
CARDIAC FAILURE			
alternative dictionary used: MedDRA 25			
subjects affected / exposed	0 / 34 (0.00%)	1 / 69 (1.45%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
SINUS NODE DYSFUNCTION			
alternative dictionary used: MedDRA 25			

subjects affected / exposed	0 / 34 (0.00%)	0 / 69 (0.00%)	1 / 66 (1.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
MYOCARDITIS			
alternative dictionary used: MedDRA 25			
subjects affected / exposed	0 / 34 (0.00%)	1 / 69 (1.45%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
LEFT VENTRICULAR DYSFUNCTION			
alternative dictionary used: MedDRA 25			
subjects affected / exposed	0 / 34 (0.00%)	0 / 69 (0.00%)	1 / 66 (1.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ARTERIOSPASM CORONARY			
alternative dictionary used: MedDRA 25			
subjects affected / exposed	0 / 34 (0.00%)	1 / 69 (1.45%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
SINUS TACHYCARDIA			
alternative dictionary used: MedDRA 25			
subjects affected / exposed	0 / 34 (0.00%)	0 / 69 (0.00%)	1 / 66 (1.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
CEREBRAL ISCHAEMIA			
alternative dictionary used: MedDRA 25			
subjects affected / exposed	0 / 34 (0.00%)	1 / 69 (1.45%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 0
CEREBROVASCULAR ACCIDENT			
alternative dictionary used: MedDRA 25			

subjects affected / exposed	0 / 34 (0.00%)	0 / 69 (0.00%)	1 / 66 (1.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
POSTERIOR REVERSIBLE ENCEPHALOPATHY SYNDROME			
alternative dictionary used: MedDRA 25			
subjects affected / exposed	0 / 34 (0.00%)	1 / 69 (1.45%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
SYNCOPE			
alternative dictionary used: MedDRA 25			
subjects affected / exposed	0 / 34 (0.00%)	2 / 69 (2.90%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
ANAEMIA			
alternative dictionary used: MedDRA 25			
subjects affected / exposed	0 / 34 (0.00%)	1 / 69 (1.45%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
SPLENIC HAEMORRHAGE			
alternative dictionary used: MedDRA 25			
subjects affected / exposed	1 / 34 (2.94%)	0 / 69 (0.00%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
NEUTROPENIA			
alternative dictionary used: MedDRA 25			
subjects affected / exposed	0 / 34 (0.00%)	1 / 69 (1.45%)	1 / 66 (1.52%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
FEBRILE NEUTROPENIA			
alternative dictionary used: MedDRA 25			

subjects affected / exposed	0 / 34 (0.00%)	0 / 69 (0.00%)	1 / 66 (1.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1
Ear and labyrinth disorders			
VERTIGO			
alternative dictionary used: MedDRA 25			
subjects affected / exposed	0 / 34 (0.00%)	1 / 69 (1.45%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
DIPLOPIA			
alternative dictionary used: MedDRA 25			
subjects affected / exposed	0 / 34 (0.00%)	0 / 69 (0.00%)	1 / 66 (1.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
FISTULA OF SMALL INTESTINE			
alternative dictionary used: MedDRA 25			
subjects affected / exposed	0 / 34 (0.00%)	0 / 69 (0.00%)	1 / 66 (1.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
GASTRIC PERFORATION			
alternative dictionary used: MedDRA 25			
subjects affected / exposed	0 / 34 (0.00%)	0 / 69 (0.00%)	1 / 66 (1.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
GASTRITIS			
alternative dictionary used: MedDRA 25			
subjects affected / exposed	0 / 34 (0.00%)	1 / 69 (1.45%)	1 / 66 (1.52%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
GASTROINTESTINAL HAEMORRHAGE			
alternative dictionary used: MedDRA 25			

subjects affected / exposed	0 / 34 (0.00%)	1 / 69 (1.45%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
GASTROINTESTINAL OBSTRUCTION			
alternative dictionary used: MedDRA 25			
subjects affected / exposed	0 / 34 (0.00%)	0 / 69 (0.00%)	1 / 66 (1.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
DYSPHAGIA			
alternative dictionary used: MedDRA 25			
subjects affected / exposed	1 / 34 (2.94%)	2 / 69 (2.90%)	2 / 66 (3.03%)
occurrences causally related to treatment / all	1 / 1	2 / 2	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
DUODENAL ULCER			
alternative dictionary used: MedDRA 25			
subjects affected / exposed	0 / 34 (0.00%)	0 / 69 (0.00%)	1 / 66 (1.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
DIARRHOEA			
alternative dictionary used: MedDRA 25			
subjects affected / exposed	0 / 34 (0.00%)	8 / 69 (11.59%)	1 / 66 (1.52%)
occurrences causally related to treatment / all	0 / 0	11 / 11	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
DIAPHRAGMATIC HERNIA			
alternative dictionary used: MedDRA 25			
subjects affected / exposed	1 / 34 (2.94%)	0 / 69 (0.00%)	2 / 66 (3.03%)
occurrences causally related to treatment / all	1 / 1	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ABDOMINAL WALL HAEMATOMA			
alternative dictionary used: MedDRA 25			
subjects affected / exposed	0 / 34 (0.00%)	0 / 69 (0.00%)	1 / 66 (1.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

ABDOMINAL PAIN			
alternative dictionary used: MedDRA 25			
subjects affected / exposed	0 / 34 (0.00%)	1 / 69 (1.45%)	1 / 66 (1.52%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HAEMOPERITONEUM			
alternative dictionary used: MedDRA 25			
subjects affected / exposed	1 / 34 (2.94%)	0 / 69 (0.00%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HERNIAL EVENTRATION			
alternative dictionary used: MedDRA 25			
subjects affected / exposed	0 / 34 (0.00%)	0 / 69 (0.00%)	1 / 66 (1.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
IMPAIRED GASTRIC EMPTYING			
alternative dictionary used: MedDRA 25			
subjects affected / exposed	0 / 34 (0.00%)	0 / 69 (0.00%)	2 / 66 (3.03%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
VOMITING			
alternative dictionary used: MedDRA 25			
subjects affected / exposed	1 / 34 (2.94%)	4 / 69 (5.80%)	2 / 66 (3.03%)
occurrences causally related to treatment / all	1 / 1	4 / 4	3 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
UPPER GASTROINTESTINAL HAEMORRHAGE			
alternative dictionary used: MedDRA 25			
subjects affected / exposed	0 / 34 (0.00%)	1 / 69 (1.45%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
TERMINAL ILEITIS			
alternative dictionary used: MedDRA 25			

subjects affected / exposed	0 / 34 (0.00%)	0 / 69 (0.00%)	1 / 66 (1.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
SMALL INTESTINAL OBSTRUCTION			
alternative dictionary used: MedDRA 25			
subjects affected / exposed	0 / 34 (0.00%)	1 / 69 (1.45%)	1 / 66 (1.52%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
SMALL INTESTINAL HAEMORRHAGE			
alternative dictionary used: MedDRA 25			
subjects affected / exposed	0 / 34 (0.00%)	0 / 69 (0.00%)	1 / 66 (1.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PEPTIC ULCER HAEMORRHAGE			
alternative dictionary used: MedDRA 25			
subjects affected / exposed	0 / 34 (0.00%)	1 / 69 (1.45%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PANCREATITIS			
alternative dictionary used: MedDRA 25			
subjects affected / exposed	0 / 34 (0.00%)	0 / 69 (0.00%)	1 / 66 (1.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
OESOPHAGEAL ULCER			
alternative dictionary used: MedDRA 25			
subjects affected / exposed	0 / 34 (0.00%)	1 / 69 (1.45%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
OESOPHAGEAL STENOSIS			
alternative dictionary used: MedDRA 25			
subjects affected / exposed	0 / 34 (0.00%)	1 / 69 (1.45%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

OESOPHAGEAL FISTULA			
alternative dictionary used: MedDRA 25			
subjects affected / exposed	0 / 34 (0.00%)	1 / 69 (1.45%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
INTESTINAL OBSTRUCTION			
alternative dictionary used: MedDRA 25			
subjects affected / exposed	1 / 34 (2.94%)	2 / 69 (2.90%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	0 / 1	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
MELAENA			
alternative dictionary used: MedDRA 25			
subjects affected / exposed	0 / 34 (0.00%)	1 / 69 (1.45%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
NAUSEA			
alternative dictionary used: MedDRA 25			
subjects affected / exposed	1 / 34 (2.94%)	4 / 69 (5.80%)	2 / 66 (3.03%)
occurrences causally related to treatment / all	1 / 1	4 / 4	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
PERFORATION BILE DUCT			
alternative dictionary used: MedDRA 25			
subjects affected / exposed	0 / 34 (0.00%)	0 / 69 (0.00%)	1 / 66 (1.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CHOLECYSTITIS			
alternative dictionary used: MedDRA 25			
subjects affected / exposed	0 / 34 (0.00%)	1 / 69 (1.45%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
ACUTE KIDNEY INJURY			
alternative dictionary used: MedDRA 25			

subjects affected / exposed	1 / 34 (2.94%)	3 / 69 (4.35%)	1 / 66 (1.52%)
occurrences causally related to treatment / all	0 / 1	3 / 3	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CYSTITIS HAEMORRHAGIC			
alternative dictionary used: MedDRA 25			
subjects affected / exposed	0 / 34 (0.00%)	0 / 69 (0.00%)	1 / 66 (1.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
BACK PAIN			
alternative dictionary used: MedDRA 25			
subjects affected / exposed	1 / 34 (2.94%)	0 / 69 (0.00%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
ABDOMINAL INFECTION			
alternative dictionary used: MedDRA 25			
subjects affected / exposed	0 / 34 (0.00%)	0 / 69 (0.00%)	1 / 66 (1.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ENDOCARDITIS			
alternative dictionary used: MedDRA 25			
subjects affected / exposed	1 / 34 (2.94%)	0 / 69 (0.00%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
EMPYEMA			
alternative dictionary used: MedDRA 25			
subjects affected / exposed	0 / 34 (0.00%)	3 / 69 (4.35%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	0 / 0	5 / 5	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
DEVICE RELATED INFECTION			
alternative dictionary used: MedDRA 25			

subjects affected / exposed	1 / 34 (2.94%)	1 / 69 (1.45%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ATYPICAL PNEUMONIA			
alternative dictionary used: MedDRA 25			
subjects affected / exposed	0 / 34 (0.00%)	1 / 69 (1.45%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ENDOCARDITIS BACTERIAL			
alternative dictionary used: MedDRA 25			
subjects affected / exposed	1 / 34 (2.94%)	0 / 69 (0.00%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ENTEROCOLITIS INFECTIOUS			
alternative dictionary used: MedDRA 25			
subjects affected / exposed	0 / 34 (0.00%)	0 / 69 (0.00%)	1 / 66 (1.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
INFECTED SEROMA			
alternative dictionary used: MedDRA 25			
subjects affected / exposed	0 / 34 (0.00%)	0 / 69 (0.00%)	1 / 66 (1.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
INFECTION			
alternative dictionary used: MedDRA 25			
subjects affected / exposed	0 / 34 (0.00%)	0 / 69 (0.00%)	2 / 66 (3.03%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
INFECTIOUS PLEURAL EFFUSION			
alternative dictionary used: MedDRA 25			
subjects affected / exposed	0 / 34 (0.00%)	0 / 69 (0.00%)	1 / 66 (1.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

INTERVERTEBRAL DISCITIS			
alternative dictionary used: MedDRA 25			
subjects affected / exposed	1 / 34 (2.94%)	0 / 69 (0.00%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PERITONITIS			
alternative dictionary used: MedDRA 25			
subjects affected / exposed	0 / 34 (0.00%)	0 / 69 (0.00%)	1 / 66 (1.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1
PNEUMONIA			
alternative dictionary used: MedDRA 25			
subjects affected / exposed	2 / 34 (5.88%)	3 / 69 (4.35%)	2 / 66 (3.03%)
occurrences causally related to treatment / all	1 / 2	1 / 3	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PNEUMONIA KLEBSIELLA			
alternative dictionary used: MedDRA 25			
subjects affected / exposed	0 / 34 (0.00%)	1 / 69 (1.45%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PYELONEPHRITIS ACUTE			
alternative dictionary used: MedDRA 25			
subjects affected / exposed	0 / 34 (0.00%)	1 / 69 (1.45%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
SEPSIS			
alternative dictionary used: MedDRA 25			
subjects affected / exposed	1 / 34 (2.94%)	2 / 69 (2.90%)	1 / 66 (1.52%)
occurrences causally related to treatment / all	1 / 1	1 / 2	1 / 1
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 0
SEPTIC SHOCK			
alternative dictionary used: MedDRA 25			

subjects affected / exposed	0 / 34 (0.00%)	1 / 69 (1.45%)	1 / 66 (1.52%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
SERRATIA SEPSIS			
alternative dictionary used: MedDRA 25			
subjects affected / exposed	0 / 34 (0.00%)	1 / 69 (1.45%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
SPONTANEOUS BACTERIAL PERITONITIS			
alternative dictionary used: MedDRA 25			
subjects affected / exposed	0 / 34 (0.00%)	1 / 69 (1.45%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
HYPOKALAEMIA			
alternative dictionary used: MedDRA 25			
subjects affected / exposed	0 / 34 (0.00%)	1 / 69 (1.45%)	2 / 66 (3.03%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HYPERGLYCAEMIA			
alternative dictionary used: MedDRA 25			
subjects affected / exposed	0 / 34 (0.00%)	1 / 69 (1.45%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
DEHYDRATION			
alternative dictionary used: MedDRA 25			
subjects affected / exposed	0 / 34 (0.00%)	2 / 69 (2.90%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
DECREASED APPETITE			
alternative dictionary used: MedDRA 25			

subjects affected / exposed	0 / 34 (0.00%)	1 / 69 (1.45%)	1 / 66 (1.52%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HYPOMAGNESAEMIA			
alternative dictionary used: MedDRA 25			
subjects affected / exposed	1 / 34 (2.94%)	1 / 69 (1.45%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HYPONATRAEMIA			
alternative dictionary used: MedDRA 25			
subjects affected / exposed	0 / 34 (0.00%)	1 / 69 (1.45%)	1 / 66 (1.52%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Control Arm	Experimental Arm 2	Experimental Arm 1
Total subjects affected by non-serious adverse events			
subjects affected / exposed	34 / 34 (100.00%)	69 / 69 (100.00%)	66 / 66 (100.00%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) - OTHER, SPECIFY			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	0 / 34 (0.00%)	3 / 69 (4.35%)	5 / 66 (7.58%)
occurrences (all)	0	4	5
TUMOR PAIN			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 34 (2.94%)	1 / 69 (1.45%)	0 / 66 (0.00%)
occurrences (all)	1	1	0
Vascular disorders			
VASCULAR DISORDERS - OTHER, SPECIFY			
alternative dictionary used: CTCAE 4.0			

subjects affected / exposed	0 / 34 (0.00%)	1 / 69 (1.45%)	0 / 66 (0.00%)
occurrences (all)	0	2	0
HEMATOMA			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	0 / 34 (0.00%)	2 / 69 (2.90%)	1 / 66 (1.52%)
occurrences (all)	0	2	1
HOT FLASHES			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 34 (2.94%)	0 / 69 (0.00%)	0 / 66 (0.00%)
occurrences (all)	1	0	0
HYPERTENSION			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	5 / 34 (14.71%)	14 / 69 (20.29%)	14 / 66 (21.21%)
occurrences (all)	6	32	36
HYPOTENSION			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 34 (2.94%)	1 / 69 (1.45%)	1 / 66 (1.52%)
occurrences (all)	1	1	1
SUPERFICIAL THROMBOPHLEBITIS			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	0 / 34 (0.00%)	2 / 69 (2.90%)	0 / 66 (0.00%)
occurrences (all)	0	2	0
THROMBOEMBOLIC EVENT			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	2 / 34 (5.88%)	3 / 69 (4.35%)	7 / 66 (10.61%)
occurrences (all)	2	4	10
General disorders and administration site conditions			
CHILLS			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	0 / 34 (0.00%)	3 / 69 (4.35%)	1 / 66 (1.52%)
occurrences (all)	0	4	1
EDEMA LIMBS			
alternative dictionary used: CTCAE 4.0			

subjects affected / exposed	0 / 34 (0.00%)	2 / 69 (2.90%)	2 / 66 (3.03%)
occurrences (all)	0	2	2
FATIGUE			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	16 / 34 (47.06%)	26 / 69 (37.68%)	27 / 66 (40.91%)
occurrences (all)	28	50	50
FEVER			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	4 / 34 (11.76%)	9 / 69 (13.04%)	6 / 66 (9.09%)
occurrences (all)	5	18	6
FLU LIKE SYMPTOMS			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 34 (2.94%)	3 / 69 (4.35%)	2 / 66 (3.03%)
occurrences (all)	1	3	2
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - OTHER, SPECIFY			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	12 / 34 (35.29%)	12 / 69 (17.39%)	19 / 66 (28.79%)
occurrences (all)	18	33	66
HEADACHE			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	2 / 34 (5.88%)	0 / 69 (0.00%)	1 / 66 (1.52%)
occurrences (all)	2	0	1
HYPOTHERMIA			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 34 (2.94%)	0 / 69 (0.00%)	0 / 66 (0.00%)
occurrences (all)	1	0	0
INFUSION RELATED REACTION			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	0 / 34 (0.00%)	3 / 69 (4.35%)	2 / 66 (3.03%)
occurrences (all)	0	3	2
INFUSION SITE EXTRAVASATION			
alternative dictionary used: CTCAE 4.0			

subjects affected / exposed	0 / 34 (0.00%)	0 / 69 (0.00%)	1 / 66 (1.52%)
occurrences (all)	0	0	2
LOCALIZED EDEMA			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	0 / 34 (0.00%)	1 / 69 (1.45%)	0 / 66 (0.00%)
occurrences (all)	0	1	0
NON-CARDIAC CHEST PAIN			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	0 / 34 (0.00%)	1 / 69 (1.45%)	3 / 66 (4.55%)
occurrences (all)	0	1	3
PAIN			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	0 / 34 (0.00%)	1 / 69 (1.45%)	3 / 66 (4.55%)
occurrences (all)	0	1	4
Immune system disorders			
ALLERGIC REACTION			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	2 / 34 (5.88%)	2 / 69 (2.90%)	1 / 66 (1.52%)
occurrences (all)	2	2	1
IMMUNE SYSTEM DISORDERS - OTHER, SPECIFY			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	0 / 34 (0.00%)	0 / 69 (0.00%)	1 / 66 (1.52%)
occurrences (all)	0	0	1
Reproductive system and breast disorders			
ERECTILE DYSFUNCTION			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 34 (2.94%)	0 / 69 (0.00%)	0 / 66 (0.00%)
occurrences (all)	1	0	0
IRREGULAR MENSTRUATION			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	0 / 34 (0.00%)	1 / 69 (1.45%)	0 / 66 (0.00%)
occurrences (all)	0	1	0
REPRODUCTIVE SYSTEM AND BREAST DISORDERS - OTHER, SPECIFY			

alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	0 / 34 (0.00%)	1 / 69 (1.45%)	0 / 66 (0.00%)
occurrences (all)	0	1	0
VAGINAL DRYNESS			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	0 / 34 (0.00%)	1 / 69 (1.45%)	0 / 66 (0.00%)
occurrences (all)	0	1	0
Respiratory, thoracic and mediastinal disorders			
COUGH			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 34 (2.94%)	4 / 69 (5.80%)	3 / 66 (4.55%)
occurrences (all)	1	5	3
ALLERGIC RHINITIS			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	0 / 34 (0.00%)	0 / 69 (0.00%)	1 / 66 (1.52%)
occurrences (all)	0	0	1
ASPIRATION			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	0 / 34 (0.00%)	2 / 69 (2.90%)	1 / 66 (1.52%)
occurrences (all)	0	3	1
BRONCHIAL FISTULA			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	0 / 34 (0.00%)	1 / 69 (1.45%)	0 / 66 (0.00%)
occurrences (all)	0	1	0
CHYLOTHORAX			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	0 / 34 (0.00%)	0 / 69 (0.00%)	1 / 66 (1.52%)
occurrences (all)	0	0	1
DYSPNEA			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	2 / 34 (5.88%)	3 / 69 (4.35%)	4 / 66 (6.06%)
occurrences (all)	2	5	5
EPISTAXIS			
alternative dictionary used: CTCAE 4.0			

subjects affected / exposed	2 / 34 (5.88%)	13 / 69 (18.84%)	1 / 66 (1.52%)
occurrences (all)	2	14	1
HICCUPS			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	2 / 34 (5.88%)	1 / 69 (1.45%)	1 / 66 (1.52%)
occurrences (all)	2	1	1
LUNG INFECTION			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 34 (2.94%)	0 / 69 (0.00%)	0 / 66 (0.00%)
occurrences (all)	1	0	0
NASAL CONGESTION			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	0 / 34 (0.00%)	0 / 69 (0.00%)	1 / 66 (1.52%)
occurrences (all)	0	0	1
PLEURAL EFFUSION			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	3 / 34 (8.82%)	6 / 69 (8.70%)	7 / 66 (10.61%)
occurrences (all)	3	9	10
PNEUMOTHORAX			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	0 / 34 (0.00%)	4 / 69 (5.80%)	1 / 66 (1.52%)
occurrences (all)	0	4	1
RESPIRATORY FAILURE			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 34 (2.94%)	1 / 69 (1.45%)	1 / 66 (1.52%)
occurrences (all)	1	1	1
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - OTHER, SPECIFY			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	0 / 34 (0.00%)	7 / 69 (10.14%)	5 / 66 (7.58%)
occurrences (all)	0	8	5
RETINOIC ACID SYNDROME			
alternative dictionary used: CTCAE 4.0			

subjects affected / exposed	0 / 34 (0.00%)	0 / 69 (0.00%)	1 / 66 (1.52%)
occurrences (all)	0	0	1
SORE THROAT			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 34 (2.94%)	1 / 69 (1.45%)	1 / 66 (1.52%)
occurrences (all)	1	1	1
PNEUMONITIS			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 34 (2.94%)	0 / 69 (0.00%)	1 / 66 (1.52%)
occurrences (all)	1	0	1
Psychiatric disorders			
ANXIETY			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 34 (2.94%)	4 / 69 (5.80%)	2 / 66 (3.03%)
occurrences (all)	1	4	2
DELIRIUM			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 34 (2.94%)	1 / 69 (1.45%)	1 / 66 (1.52%)
occurrences (all)	1	1	1
DEPRESSION			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	0 / 34 (0.00%)	1 / 69 (1.45%)	2 / 66 (3.03%)
occurrences (all)	0	1	2
INSOMNIA			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	0 / 34 (0.00%)	1 / 69 (1.45%)	6 / 66 (9.09%)
occurrences (all)	0	1	6
PSYCHOSIS			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	0 / 34 (0.00%)	1 / 69 (1.45%)	0 / 66 (0.00%)
occurrences (all)	0	1	0
Investigations			
ASPARTATE AMINOTRANSFERASE INCREASED			
alternative dictionary used: CTCAE 4.0			

subjects affected / exposed	0 / 34 (0.00%)	2 / 69 (2.90%)	3 / 66 (4.55%)
occurrences (all)	0	6	3
CREATININE INCREASED alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	4 / 34 (11.76%)	5 / 69 (7.25%)	4 / 66 (6.06%)
occurrences (all)	6	9	4
EJECTION FRACTION DECREASED alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	0 / 34 (0.00%)	3 / 69 (4.35%)	2 / 66 (3.03%)
occurrences (all)	0	3	2
ALANINE AMINOTRANSFERASE INCREASED alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	2 / 34 (5.88%)	2 / 69 (2.90%)	3 / 66 (4.55%)
occurrences (all)	2	4	3
INVESTIGATIONS - OTHER, SPECIFY alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 34 (2.94%)	5 / 69 (7.25%)	3 / 66 (4.55%)
occurrences (all)	1	8	3
LYMPHOCYTE COUNT DECREASED alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	0 / 34 (0.00%)	1 / 69 (1.45%)	0 / 66 (0.00%)
occurrences (all)	0	2	0
NEUTROPHIL COUNT DECREASED alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	18 / 34 (52.94%)	32 / 69 (46.38%)	36 / 66 (54.55%)
occurrences (all)	27	74	80
PLATELET COUNT DECREASED alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	2 / 34 (5.88%)	8 / 69 (11.59%)	7 / 66 (10.61%)
occurrences (all)	2	10	18
WEIGHT LOSS alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	5 / 34 (14.71%)	26 / 69 (37.68%)	13 / 66 (19.70%)
occurrences (all)	6	34	14

WHITE BLOOD CELL DECREASED			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	2 / 34 (5.88%)	13 / 69 (18.84%)	7 / 66 (10.61%)
occurrences (all)	2	38	40
Injury, poisoning and procedural complications			
ESOPHAGEAL ANASTOMOTIC LEAK			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 34 (2.94%)	4 / 69 (5.80%)	1 / 66 (1.52%)
occurrences (all)	1	4	1
BURN			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	0 / 34 (0.00%)	1 / 69 (1.45%)	0 / 66 (0.00%)
occurrences (all)	0	1	0
FALL			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 34 (2.94%)	1 / 69 (1.45%)	0 / 66 (0.00%)
occurrences (all)	1	1	0
FRACTURE			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 34 (2.94%)	0 / 69 (0.00%)	1 / 66 (1.52%)
occurrences (all)	1	0	1
GASTRIC ANASTOMOTIC LEAK			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 34 (2.94%)	1 / 69 (1.45%)	0 / 66 (0.00%)
occurrences (all)	1	1	0
INJURY, POISONING AND PROCEDURAL COMPLICATIONS - OTHER, SPECIFY			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 34 (2.94%)	4 / 69 (5.80%)	7 / 66 (10.61%)
occurrences (all)	1	5	9
INTRAOPERATIVE HEMORRHAGE			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	0 / 34 (0.00%)	0 / 69 (0.00%)	1 / 66 (1.52%)
occurrences (all)	0	0	1
POSTOPERATIVE HEMORRHAGE			

alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 34 (2.94%)	0 / 69 (0.00%)	0 / 66 (0.00%)
occurrences (all)	1	0	0
WOUND COMPLICATION			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 34 (2.94%)	0 / 69 (0.00%)	2 / 66 (3.03%)
occurrences (all)	1	0	2
WOUND DEHISCENCE			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	2 / 34 (5.88%)	2 / 69 (2.90%)	3 / 66 (4.55%)
occurrences (all)	2	2	5
GASTROINTESTINAL ANASTOMOTIC LEAK			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 34 (2.94%)	0 / 69 (0.00%)	2 / 66 (3.03%)
occurrences (all)	1	0	2
Cardiac disorders			
HEART FAILURE			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	0 / 34 (0.00%)	1 / 69 (1.45%)	0 / 66 (0.00%)
occurrences (all)	0	2	0
CONDUCTION DISORDER			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 34 (2.94%)	0 / 69 (0.00%)	0 / 66 (0.00%)
occurrences (all)	1	0	0
CARDIAC DISORDERS - OTHER, SPECIFY			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	0 / 34 (0.00%)	4 / 69 (5.80%)	2 / 66 (3.03%)
occurrences (all)	0	4	2
ATRIAL FIBRILLATION			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	0 / 34 (0.00%)	1 / 69 (1.45%)	3 / 66 (4.55%)
occurrences (all)	0	1	3
MITRAL VALVE DISEASE			
alternative dictionary used: CTCAE 4.0			

subjects affected / exposed	0 / 34 (0.00%)	1 / 69 (1.45%)	0 / 66 (0.00%)
occurrences (all)	0	1	0
ACUTE CORONARY SYNDROME			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 34 (2.94%)	0 / 69 (0.00%)	0 / 66 (0.00%)
occurrences (all)	1	0	0
LEFT VENTRICULAR SYSTOLIC DYSFUNCTION			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	0 / 34 (0.00%)	1 / 69 (1.45%)	2 / 66 (3.03%)
occurrences (all)	0	1	2
AORTIC VALVE DISEASE			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	0 / 34 (0.00%)	1 / 69 (1.45%)	0 / 66 (0.00%)
occurrences (all)	0	1	0
VENTRICULAR TACHYCARDIA			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	0 / 34 (0.00%)	0 / 69 (0.00%)	1 / 66 (1.52%)
occurrences (all)	0	0	1
VENTRICULAR ARRHYTHMIA			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	0 / 34 (0.00%)	0 / 69 (0.00%)	1 / 66 (1.52%)
occurrences (all)	0	0	1
SINUS TACHYCARDIA			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 34 (2.94%)	1 / 69 (1.45%)	4 / 66 (6.06%)
occurrences (all)	1	1	4
SINUS BRADYCARDIA			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	0 / 34 (0.00%)	0 / 69 (0.00%)	2 / 66 (3.03%)
occurrences (all)	0	0	2
PALPITATIONS			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	0 / 34 (0.00%)	0 / 69 (0.00%)	2 / 66 (3.03%)
occurrences (all)	0	0	2

MYOCARDITIS			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	0 / 34 (0.00%)	1 / 69 (1.45%)	0 / 66 (0.00%)
occurrences (all)	0	2	0
Nervous system disorders			
HEADACHE			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	0 / 34 (0.00%)	4 / 69 (5.80%)	1 / 66 (1.52%)
occurrences (all)	0	5	1
AMNESIA			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	0 / 34 (0.00%)	0 / 69 (0.00%)	1 / 66 (1.52%)
occurrences (all)	0	0	1
APHONIA			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	0 / 34 (0.00%)	0 / 69 (0.00%)	1 / 66 (1.52%)
occurrences (all)	0	0	1
DIZZINESS			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	2 / 34 (5.88%)	5 / 69 (7.25%)	6 / 66 (9.09%)
occurrences (all)	3	5	6
DYSESTHESIA			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	0 / 34 (0.00%)	2 / 69 (2.90%)	2 / 66 (3.03%)
occurrences (all)	0	5	4
DYSGEUSIA			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	7 / 34 (20.59%)	8 / 69 (11.59%)	9 / 66 (13.64%)
occurrences (all)	14	11	11
DYSPHAGIA			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	0 / 34 (0.00%)	1 / 69 (1.45%)	0 / 66 (0.00%)
occurrences (all)	0	1	0
HEMATOMA			
alternative dictionary used: CTCAE 4.0			

subjects affected / exposed	0 / 34 (0.00%)	1 / 69 (1.45%)	0 / 66 (0.00%)
occurrences (all)	0	1	0
NERVOUS SYSTEM DISORDERS - OTHER, SPECIFY			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 34 (2.94%)	8 / 69 (11.59%)	2 / 66 (3.03%)
occurrences (all)	1	14	2
NEURALGIA			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	0 / 34 (0.00%)	2 / 69 (2.90%)	0 / 66 (0.00%)
occurrences (all)	0	3	0
PARESTHESIA			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	8 / 34 (23.53%)	11 / 69 (15.94%)	14 / 66 (21.21%)
occurrences (all)	10	15	24
PERIPHERAL MOTOR NEUROPATHY			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	0 / 34 (0.00%)	2 / 69 (2.90%)	3 / 66 (4.55%)
occurrences (all)	0	2	4
PERIPHERAL SENSORY NEUROPATHY			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	8 / 34 (23.53%)	12 / 69 (17.39%)	17 / 66 (25.76%)
occurrences (all)	10	25	30
PRESYNCOPE			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	0 / 34 (0.00%)	1 / 69 (1.45%)	0 / 66 (0.00%)
occurrences (all)	0	1	0
REVERSIBLE POSTERIOR LEUKOENCEPHALOPATHY SYNDROME			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	0 / 34 (0.00%)	1 / 69 (1.45%)	0 / 66 (0.00%)
occurrences (all)	0	1	0
STROKE			
alternative dictionary used: CTCAE 4.0			

subjects affected / exposed	1 / 34 (2.94%)	0 / 69 (0.00%)	1 / 66 (1.52%)
occurrences (all)	1	0	1
SYNCOPE			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 34 (2.94%)	3 / 69 (4.35%)	0 / 66 (0.00%)
occurrences (all)	1	3	0
ISCHEMIA CEREBROVASCULAR			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	0 / 34 (0.00%)	1 / 69 (1.45%)	0 / 66 (0.00%)
occurrences (all)	0	2	0
Blood and lymphatic system disorders			
ANEMIA			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	2 / 34 (5.88%)	15 / 69 (21.74%)	8 / 66 (12.12%)
occurrences (all)	5	51	25
LEUKOCYTOSIS			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	0 / 34 (0.00%)	3 / 69 (4.35%)	0 / 66 (0.00%)
occurrences (all)	0	3	0
FEBRILE NEUTROPENIA			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	0 / 34 (0.00%)	0 / 69 (0.00%)	1 / 66 (1.52%)
occurrences (all)	0	0	2
BLOOD AND LYMPHATIC SYSTEM DISORDERS - OTHER, SPECIFY			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 34 (2.94%)	0 / 69 (0.00%)	1 / 66 (1.52%)
occurrences (all)	1	0	1
Ear and labyrinth disorders			
VERTIGO			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	3 / 34 (8.82%)	3 / 69 (4.35%)	2 / 66 (3.03%)
occurrences (all)	3	3	3
TINNITUS			
alternative dictionary used: CTCAE 4.0			

subjects affected / exposed	1 / 34 (2.94%)	0 / 69 (0.00%)	1 / 66 (1.52%)
occurrences (all)	1	0	1
HEARING IMPAIRED			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	0 / 34 (0.00%)	1 / 69 (1.45%)	3 / 66 (4.55%)
occurrences (all)	0	1	4
Eye disorders			
EYE DISORDERS - OTHER, SPECIFY			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 34 (2.94%)	0 / 69 (0.00%)	2 / 66 (3.03%)
occurrences (all)	2	0	2
DRY EYE			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 34 (2.94%)	1 / 69 (1.45%)	1 / 66 (1.52%)
occurrences (all)	1	1	2
CONJUNCTIVITIS			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	0 / 34 (0.00%)	1 / 69 (1.45%)	2 / 66 (3.03%)
occurrences (all)	0	1	2
BLURRED VISION			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 34 (2.94%)	0 / 69 (0.00%)	1 / 66 (1.52%)
occurrences (all)	1	0	2
Gastrointestinal disorders			
CHEILITIS			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	0 / 34 (0.00%)	1 / 69 (1.45%)	1 / 66 (1.52%)
occurrences (all)	0	1	1
BLOATING			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	0 / 34 (0.00%)	0 / 69 (0.00%)	2 / 66 (3.03%)
occurrences (all)	0	0	2
ANAL HEMORRHAGE			
alternative dictionary used: CTCAE 4.0			

subjects affected / exposed	0 / 34 (0.00%)	1 / 69 (1.45%)	0 / 66 (0.00%)
occurrences (all)	0	2	0
ABDOMINAL PAIN			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	5 / 34 (14.71%)	9 / 69 (13.04%)	8 / 66 (12.12%)
occurrences (all)	6	11	16
COLITIS			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	0 / 34 (0.00%)	1 / 69 (1.45%)	0 / 66 (0.00%)
occurrences (all)	0	1	0
CONSTIPATION			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	3 / 34 (8.82%)	5 / 69 (7.25%)	10 / 66 (15.15%)
occurrences (all)	4	6	12
DIARRHEA			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	16 / 34 (47.06%)	55 / 69 (79.71%)	45 / 66 (68.18%)
occurrences (all)	24	179	93
DRY MOUTH			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 34 (2.94%)	1 / 69 (1.45%)	1 / 66 (1.52%)
occurrences (all)	1	1	1
DUODENAL FISTULA			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	0 / 34 (0.00%)	0 / 69 (0.00%)	2 / 66 (3.03%)
occurrences (all)	0	0	3
ESOPHAGEAL PAIN			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 34 (2.94%)	0 / 69 (0.00%)	1 / 66 (1.52%)
occurrences (all)	1	0	1
ESOPHAGEAL STENOSIS			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	0 / 34 (0.00%)	1 / 69 (1.45%)	0 / 66 (0.00%)
occurrences (all)	0	2	0

ESOPHAGEAL FISTULA			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	0 / 34 (0.00%)	3 / 69 (4.35%)	0 / 66 (0.00%)
occurrences (all)	0	5	0
ENTEROCOLITIS			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	0 / 34 (0.00%)	0 / 69 (0.00%)	1 / 66 (1.52%)
occurrences (all)	0	0	1
DYSPHAGIA			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	5 / 34 (14.71%)	8 / 69 (11.59%)	9 / 66 (13.64%)
occurrences (all)	7	10	11
DYSPEPSIA			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	0 / 34 (0.00%)	4 / 69 (5.80%)	3 / 66 (4.55%)
occurrences (all)	0	4	4
DYSGEUSIA			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	0 / 34 (0.00%)	0 / 69 (0.00%)	1 / 66 (1.52%)
occurrences (all)	0	0	1
DUODENAL ULCER			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	0 / 34 (0.00%)	1 / 69 (1.45%)	1 / 66 (1.52%)
occurrences (all)	0	1	1
ESOPHAGEAL HEMORRHAGE			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	0 / 34 (0.00%)	1 / 69 (1.45%)	0 / 66 (0.00%)
occurrences (all)	0	1	0
ILEAL OBSTRUCTION			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	0 / 34 (0.00%)	1 / 69 (1.45%)	0 / 66 (0.00%)
occurrences (all)	0	2	0
ESOPHAGEAL ULCER			
alternative dictionary used: CTCAE 4.0			

subjects affected / exposed	1 / 34 (2.94%)	1 / 69 (1.45%)	0 / 66 (0.00%)
occurrences (all)	1	2	0
HEMORRHOIDAL HEMORRHAGE alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	0 / 34 (0.00%)	0 / 69 (0.00%)	1 / 66 (1.52%)
occurrences (all)	0	0	1
GINGIVAL PAIN alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	0 / 34 (0.00%)	1 / 69 (1.45%)	0 / 66 (0.00%)
occurrences (all)	0	1	0
GASTROPARESIS alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	0 / 34 (0.00%)	0 / 69 (0.00%)	1 / 66 (1.52%)
occurrences (all)	0	0	1
GASTROINTESTINAL PAIN alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	0 / 34 (0.00%)	2 / 69 (2.90%)	0 / 66 (0.00%)
occurrences (all)	0	2	0
GASTROINTESTINAL DISORDERS - OTHER, SPECIFY alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	7 / 34 (20.59%)	6 / 69 (8.70%)	10 / 66 (15.15%)
occurrences (all)	11	7	16
GASTROESOPHAGEAL REFLUX DISEASE alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	2 / 34 (5.88%)	5 / 69 (7.25%)	2 / 66 (3.03%)
occurrences (all)	2	5	2
GASTRITIS alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	0 / 34 (0.00%)	1 / 69 (1.45%)	1 / 66 (1.52%)
occurrences (all)	0	3	1
GASTRIC STENOSIS alternative dictionary used: CTCAE 4.0			

subjects affected / exposed	0 / 34 (0.00%)	0 / 69 (0.00%)	1 / 66 (1.52%)
occurrences (all)	0	0	1
GASTRIC HEMORRHAGE			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	0 / 34 (0.00%)	1 / 69 (1.45%)	0 / 66 (0.00%)
occurrences (all)	0	1	0
GASTRIC FISTULA			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	0 / 34 (0.00%)	0 / 69 (0.00%)	1 / 66 (1.52%)
occurrences (all)	0	0	1
FLATULENCE			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	0 / 34 (0.00%)	3 / 69 (4.35%)	0 / 66 (0.00%)
occurrences (all)	0	3	0
ESOPHAGITIS			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 34 (2.94%)	0 / 69 (0.00%)	1 / 66 (1.52%)
occurrences (all)	1	0	1
HEMORRHOIDS			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	0 / 34 (0.00%)	1 / 69 (1.45%)	1 / 66 (1.52%)
occurrences (all)	0	1	1
TOOTHACHE			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	0 / 34 (0.00%)	0 / 69 (0.00%)	2 / 66 (3.03%)
occurrences (all)	0	0	2
STOMACH PAIN			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 34 (2.94%)	0 / 69 (0.00%)	3 / 66 (4.55%)
occurrences (all)	1	0	3
SMALL INTESTINAL OBSTRUCTION			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 34 (2.94%)	1 / 69 (1.45%)	1 / 66 (1.52%)
occurrences (all)	1	1	1

RECTAL MUCOSITIS			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	0 / 34 (0.00%)	0 / 69 (0.00%)	1 / 66 (1.52%)
occurrences (all)	0	0	1
PERIODONTAL DISEASE			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	0 / 34 (0.00%)	1 / 69 (1.45%)	1 / 66 (1.52%)
occurrences (all)	0	1	1
PANCREATITIS			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	0 / 34 (0.00%)	0 / 69 (0.00%)	1 / 66 (1.52%)
occurrences (all)	0	0	1
PANCREATIC FISTULA			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	0 / 34 (0.00%)	0 / 69 (0.00%)	1 / 66 (1.52%)
occurrences (all)	0	0	1
ORAL PAIN			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	0 / 34 (0.00%)	0 / 69 (0.00%)	1 / 66 (1.52%)
occurrences (all)	0	0	1
ORAL DYSESTHESIA			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	0 / 34 (0.00%)	1 / 69 (1.45%)	0 / 66 (0.00%)
occurrences (all)	0	1	0
NAUSEA			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	20 / 34 (58.82%)	38 / 69 (55.07%)	37 / 66 (56.06%)
occurrences (all)	33	71	69
MUCOSITIS ORAL			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	5 / 34 (14.71%)	22 / 69 (31.88%)	17 / 66 (25.76%)
occurrences (all)	7	46	26
JEJUNAL HEMORRHAGE			
alternative dictionary used: CTCAE 4.0			

subjects affected / exposed	0 / 34 (0.00%)	0 / 69 (0.00%)	1 / 66 (1.52%)
occurrences (all)	0	0	1
JEJUNAL FISTULA			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	0 / 34 (0.00%)	1 / 69 (1.45%)	0 / 66 (0.00%)
occurrences (all)	0	1	0
INTRA-ABDOMINAL HEMORRHAGE			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 34 (2.94%)	0 / 69 (0.00%)	1 / 66 (1.52%)
occurrences (all)	1	0	1
UPPER GASTROINTESTINAL HEMORRHAGE			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	0 / 34 (0.00%)	2 / 69 (2.90%)	0 / 66 (0.00%)
occurrences (all)	0	3	0
ILEUS			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	0 / 34 (0.00%)	0 / 69 (0.00%)	1 / 66 (1.52%)
occurrences (all)	0	0	1
VOMITING			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	6 / 34 (17.65%)	20 / 69 (28.99%)	15 / 66 (22.73%)
occurrences (all)	7	37	20
Hepatobiliary disorders			
CHOLECYSTITIS			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 34 (2.94%)	1 / 69 (1.45%)	0 / 66 (0.00%)
occurrences (all)	1	1	0
HEPATITIS VIRAL			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	0 / 34 (0.00%)	1 / 69 (1.45%)	1 / 66 (1.52%)
occurrences (all)	0	1	1
HEPATOBILIARY DISORDERS - OTHER, SPECIFY			
alternative dictionary used: CTCAE 4.0			

subjects affected / exposed	0 / 34 (0.00%)	1 / 69 (1.45%)	2 / 66 (3.03%)
occurrences (all)	0	1	2
Skin and subcutaneous tissue disorders			
ALOPECIA			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	6 / 34 (17.65%)	8 / 69 (11.59%)	10 / 66 (15.15%)
occurrences (all)	7	8	12
DRY SKIN			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	2 / 34 (5.88%)	8 / 69 (11.59%)	5 / 66 (7.58%)
occurrences (all)	2	12	5
HYPERHIDROSIS			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	0 / 34 (0.00%)	1 / 69 (1.45%)	0 / 66 (0.00%)
occurrences (all)	0	1	0
NAIL DISCOLORATION			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	0 / 34 (0.00%)	1 / 69 (1.45%)	2 / 66 (3.03%)
occurrences (all)	0	1	2
NAIL RIDGING			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 34 (2.94%)	1 / 69 (1.45%)	0 / 66 (0.00%)
occurrences (all)	1	1	0
PALMAR-PLANTAR ERYTHRODYSESTHESIA SYNDROME			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	2 / 34 (5.88%)	7 / 69 (10.14%)	8 / 66 (12.12%)
occurrences (all)	4	9	13
PRURITUS			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	0 / 34 (0.00%)	3 / 69 (4.35%)	4 / 66 (6.06%)
occurrences (all)	0	3	5
RASH ACNEIFORM			
alternative dictionary used: CTCAE 4.0			

subjects affected / exposed	1 / 34 (2.94%)	2 / 69 (2.90%)	1 / 66 (1.52%)
occurrences (all)	1	2	3
RASH MACULO-PAPULAR			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	0 / 34 (0.00%)	6 / 69 (8.70%)	3 / 66 (4.55%)
occurrences (all)	0	6	3
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - OTHER, SPECIFY			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	2 / 34 (5.88%)	9 / 69 (13.04%)	7 / 66 (10.61%)
occurrences (all)	2	11	10
SKIN HYPOPIGMENTATION			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	0 / 34 (0.00%)	0 / 69 (0.00%)	1 / 66 (1.52%)
occurrences (all)	0	0	1
URTICARIA			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	0 / 34 (0.00%)	0 / 69 (0.00%)	1 / 66 (1.52%)
occurrences (all)	0	0	1
ERYTHEMA MULTIFORME			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	0 / 34 (0.00%)	1 / 69 (1.45%)	0 / 66 (0.00%)
occurrences (all)	0	1	0
Renal and urinary disorders			
ACUTE KIDNEY INJURY			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 34 (2.94%)	9 / 69 (13.04%)	3 / 66 (4.55%)
occurrences (all)	1	15	15
CHRONIC KIDNEY DISEASE			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	0 / 34 (0.00%)	1 / 69 (1.45%)	2 / 66 (3.03%)
occurrences (all)	0	1	4
HEMATURIA			
alternative dictionary used: CTCAE 4.0			

subjects affected / exposed	1 / 34 (2.94%)	0 / 69 (0.00%)	1 / 66 (1.52%)
occurrences (all)	1	0	1
RENAL AND URINARY DISORDERS - OTHER, SPECIFY			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	2 / 34 (5.88%)	5 / 69 (7.25%)	1 / 66 (1.52%)
occurrences (all)	2	5	1
URINARY FREQUENCY			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	0 / 34 (0.00%)	0 / 69 (0.00%)	1 / 66 (1.52%)
occurrences (all)	0	0	2
URINARY RETENTION			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	0 / 34 (0.00%)	0 / 69 (0.00%)	1 / 66 (1.52%)
occurrences (all)	0	0	1
CYSTITIS NONINFECTIVE			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	0 / 34 (0.00%)	0 / 69 (0.00%)	1 / 66 (1.52%)
occurrences (all)	0	0	1
Endocrine disorders			
HYPERTHYROIDISM			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	0 / 34 (0.00%)	0 / 69 (0.00%)	1 / 66 (1.52%)
occurrences (all)	0	0	2
HYPOTHYROIDISM			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	0 / 34 (0.00%)	1 / 69 (1.45%)	0 / 66 (0.00%)
occurrences (all)	0	1	0
Musculoskeletal and connective tissue disorders			
GENERALIZED MUSCLE WEAKNESS			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	0 / 34 (0.00%)	1 / 69 (1.45%)	0 / 66 (0.00%)
occurrences (all)	0	1	0
ARTHRITIS			
alternative dictionary used: CTCAE 4.0			

subjects affected / exposed	0 / 34 (0.00%)	1 / 69 (1.45%)	1 / 66 (1.52%)
occurrences (all)	0	2	1
BACK PAIN			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	3 / 34 (8.82%)	1 / 69 (1.45%)	1 / 66 (1.52%)
occurrences (all)	3	1	2
BONE PAIN			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	0 / 34 (0.00%)	2 / 69 (2.90%)	2 / 66 (3.03%)
occurrences (all)	0	2	2
BUTTOCK PAIN			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	0 / 34 (0.00%)	1 / 69 (1.45%)	0 / 66 (0.00%)
occurrences (all)	0	1	0
FLANK PAIN			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 34 (2.94%)	0 / 69 (0.00%)	1 / 66 (1.52%)
occurrences (all)	1	0	1
ARTHRALGIA			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 34 (2.94%)	0 / 69 (0.00%)	0 / 66 (0.00%)
occurrences (all)	2	0	0
JOINT EFFUSION			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	0 / 34 (0.00%)	1 / 69 (1.45%)	0 / 66 (0.00%)
occurrences (all)	0	1	0
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDER - OTHER, SPECIFY			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 34 (2.94%)	5 / 69 (7.25%)	2 / 66 (3.03%)
occurrences (all)	1	7	2
MYALGIA			
alternative dictionary used: CTCAE 4.0			

subjects affected / exposed	0 / 34 (0.00%)	2 / 69 (2.90%)	1 / 66 (1.52%)
occurrences (all)	0	2	3
NECK PAIN			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	0 / 34 (0.00%)	0 / 69 (0.00%)	1 / 66 (1.52%)
occurrences (all)	0	0	1
PAIN IN EXTREMITY			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	0 / 34 (0.00%)	1 / 69 (1.45%)	1 / 66 (1.52%)
occurrences (all)	0	1	1
MUSCLE WEAKNESS RIGHT-SIDED			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	0 / 34 (0.00%)	0 / 69 (0.00%)	1 / 66 (1.52%)
occurrences (all)	0	0	1
Infections and infestations			
LUNG INFECTION			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	3 / 34 (8.82%)	8 / 69 (11.59%)	6 / 66 (9.09%)
occurrences (all)	3	8	6
CATHETER RELATED INFECTION			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	0 / 34 (0.00%)	3 / 69 (4.35%)	2 / 66 (3.03%)
occurrences (all)	0	3	3
ENDOCARDITIS INFECTIVE			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 34 (2.94%)	0 / 69 (0.00%)	0 / 66 (0.00%)
occurrences (all)	2	0	0
ENTEROCOLITIS INFECTIOUS			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	0 / 34 (0.00%)	0 / 69 (0.00%)	1 / 66 (1.52%)
occurrences (all)	0	0	1
ESOPHAGEAL INFECTION			
alternative dictionary used: CTCAE 4.0			

subjects affected / exposed	1 / 34 (2.94%)	0 / 69 (0.00%)	0 / 66 (0.00%)
occurrences (all)	1	0	0
INFECTIONS AND INFESTATIONS - OTHER, SPECIFY			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	3 / 34 (8.82%)	16 / 69 (23.19%)	13 / 66 (19.70%)
occurrences (all)	3	19	18
ABDOMINAL INFECTION			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	0 / 34 (0.00%)	0 / 69 (0.00%)	1 / 66 (1.52%)
occurrences (all)	0	0	1
MEDIASTINAL INFECTION			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	0 / 34 (0.00%)	1 / 69 (1.45%)	0 / 66 (0.00%)
occurrences (all)	0	1	0
NAIL INFECTION			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	0 / 34 (0.00%)	1 / 69 (1.45%)	0 / 66 (0.00%)
occurrences (all)	0	1	0
PARONYCHIA			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	0 / 34 (0.00%)	1 / 69 (1.45%)	0 / 66 (0.00%)
occurrences (all)	0	1	0
PHARYNGITIS			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	0 / 34 (0.00%)	0 / 69 (0.00%)	1 / 66 (1.52%)
occurrences (all)	0	0	1
PLEURAL INFECTION			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	0 / 34 (0.00%)	1 / 69 (1.45%)	0 / 66 (0.00%)
occurrences (all)	0	1	0
RHINITIS INFECTIVE			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	0 / 34 (0.00%)	0 / 69 (0.00%)	2 / 66 (3.03%)
occurrences (all)	0	0	2

SINUSITIS			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	0 / 34 (0.00%)	0 / 69 (0.00%)	1 / 66 (1.52%)
occurrences (all)	0	0	1
SKIN INFECTION			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	0 / 34 (0.00%)	3 / 69 (4.35%)	1 / 66 (1.52%)
occurrences (all)	0	3	1
UPPER RESPIRATORY INFECTION			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	0 / 34 (0.00%)	2 / 69 (2.90%)	4 / 66 (6.06%)
occurrences (all)	0	2	4
URINARY TRACT INFECTION			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 34 (2.94%)	2 / 69 (2.90%)	4 / 66 (6.06%)
occurrences (all)	1	2	6
WOUND INFECTION			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	0 / 34 (0.00%)	2 / 69 (2.90%)	2 / 66 (3.03%)
occurrences (all)	0	2	2
SEPSIS			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	2 / 34 (5.88%)	4 / 69 (5.80%)	3 / 66 (4.55%)
occurrences (all)	2	5	3
Metabolism and nutrition disorders			
HYPOALBUMINEMIA			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	0 / 34 (0.00%)	1 / 69 (1.45%)	0 / 66 (0.00%)
occurrences (all)	0	1	0
DEHYDRATION			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	0 / 34 (0.00%)	4 / 69 (5.80%)	0 / 66 (0.00%)
occurrences (all)	0	7	0
GLUCOSE INTOLERANCE			
alternative dictionary used: CTCAE 4.0			

subjects affected / exposed	0 / 34 (0.00%)	0 / 69 (0.00%)	1 / 66 (1.52%)
occurrences (all)	0	0	1
HYPERGLYCEMIA			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	0 / 34 (0.00%)	3 / 69 (4.35%)	1 / 66 (1.52%)
occurrences (all)	0	3	1
HYPERKALEMIA			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	0 / 34 (0.00%)	0 / 69 (0.00%)	1 / 66 (1.52%)
occurrences (all)	0	0	1
HYPERNATREMIA			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	0 / 34 (0.00%)	1 / 69 (1.45%)	0 / 66 (0.00%)
occurrences (all)	0	2	0
HYPERURICEMIA			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 34 (2.94%)	0 / 69 (0.00%)	0 / 66 (0.00%)
occurrences (all)	1	0	0
ANOREXIA			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	12 / 34 (35.29%)	21 / 69 (30.43%)	20 / 66 (30.30%)
occurrences (all)	18	37	44
HYPOCALCEMIA			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	0 / 34 (0.00%)	3 / 69 (4.35%)	2 / 66 (3.03%)
occurrences (all)	0	3	3
HYPOKALEMIA			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	5 / 34 (14.71%)	15 / 69 (21.74%)	5 / 66 (7.58%)
occurrences (all)	6	23	8
HYPOMAGNESEMIA			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 34 (2.94%)	7 / 69 (10.14%)	3 / 66 (4.55%)
occurrences (all)	3	8	4

HYPONATREMIA			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	0 / 34 (0.00%)	3 / 69 (4.35%)	3 / 66 (4.55%)
occurrences (all)	0	5	6
HYPOPHOSPHATEMIA			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 34 (2.94%)	0 / 69 (0.00%)	1 / 66 (1.52%)
occurrences (all)	1	0	2
METABOLISM AND NUTRITION DISORDERS - OTHER, SPECIFY			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 34 (2.94%)	5 / 69 (7.25%)	0 / 66 (0.00%)
occurrences (all)	2	6	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
03 March 2015	1. To address comments received after the VHP submission to competent authorities about the minimization procedure used for randomization, it was specified that no random component was added to the minimization algorithm and a reference to appendix K was added in the corresponding protocol section. 2. To address the comment received after the VHP submission to competent authorities that the trial protocol does not state how missing values will be handled, it was clarified in the protocol section on "Statistical methods" that the primary analysis of the major pathological response rate will be performed in the per-protocol population with a non-missing assessment of pathological response. This will include all patients in the per protocol population who: have been resected, and for whom the tumor regression according to Becker et al. has been assessed by the central pathology laboratory or have not been operated or resected for any reason and will be considered as not having a major pathological response in the analysis. Missing data for the primary endpoint will only occur if a patient is resected and the pathological assessment of the resection specimen is not possible. These patients will be removed from the analysis. 3. The maximum total number of patients to be screened in order to randomize the required 225 patients with HER-2 positive disease was modified to reflect the recent knowledge published in the literature about the frequency of HER-2 positivity in Gastric cancer. This frequency could indeed be as low as 10% and therefore a maximum of 2250 patients will have to be screened. 4. ISH (In Situ Hybridization) has been mentioned instead of FISH (Fluorescence In Situ Hybridization) for South Korea.
30 November 2015	Roche Protocol Review Committee feedback led to a decision to follow patients longer after pertuzumab and trastuzumab exposure in terms of pregnancy. In the amendment, any new pregnancy within 6 months after last dose of pertuzumab (within 7 months after last dose of trastuzumab as per the Herceptin Global Enhanced PV Pregnancy Program) must be reported to the EORTC Pharmacovigilance Unit. The current protocol requires reporting up to 180 days, and this time frame was extended up to 7 months with this amendment.

19 October 2017	1. Change of chemotherapy backbone: in Europe, the regimen was to be selected between FLOT, CapOX por mFOLFOX6; in Asia, cisplatin + capecitabine or 5-FU. This scientific amendment was necessary after the presentation of the results of the FLOT-4-trial at ASCO 2017, which demonstrated a significantly better progression-free and overall survival for perioperative treatment with FLOT, as compared to ECF. Both, dose modification and supportive care recommendations for treatment with FLOT have been inspired by those used in the FLOT-4 study, which were generously provided by the author. Cisplatin is being kept as an option as it is still standard of care in Korea, and efficacy benefit of other regimen yet have to be demonstrated in these patients. 2. A safety run has been introduced in the protocol, given the change of background chemotherapies. 3. A definition of 'high dose corticosteroids' was inserted. 4. Clarification was added, that Dihydropyrimidine dehydrogenase deficiency (DPD) testing should be done according to local guidelines. 5. Dose reduction upon grade 2 or 3 nausea or vomiting has been adapted. 6. Recommendations regarding the procedures in case of tubular damage and low Mg/Ca were added. 7. Measures to be taken after assessment of ototoxicity and sensory neural damage were clarified.
25 February 2019	1. Upon update of the Trastuzumab's IB the following changes have been implemented in the protocol and PISIC Eligibility criteria: - Protocol eligibility: exclusion of patients with interstitial lung disease - Clinical evaluation: adding additional monitoring for cardiac function after the chemotherapies in adjuvant and during the follow-up period with 6 monthly assessment for 2 years after last dose of trastuzumab. 2. Swiss Competent Authorities requires to specify side effects related to Leucoverin 3. Clarification of dose banding 4. Annex 3/GDPR adaptation of the PISIC.
10 May 2019	1. Upon update of the Trastuzumab's Summary of Product Characteristics (SmPC) and Pertuzumab's SmPC the side effects in the patient information sheet have been updated 2. Wording on the timing of surgery was aligned with the wording in the protocol summary 3. A change in biobank was implemented.
02 February 2021	1. Upon update of the Herceptin's SmPC and and Pertuzumab's SmPC the side effects in the patient information sheet have been updated 2. COVID-19 Addendum to patient information sheets 3. Protocol: assessments during the follow up period were updated.

07 December 2021	1. Patient information sheets and addenda to patient information sheets Risk and side effects related to trastuzumab and Risk and side effects related to pertuzumab have been updated according to the new version of the IB. 2. Protocol • To confirm progression by pathological assessment (regarding the primary endpoint) at surgery. In case of local progression by imaging during the neo-adjuvant treatment, if the patient is judged operable, every effort were to be made to confirm the progression at surgery. If progression was not confirmed, patients could stay under protocol treatment and start adjuvant treatment as per protocol. • To specify prerequisites for central pathology review. Pathology report was to be sent to EORTC. Personal data of the patient must have been anonymized and replaced by the EORTC sequential identification number allocated to this patient at the time of randomization. • Elderly Minimal Dataset Comprehensive Geriatric Assessment only once before randomization was needed.
20 June 2022	1. Patient information sheets and addenda to patient information sheets • To align PISIC cisplatin and PISIC flot-folfox-capox. Safety information from the Trial Petrarca were added. • Risk and side effects related to pertuzumab have been updated according to the new version of the IB. 2. Protocol • Additional clarification wished from the supporting company. In case of local progression diagnosed by imaging during the neo-adjuvant treatment, if the patient was judged operable, every effort should have been made to confirm the microscopic/macroscopic progression at surgery • Implementation of the updated IB. Serious adverse events (incl. life-threatening events) compatible with infusion-related reactions with pertuzumab have been infrequently reported (less than 1% of patients).
13 October 2023	1. The end of the study was clarified. Indeed, due to the early termination of the study, this phase II study will not transition to phase III and no IDMC will occur at the end of phase II. The study will not be transitioned to CTR. 2. A new translational research project and exploratory endpoints were added following the surgical quality assurance. In addition, further clarification was made on the end of treatment and minor updates were implemented such as the name and address of the company performing the central assessment of HER-2 expression.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported