Clinical trial results:
Phase III international, randomized study of Trabectedin plus Pegylated Liposomal Doxorubicin (PLD) versus Carboplatin plus PLD in patients with ovarian cancer progressing within 6-12 months of last platinum

Summary

EudraCT number	2010-022949-17
Trial protocol	IT GB FI BE NL DK DE ES AT NO
Global end of trial date	09 April 2021

Results information

Result version number	v1 (current)
This version publication date	15 September 2022
First version publication date	15 September 2022

Trial information

Trial identification

Sponsor protocol code	ET-D-009-10

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Istituto di Ricerche Farmacologiche Mario Negri IRCCS
Sponsor organisation address	Via Mario Negri 2, Milan, Italy, 20156
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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	09 April 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	09 April 2021
Global end of trial reached?	Yes
Global end of trial date	09 April 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To demonstrate that the combination of trabectedin (Yondelis®) and pegylated liposomal doxorubicin (PLD) prolongs overall survival (OS) over carboplatin and PLD in patients with relapsed ovarian cancer progressing within 6-12 months after end of last platinum.

Protection of trial subjects:

NA

Background therapy:

In both arms PLD was administered as background therapy

Evidence for comparator: -

Actual start date of recruitment	08 January 2014
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Netherlands: 24
Country: Number of subjects enrolled	Norway: 5
Country: Number of subjects enrolled	Spain: 108
Country: Number of subjects enrolled	United Kingdom: 25
Country: Number of subjects enrolled	Austria: 22
Country: Number of subjects enrolled	Belgium: 10
Country: Number of subjects enrolled	Denmark: 15
Country: Number of subjects enrolled	Finland: 25
Country: Number of subjects enrolled	Germany: 58
Country: Number of subjects enrolled	Italy: 283
Country: Number of subjects enrolled	Switzerland: 42
Worldwide total number of subjects	617
EEA total number of subjects	550

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37	0

wk	
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)	330
From 65 to 84 years	285
85 years and over	2

Subject disposition

Recruitment

Recruitment details:

The randomization started in Dec2011 but had to be put onto temporary hold just a month later (with one patient randomized) due to the worldwide shortage of PLD. AIFA approved the study restart on Aug 2013 whereas the Central EC approved the study restart on Sept 2013. Patients' accrual recommenced on Jan 8th 2014 and ended on Sept18th 2017.

Pre-assignment

Screening details:

NA

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	ARM A: Carboplatin+PLD

Arm description: -

Arm type	Active comparator
Investigational medicinal product name	carboplatin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

PLD 30 mg/m² i.v. as a 1-hour infusion followed by carboplatin AUC 5 i.v. as a 30 min infusion on Day 1 every 4 weeks. A 4-week schedule defines a cycle of treatment

Arm title	ARM B: Trabectedin+PLD

Arm description: -

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

Dosage and administration details:

PLD 30 mg/m2 i.v. infusion immediately followed by trabectedin 1.1 mg/m2 3-hour i.v. infusion on Day 1 every 3 weeks. A 3-week schedule defines a cycle of treatment.

Number of subjects in period 1	ARM A: Carboplatin+PLD	ARM B: Trabectedin+PLD
Started	306	311
Completed	306	311

Baseline characteristics

Reporting groups	
Reporting group title	overall trial

Reporting group description: -

Reporting group values	overall trial	Total	
Number of subjects	617	617	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	330	330	
From 65-84 years	285	285	
85 years and over	2	2	
Age continuous Units: years			
median	64		
inter-quartile range (Q1-Q3)	55 to 70	-	
Gender categorical Units: Subjects			
Female	617	617	

Subject analysis sets	
Subject analysis set title	Intention to treat
Subject analysis set type	Intention-to-treat

Subject analysis set description:

the ITT analysis set included all subjets who provided informed consent and were randomized to either carboplatin+PLD arm or trabectedin+PLD arm, without major deviations of the eligibility criteria. Subjects were considered in the randomization arm regardless of the treatment they received.

Subject analysis set title	safety analysis set
Subject analysis set type	Safety analysis

Subject analysis set description:

the Safety Analysis Set included all subjects of ITT analysis set who received at least one dose of treatment. Subjects were considered in the arm of the treatment they actually received.

Reporting group values	Intention to treat	safety analysis set	
Number of subjects	611	598	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	

Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	327	317	
From 65-84 years	282	279	
85 years and over	2	2	
Age continuous			
Units: years			
median	64	64	
inter-quartile range (Q1-Q3)	55 to 71	55 to 71	
Gender categorical			
Units: Subjects			
Female			

End points

End points reporting groups

Reporting group title	ARM A: Carboplatin+PLD
Reporting group description: -	
Reporting group title	ARM B: Trabectedin+PLD
Reporting group description: -	
Subject analysis set title	Intention to treat
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
the ITT analysis set included all subjets who provided informed consent and were randomized to either carboplatin+PLD arm or trabectedin+PLD arm, without major deviations of the eligibility criteria. Subjects were considered in the randomization arm regardless of the treatment they received.	
Subject analysis set title	safety analysis set
Subject analysis set type	Safety analysis
Subject analysis set description:	
the Safety Analysis Set included all subjects of ITT analysis set who received at least one dose of treatment. Subjects were considered in the arm of the treatment they actually received.	

Primary: overall survival

End point title	overall survival
End point description:	
End point type	Primary
End point timeframe:	
from randomization to death or end of trial	

End point values	ARM A: Carboplatin+PLD	ARM B: Trabectedin+PLD	Intention to treat	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	304	307	611	
Units: patients	231	240	471	

Statistical analyses

Statistical analysis title	overall survival
Comparison groups	ARM A: Carboplatin+PLD v ARM B: Trabectedin+PLD
Number of subjects included in analysis	611
Analysis specification	Pre-specified
Analysis type	superiority[1]
Parameter estimate	Hazard ratio (HR)
Point estimate	1.13

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.94
upper limit	1.35

Notes:

[1] - For the primary analysis, OS between treatment arms will be compared by the log-rank test. Cox regression will be used to calculate the risk reduction and to evaluate the influence of the randomization variables and other potential prognostic factors on the time to event endpoint.

Adverse events

Adverse events information	
Timeframe for reporting adverse events: from informed consent signature until 30 days after the last administration of study treatments	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	22

Reporting groups	
Reporting group title	Arm A
Reporting group description: Carboplatin + PLD	
Reporting group title	Arm B
Reporting group description: Trabectedin + PLD	

Serious adverse events	Arm A	Arm B	
Total subjects affected by serious adverse events			
subjects affected / exposed	66 / 294 (22.45%)	130 / 304 (42.76%)	
number of deaths (all causes)	228	238	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Colon cancer			
subjects affected / exposed	0 / 294 (0.00%)	1 / 304 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant bowel obstruction			
subjects affected / exposed	0 / 294 (0.00%)	1 / 304 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Acute myeloid leukaemia			
subjects affected / exposed	0 / 294 (0.00%)	1 / 304 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Ascites			

subjects affected / exposed	0 / 294 (0.00%)	1 / 304 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ascites, pyrexia, pancytopenia, deep vein thrombosis			
subjects affected / exposed	0 / 294 (0.00%)	1 / 304 (0.33%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Metastasis to lung, pharyngitis			
subjects affected / exposed	0 / 294 (0.00%)	1 / 304 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myelodysplastic syndrome			
subjects affected / exposed	1 / 294 (0.34%)	0 / 304 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	1 / 294 (0.34%)	3 / 304 (0.99%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Jugular vein thrombosis			
subjects affected / exposed	0 / 294 (0.00%)	1 / 304 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Shock haemorrhagic			
subjects affected / exposed	0 / 294 (0.00%)	1 / 304 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombosis			
subjects affected / exposed	2 / 294 (0.68%)	0 / 304 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vena cava thrombosis			

subjects affected / exposed	0 / 294 (0.00%)	1 / 304 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Portacath insertion			
subjects affected / exposed	0 / 294 (0.00%)	1 / 304 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stent placement			
subjects affected / exposed	1 / 294 (0.34%)	0 / 304 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Obstruction			
subjects affected / exposed	0 / 294 (0.00%)	1 / 304 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Asthenia, vomiting			
subjects affected / exposed	0 / 294 (0.00%)	1 / 304 (0.33%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Death			
subjects affected / exposed	1 / 294 (0.34%)	0 / 304 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Decreased appetite			
subjects affected / exposed	0 / 294 (0.00%)	2 / 304 (0.66%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Disease Progression			
subjects affected / exposed	1 / 294 (0.34%)	2 / 304 (0.66%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

Extravasation			
subjects affected / exposed	0 / 294 (0.00%)	1 / 304 (0.33%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fatigue			
subjects affected / exposed	0 / 294 (0.00%)	1 / 304 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fatigue, cachexia, hepatic enzyme increased			
subjects affected / exposed	0 / 294 (0.00%)	1 / 304 (0.33%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical health deterioration			
subjects affected / exposed	3 / 294 (1.02%)	2 / 304 (0.66%)	
occurrences causally related to treatment / all	1 / 4	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malaise			
subjects affected / exposed	0 / 294 (0.00%)	1 / 304 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mucosal inflamation			
subjects affected / exposed	1 / 294 (0.34%)	1 / 304 (0.33%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	1 / 294 (0.34%)	8 / 304 (2.63%)	
occurrences causally related to treatment / all	0 / 1	2 / 11	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Infusion related reaction			
subjects affected / exposed	0 / 294 (0.00%)	1 / 304 (0.33%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Reproductive system and breast disorders			
Metrorrhagia, asthenia			
subjects affected / exposed	0 / 294 (0.00%)	1 / 304 (0.33%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	0 / 294 (0.00%)	1 / 304 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonitis			
subjects affected / exposed	0 / 294 (0.00%)	1 / 304 (0.33%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute respiratory distress syndrome			
subjects affected / exposed	0 / 294 (0.00%)	1 / 304 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Aspiration			
subjects affected / exposed	0 / 294 (0.00%)	1 / 304 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Bronchospasm			
subjects affected / exposed	0 / 294 (0.00%)	1 / 304 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 294 (0.34%)	0 / 304 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Dyspnoea			

subjects affected / exposed	0 / 294 (0.00%)	5 / 304 (1.64%)	
occurrences causally related to treatment / all	0 / 0	1 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epistaxis			
subjects affected / exposed	1 / 294 (0.34%)	0 / 304 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemothorax			
subjects affected / exposed	1 / 294 (0.34%)	0 / 304 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Lung infection			
subjects affected / exposed	0 / 294 (0.00%)	2 / 304 (0.66%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	2 / 294 (0.68%)	1 / 304 (0.33%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion, pulmonary embolism			
subjects affected / exposed	0 / 294 (0.00%)	1 / 304 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax			
subjects affected / exposed	1 / 294 (0.34%)	0 / 304 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	0 / 294 (0.00%)	6 / 304 (1.97%)	
occurrences causally related to treatment / all	0 / 0	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary oedema			

subjects affected / exposed	0 / 294 (0.00%)	1 / 304 (0.33%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Respiratory failure			
subjects affected / exposed	1 / 294 (0.34%)	0 / 304 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Respiratory tract infection			
subjects affected / exposed	1 / 294 (0.34%)	1 / 304 (0.33%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Electrocardiogram ST segment elevation			
subjects affected / exposed	1 / 294 (0.34%)	0 / 304 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 294 (0.00%)	1 / 304 (0.33%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transaminases increased			
subjects affected / exposed	0 / 294 (0.00%)	1 / 304 (0.33%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Concussion			
subjects affected / exposed	0 / 294 (0.00%)	1 / 304 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fracture			

subjects affected / exposed	1 / 294 (0.34%)	0 / 304 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hip Fracture			
subjects affected / exposed	0 / 294 (0.00%)	1 / 304 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Laceration			
subjects affected / exposed	0 / 294 (0.00%)	1 / 304 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pelvic fracture			
subjects affected / exposed	1 / 294 (0.34%)	0 / 304 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting, phlebitis			
subjects affected / exposed	0 / 294 (0.00%)	1 / 304 (0.33%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound dehiscence			
subjects affected / exposed	0 / 294 (0.00%)	2 / 304 (0.66%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	0 / 294 (0.00%)	1 / 304 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure			
subjects affected / exposed	0 / 294 (0.00%)	1 / 304 (0.33%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			

subjects affected / exposed	0 / 294 (0.00%)	1 / 304 (0.33%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	1 / 294 (0.34%)	0 / 304 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Left ventricular systolic dysfunction			
subjects affected / exposed	0 / 294 (0.00%)	1 / 304 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain chest			
subjects affected / exposed	0 / 294 (0.00%)	1 / 304 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Dizziness			
subjects affected / exposed	1 / 294 (0.34%)	0 / 304 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysarthria			
subjects affected / exposed	0 / 294 (0.00%)	1 / 304 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	1 / 294 (0.34%)	0 / 304 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Febrile Neutropenia			
subjects affected / exposed	1 / 294 (0.34%)	12 / 304 (3.95%)	
occurrences causally related to treatment / all	1 / 1	11 / 12	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epistaxis, pancytopenia			

subjects affected / exposed	1 / 294 (0.34%)	0 / 304 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anaemia			
subjects affected / exposed	0 / 294 (0.00%)	1 / 304 (0.33%)	
occurrences causally related to treatment / all	0 / 0	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia, stomatitis, platelet count decreased			
subjects affected / exposed	0 / 294 (0.00%)	1 / 304 (0.33%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia, anaemia, otitis media			
subjects affected / exposed	0 / 294 (0.00%)	1 / 304 (0.33%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukopenia			
subjects affected / exposed	0 / 294 (0.00%)	2 / 304 (0.66%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	0 / 294 (0.00%)	6 / 304 (1.97%)	
occurrences causally related to treatment / all	0 / 0	6 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia, anaemia			
subjects affected / exposed	0 / 294 (0.00%)	1 / 304 (0.33%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia, thrombocytopenia			
subjects affected / exposed	1 / 294 (0.34%)	2 / 304 (0.66%)	
occurrences causally related to treatment / all	1 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancytopenia			

subjects affected / exposed	2 / 294 (0.68%)	1 / 304 (0.33%)	
occurrences causally related to treatment / all	2 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancytopenia, pyrexia			
subjects affected / exposed	0 / 294 (0.00%)	1 / 304 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal sepsisClostridium difficile infection Pancytopenia			
subjects affected / exposed	0 / 294 (0.00%)	1 / 304 (0.33%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	4 / 294 (1.36%)	3 / 304 (0.99%)	
occurrences causally related to treatment / all	7 / 7	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transaminases increased, febrile neutropenia			
subjects affected / exposed	0 / 294 (0.00%)	1 / 304 (0.33%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain, decreased appetite			
subjects affected / exposed	0 / 294 (0.00%)	1 / 304 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper gastrointestinal haemorrhage			
subjects affected / exposed	1 / 294 (0.34%)	0 / 304 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal Pain			
subjects affected / exposed	6 / 294 (2.04%)	8 / 304 (2.63%)	
occurrences causally related to treatment / all	0 / 7	0 / 9	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal Pain, ileal obstruction,			

constipation			
subjects affected / exposed	0 / 294 (0.00%)	1 / 304 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal hernia			
subjects affected / exposed	1 / 294 (0.34%)	0 / 304 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute Pancreatitis			
subjects affected / exposed	0 / 294 (0.00%)	1 / 304 (0.33%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ascites			
subjects affected / exposed	2 / 294 (0.68%)	0 / 304 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bowel obstruction			
subjects affected / exposed	1 / 294 (0.34%)	0 / 304 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bowel occlusion			
subjects affected / exposed	1 / 294 (0.34%)	0 / 304 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	2 / 294 (0.68%)	1 / 304 (0.33%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhea			
subjects affected / exposed	2 / 294 (0.68%)	0 / 304 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enteritis			

subjects affected / exposed	0 / 294 (0.00%)	1 / 304 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Faecaloma			
subjects affected / exposed	1 / 294 (0.34%)	0 / 304 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	1 / 294 (0.34%)	0 / 304 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorder			
subjects affected / exposed	1 / 294 (0.34%)	0 / 304 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal obstruction			
subjects affected / exposed	1 / 294 (0.34%)	0 / 304 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Ileus			
subjects affected / exposed	4 / 294 (1.36%)	4 / 304 (1.32%)	
occurrences causally related to treatment / all	0 / 5	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 1	
Intestinal haemorrhage			
subjects affected / exposed	0 / 294 (0.00%)	1 / 304 (0.33%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal ischaemia			
subjects affected / exposed	1 / 294 (0.34%)	0 / 304 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal obstruction			

subjects affected / exposed	8 / 294 (2.72%)	5 / 304 (1.64%)	
occurrences causally related to treatment / all	0 / 11	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal occlusion			
subjects affected / exposed	0 / 294 (0.00%)	4 / 304 (1.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 1	
Intestinal perforation			
subjects affected / exposed	0 / 294 (0.00%)	1 / 304 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestinal obstruction			
subjects affected / exposed	1 / 294 (0.34%)	0 / 304 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	0 / 294 (0.00%)	6 / 304 (1.97%)	
occurrences causally related to treatment / all	0 / 0	4 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea, asthenia, decreased appetite			
subjects affected / exposed	0 / 294 (0.00%)	1 / 304 (0.33%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea, vomiting			
subjects affected / exposed	1 / 294 (0.34%)	5 / 304 (1.64%)	
occurrences causally related to treatment / all	1 / 1	4 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea, vomiting, constipation			
subjects affected / exposed	0 / 294 (0.00%)	1 / 304 (0.33%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea, vomiting, constipation, abdominal pain			

subjects affected / exposed	0 / 294 (0.00%)	1 / 304 (0.33%)		
occurrences causally related to treatment / all	0 / 0	1 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
Nausea, vomiting, hyponatraemia				
subjects affected / exposed	1 / 294 (0.34%)	0 / 304 (0.00%)		
occurrences causally related to treatment / all	1 / 1	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Occlusion				
subjects affected / exposed	1 / 294 (0.34%)	0 / 304 (0.00%)		
occurrences causally related to treatment / all	0 / 1	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Oesophagitis, nausea, vomiting				
subjects affected / exposed	0 / 294 (0.00%)	1 / 304 (0.33%)		
occurrences causally related to treatment / all	0 / 0	1 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
Pancreatitis				
subjects affected / exposed	1 / 294 (0.34%)	0 / 304 (0.00%)		
occurrences causally related to treatment / all	0 / 1	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Small intestinal obstruction				
subjects affected / exposed	1 / 294 (0.34%)	2 / 304 (0.66%)		
occurrences causally related to treatment / all	0 / 1	0 / 2		
deaths causally related to treatment / all	0 / 0	0 / 0		
Small intestinal perforation				
subjects affected / exposed	0 / 294 (0.00%)	1 / 304 (0.33%)		
occurrences causally related to treatment / all	0 / 0	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 1		
Subileus				
subjects affected / exposed	2 / 294 (0.68%)	2 / 304 (0.66%)		
occurrences causally related to treatment / all	0 / 3	0 / 2		
deaths causally related to treatment / all	0 / 0	0 / 0		
Vomiting				

subjects affected / exposed	1 / 294 (0.34%)	10 / 304 (3.29%)	
occurrences causally related to treatment / all	1 / 1	10 / 13	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting, fatigue			
subjects affected / exposed	0 / 294 (0.00%)	1 / 304 (0.33%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Hepatobiliary disorders, vomiting, pyrexia			
subjects affected / exposed	0 / 294 (0.00%)	1 / 304 (0.33%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis			
subjects affected / exposed	0 / 294 (0.00%)	1 / 304 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholangitis acute			
subjects affected / exposed	0 / 294 (0.00%)	1 / 304 (0.33%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatitis acute			
subjects affected / exposed	0 / 294 (0.00%)	1 / 304 (0.33%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Increased Bilirubin, neutropenia, thrombocytopenia, anemia			
subjects affected / exposed	1 / 294 (0.34%)	0 / 304 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea, hypertransaminasaemia			
subjects affected / exposed	0 / 294 (0.00%)	1 / 304 (0.33%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			

Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	0 / 294 (0.00%)	1 / 304 (0.33%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 294 (0.34%)	0 / 304 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract obstruction			
subjects affected / exposed	1 / 294 (0.34%)	0 / 304 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection			
subjects affected / exposed	1 / 294 (0.34%)	0 / 304 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Arthralgia, back pain			
subjects affected / exposed	0 / 294 (0.00%)	1 / 304 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intervertebral disc compression			
subjects affected / exposed	1 / 294 (0.34%)	0 / 304 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lumbar vertebral fracture			
subjects affected / exposed	1 / 294 (0.34%)	0 / 304 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myalgia			

subjects affected / exposed	0 / 294 (0.00%)	1 / 304 (0.33%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Device related infection			
subjects affected / exposed	1 / 294 (0.34%)	5 / 304 (1.64%)	
occurrences causally related to treatment / all	0 / 1	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	0 / 294 (0.00%)	1 / 304 (0.33%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile infection			
subjects affected / exposed	0 / 294 (0.00%)	1 / 304 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulitis			
subjects affected / exposed	1 / 294 (0.34%)	0 / 304 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection			
subjects affected / exposed	0 / 294 (0.00%)	2 / 304 (0.66%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Klebsiella sepsis			
subjects affected / exposed	0 / 294 (0.00%)	1 / 304 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nasopharyngitis			
subjects affected / exposed	0 / 294 (0.00%)	1 / 304 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenic sepsis			

subjects affected / exposed	0 / 294 (0.00%)	1 / 304 (0.33%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ophthalmic herpes simplex			
subjects affected / exposed	0 / 294 (0.00%)	1 / 304 (0.33%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oral herpes			
subjects affected / exposed	0 / 294 (0.00%)	1 / 304 (0.33%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	0 / 294 (0.00%)	6 / 304 (1.97%)	
occurrences causally related to treatment / all	0 / 0	4 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyoderma			
subjects affected / exposed	1 / 294 (0.34%)	0 / 304 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	1 / 294 (0.34%)	1 / 304 (0.33%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Shock septic			
subjects affected / exposed	0 / 294 (0.00%)	1 / 304 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Metabolism and nutrition disorders			
Hyponatremia			
subjects affected / exposed	0 / 294 (0.00%)	1 / 304 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Arm A	Arm B	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	251 / 294 (85.37%)	262 / 304 (86.18%)	
Nervous system disorders			
Dysgeusia			
subjects affected / exposed	10 / 294 (3.40%)	16 / 304 (5.26%)	
occurrences (all)	16	22	
Neuropathy			
subjects affected / exposed	41 / 294 (13.95%)	39 / 304 (12.83%)	
occurrences (all)	44	45	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	84 / 294 (28.57%)	72 / 304 (23.68%)	
occurrences (all)	136	123	
Thrombocytopenia			
subjects affected / exposed	72 / 294 (24.49%)	41 / 304 (13.49%)	
occurrences (all)	152	71	
Leukopenia			
subjects affected / exposed	40 / 294 (13.61%)	44 / 304 (14.47%)	
occurrences (all)	86	102	
Neutropenia			
subjects affected / exposed	112 / 294 (38.10%)	156 / 304 (51.32%)	
occurrences (all)	307	373	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	61 / 294 (20.75%)	74 / 304 (24.34%)	
occurrences (all)	115	136	
Fatigue			
subjects affected / exposed	77 / 294 (26.19%)	74 / 304 (24.34%)	
occurrences (all)	102	124	
Mucosal inflammation			
subjects affected / exposed	25 / 294 (8.50%)	31 / 304 (10.20%)	
occurrences (all)	38	54	
Oedema			

subjects affected / exposed	9 / 294 (3.06%)	16 / 304 (5.26%)	
occurrences (all)	11	21	
Pain			
subjects affected / exposed	17 / 294 (5.78%)	33 / 304 (10.86%)	
occurrences (all)	22	43	
Pyrexia			
subjects affected / exposed	13 / 294 (4.42%)	34 / 304 (11.18%)	
occurrences (all)	19	42	
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	15 / 294 (5.10%)	8 / 304 (2.63%)	
occurrences (all)	17	8	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	111 / 294 (37.76%)	144 / 304 (47.37%)	
occurrences (all)	196	281	
Stomatitis			
subjects affected / exposed	32 / 294 (10.88%)	41 / 304 (13.49%)	
occurrences (all)	42	66	
Vomiting			
subjects affected / exposed	60 / 294 (20.41%)	94 / 304 (30.92%)	
occurrences (all)	100	162	
Abdominal pain			
subjects affected / exposed	31 / 294 (10.54%)	36 / 304 (11.84%)	
occurrences (all)	36	52	
Constipation			
subjects affected / exposed	62 / 294 (21.09%)	93 / 304 (30.59%)	
occurrences (all)	98	127	
Diarrhoea			
subjects affected / exposed	50 / 294 (17.01%)	53 / 304 (17.43%)	
occurrences (all)	71	65	
Dyspepsia			
subjects affected / exposed	9 / 294 (3.06%)	18 / 304 (5.92%)	
occurrences (all)	11	27	
Respiratory, thoracic and mediastinal disorders			

Cough			
subjects affected / exposed	15 / 294 (5.10%)	17 / 304 (5.59%)	
occurrences (all)	16	23	
Dyspnoea			
subjects affected / exposed	18 / 294 (6.12%)	33 / 304 (10.86%)	
occurrences (all)	20	40	
Hepatobiliary disorders			
Cholestasis			
subjects affected / exposed	10 / 294 (3.40%)	17 / 304 (5.59%)	
occurrences (all)	22	26	
Hepatotoxicity			
subjects affected / exposed	16 / 294 (5.44%)	85 / 304 (27.96%)	
occurrences (all)	31	213	
Skin and subcutaneous tissue disorders			
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	24 / 294 (8.16%)	36 / 304 (11.84%)	
occurrences (all)	26	45	
Dry skin			
subjects affected / exposed	15 / 294 (5.10%)	10 / 304 (3.29%)	
occurrences (all)	15	10	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	24 / 294 (8.16%)	29 / 304 (9.54%)	
occurrences (all)	39	41	
Metabolism and nutrition disorders			
Appetite disorder			
subjects affected / exposed	34 / 294 (11.56%)	40 / 304 (13.16%)	
occurrences (all)	46	53	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
01 January 2012	worldwide shortage of Pegylated Liposomal Doxorubicin (PLD - Caelyx®)	17 September 2013

Notes:

Limitations and caveats

None reported