Clinical trial results:
A Randomized, Open-Label Study Comparing the Combination of YONDELIS® and DOXIL®/CAELYX® with DOXIL®/CAELYX® Monotherapy for the Treatment of Advanced-Relapsed Epithelial Ovarian, Primary Peritoneal, or Fallopian Tube Cancer

Summary

EudraCT number	2012-004808-34
Trial protocol	GB PL
Global end of trial date	18 January 2018

Results information

Result version number	v1 (current)
This version publication date	07 March 2019
First version publication date	07 March 2019

Trial information

Trial identification

Sponsor protocol code	ET743OVC3006

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01846611
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Janssen Research & Development, LLC
Sponsor organisation address	920, Route 202 South, Raritan, NJ, United States, 08869
Public contact	Clinical Registry group, Janssen Research & Development, LLC, ClinicalTrialsEU@its.jnj.com
Scientific contact	Clinical Registry group, Janssen Research & Development, LLC, ClinicalTrialsEU@its.jnj.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	18 January 2018
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	18 January 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of the trial was to compare the overall survival (OS) after treatment with trabectedin+DOXIL combination therapy to that observed after treatment with DOXIL monotherapy for subjects with platinum-sensitive advanced-relapsed epithelial ovarian, primary peritoneal, or fallopian tube cancer who had received 2 previous lines of platinum-based chemotherapy

Protection of trial subjects:

This study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with Good Clinical Practices and applicable regulatory requirements. Vital sign measurements (temperature, pulse/heart rate, respiration rate, and blood pressure) were obtained at the screening phase of the study. Safety was evaluated based on adverse events (AEs); clinical laboratory tests (hematology, serum chemistry, and serum or urine pregnancy testing); electrocardiograms (ECGs) and LVEF (either multigated acquisition [MUGA] scans or 2-dimensional echocardiograms [2D-ECHO]); and physical examinations (including height and weight measurements).

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	04 October 2013
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Australia: 29
Country: Number of subjects enrolled	Switzerland: 1
Country: Number of subjects enrolled	China: 27
Country: Number of subjects enrolled	United Kingdom: 22
Country: Number of subjects enrolled	Israel: 10
Country: Number of subjects enrolled	New Zealand: 18
Country: Number of subjects enrolled	Poland: 8
Country: Number of subjects enrolled	Russian Federation: 246
Country: Number of subjects enrolled	United States: 204
Country: Number of subjects enrolled	South Africa: 11
Worldwide total number of subjects	576
EEA total number of subjects	30

Notes:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	362
From 65 to 84 years	212
85 years and over	2

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Total 576 subjects randomized, 289 subjects in trabectedin+DOXIL arm, 287 subjects in DOXIL arm. 8 subjects did not received study drug (3 subjects in trabectedin+DOXIL arm, 5 subjects in DOXIL arm) due to worsening of health status (5 subjects) or withdrawal of subject consent (3 subjects). 568 subjects received at least 1 dose of study drug.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Trabectedin + DOXIL

Arm description:

Subjects received DOXIL 30 milligram per meter square (mg/m^2) administered as an intravenous (IV) infusion over approximately 90 minutes followed by trabectedin 1.1 mg/m^2 administered as an IV infusion over approximately 3 hours, on Day 1 of each treatment cycle (21 days cycle) every 3 weeks. Subjects were pretreated with 20 mg dexamethasone IV (or an equivalent IV corticosteroid) approximately 30 minutes prior to initiation of infusion of DOXIL IV.

Arm type	Experimental
Investigational medicinal product name	DOXIL
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Subjects received DOXIL 30 mg/m^2 administered as an IV infusion over approximately 90 minutes.

Investigational medicinal product name	Trabectedin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Subjects received 1.1 mg/m^2 of Trabectedin administered as an IV infusion for 3 hours, on Day 1 of each treatment cycle (21 days cycle) every 3 weeks.

Investigational medicinal product name	Dexamethasone IV
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Subjects were pretreated with 20 mg dexamethasone IV (or an equivalent IV corticosteroid) approximately 30 minutes prior to initiation of infusion of DOXIL IV.

Arm title	DOXIL

Arm description:

Subjects received DOXIL 50 mg/m^2 administered as an IV infusion over approximately 90 minutes on

Day 1 of each treatment cycle (28 days cycle), every 4 weeks.

Arm type	Active comparator
Investigational medicinal product name	DOXIL
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Subjects received DOXIL 50 mg/m^2 administered as an IV infusion over approximately 90 minutes on Day 1.

Number of subjects in period 1	Trabectedin + DOXIL	DOXIL
Started	289	287
Completed	250	241
Not completed	39	46
Consent withdrawn by subject	16	21
Unspecified	19	19
Lost to follow-up	4	6

Baseline characteristics

Reporting groups	
Reporting group title	Trabectedin + DOXIL
Reporting group description:	
Subjects received DOXIL 30 milligram per meter square (mg/m^2) administered as an intravenous (IV) infusion over approximately 90 minutes followed by trabectedin 1.1 mg/m^2 administered as an IV infusion over approximately 3 hours, on Day 1 of each treatment cycle (21 days cycle) every 3 weeks. Subjects were pretreated with 20 mg dexamethasone IV (or an equivalent IV corticosteroid) approximately 30 minutes prior to initiation of infusion of DOXIL IV.	
Reporting group title	DOXIL
Reporting group description:	
Subjects received DOXIL 50 mg/m^2 administered as an IV infusion over approximately 90 minutes on Day 1 of each treatment cycle (28 days cycle), every 4 weeks.	

Reporting group values	Trabectedin + DOXIL	DOXIL	Total
Number of subjects	289	287	576
Title for AgeCategorical Units: subjects			
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	179	183	362
From 65 to 74 years	93	81	174
From 75 and above	17	23	40
Title for AgeContinuous Units: years			
arithmetic mean	59.8	59.9	
standard deviation	± 10.16	± 10.35	-
Title for Gender Units: subjects			
Female	289	287	576

End points

End points reporting groups

Reporting group title	Trabectedin + DOXIL
Reporting group description:	
Subjects received DOXIL 30 milligram per meter square (mg/m^2) administered as an intravenous (IV) infusion over approximately 90 minutes followed by trabectedin 1.1 mg/m^2 administered as an IV infusion over approximately 3 hours, on Day 1 of each treatment cycle (21 days cycle) every 3 weeks. Subjects were pretreated with 20 mg dexamethasone IV (or an equivalent IV corticosteroid) approximately 30 minutes prior to initiation of infusion of DOXIL IV.	
Reporting group title	DOXIL
Reporting group description:	
Subjects received DOXIL 50 mg/m^2 administered as an IV infusion over approximately 90 minutes on Day 1 of each treatment cycle (28 days cycle), every 4 weeks.	

Primary: Overall Survival (OS)

End point title	Overall Survival (OS)
End point description:	
OS defined as the time between the date of randomization and the date of death. Subjects who died, regardless of the cause of death, were considered to have had an event. All randomized analysis set included all subjects who were randomized to study treatment independent of whether they received study drug.	
End point type	Primary
End point timeframe:	
Up to 4.3 years	

End point values	Trabectedin + DOXIL	DOXIL		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	289	287		
Units: months				
median (confidence interval 95%)	23.82 (20.30 to 26.12)	22.21 (18.10 to 24.67)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Trabectedin + DOXIL v DOXIL
Number of subjects included in analysis	576
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5236
Method	Unstratified log rank test
Parameter estimate	Hazard ratio (HR)
Point estimate	0.925

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.727
upper limit	1.177

Secondary: Progression-Free Survival (PFS)

End point title	Progression-Free Survival (PFS)

End point description:

PFS defined as the time between the date of randomization and the date of disease progression or death. PFS was assessed using the response evaluation criteria in solid tumors (RECIST) Version 1.1. As per criteria progressive disease in case of target lesions means at least a 20 percent (%) increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 millimeter (mm). Progressive disease in case of non-target lesions means unequivocal progression of existing non-target lesions. In both cases the appearance of one or more new lesions is also considered progression. All randomized analysis set included all subjects who were randomized to study treatment independent of whether they received study drug.

End point type	Secondary

End point timeframe:

Up to 4.3 years

End point values	Trabectedin + DOXIL	DOXIL		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	289	287		
Units: months				
median (confidence interval 95%)	7.52 (6.93 to 9.43)	7.26 (6.14 to 7.59)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Trabectedin + DOXIL v DOXIL
Number of subjects included in analysis	576
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5174
Method	Unstratified log rank test
Parameter estimate	Hazard ratio (HR)
Point estimate	0.935
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.762
upper limit	1.147

Secondary: Objective Response Rate (ORR)

End point title	Objective Response Rate (ORR)

End point description:

ORR defined as the percentage of subjects with measurable disease achieving a best overall response of either complete response (CR) or partial response (PR) based on RECIST. CR: disappearance of all target and non-target lesions and normalization of tumor marker levels in non-target lesions. PR: at least a 30 percent (%) decrease in the sum of longest diameter (LD) of target lesions or persistence of one or more non-target lesion(s) or/and maintenance of tumor marker level above the normal limits. All randomized analysis set included all subjects who were randomized to study treatment independent of whether they received study drug.

End point type	Secondary

End point timeframe:

Up to 4.3 years

End point values	Trabectedin + DOXIL	DOXIL		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	289	287		
Units: Percentage of subjects				
number (confidence interval 95%)	46.0 (40.2 to 52.0)	35.9 (30.3 to 41.7)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Trabectedin + DOXIL v DOXIL
Number of subjects included in analysis	576
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0142
Method	Fisher exact
Parameter estimate	Odds ratio (OR)
Point estimate	1.523
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.075
upper limit	2.158

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to 4.3 years

Adverse event reporting additional description:

Safety population included all-treated subjects who received at least 1 dose of study drug.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19.0

Reporting groups

Reporting group title	Trabectedin + DOXIL

Reporting group description:

Subjects received DOXIL 30 milligram per meter square (mg/m^2) administered as an intravenous (IV) infusion over approximately 90 minutes followed by trabectedin 1.1 mg/m^2 administered as an IV infusion over approximately 3 hours, on Day 1 of each treatment cycle (21 days cycle) every 3 weeks. Subjects were pretreated with 20 mg dexamethasone IV (or an equivalent IV corticosteroid) approximately 30 minutes prior to initiation of infusion of DOXIL IV.

Reporting group title	DOXIL

Reporting group description:

Subjects received DOXIL 50 mg/m^2 administered as an IV infusion over approximately 90 minutes on Day 1 of each treatment cycle (28 days cycle), every 4 weeks.

Serious adverse events	Trabectedin + DOXIL	DOXIL	
Total subjects affected by serious adverse events			
subjects affected / exposed	118 / 289 (40.83%)	58 / 287 (20.21%)	
number of deaths (all causes)	132	131	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Lymphangiosis Carcinomatosa			
subjects affected / exposed	1 / 289 (0.35%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Malignant Pleural Effusion			
subjects affected / exposed	0 / 289 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to Abdominal Wall			

subjects affected / exposed	0 / 289 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to Central Nervous System			
subjects affected / exposed	0 / 289 (0.00%)	1 / 287 (0.35%)	
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 / 289 (0.35%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal Cell Carcinoma			
subjects affected / exposed	0 / 289 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Capillary Leak Syndrome			
subjects affected / exposed	0 / 289 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Deep Vein Thrombosis			
subjects affected / exposed	3 / 289 (1.04%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Embolism			
subjects affected / exposed	1 / 289 (0.35%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Flushing			
subjects affected / exposed	0 / 289 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertension			

subjects affected / exposed	0 / 289 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pelvic Venous Thrombosis			
subjects affected / exposed	1 / 289 (0.35%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombophlebitis			
subjects affected / exposed	2 / 289 (0.69%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 289 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Catheter Site Inflammation			
subjects affected / exposed	1 / 289 (0.35%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest Discomfort			
subjects affected / exposed	0 / 289 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest Pain			
subjects affected / exposed	0 / 289 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Death			
subjects affected / exposed	4 / 289 (1.38%)	2 / 287 (0.70%)	
occurrences causally related to treatment / all	0 / 4	0 / 2	
deaths causally related to treatment / all	0 / 4	0 / 2	
Fatigue			

subjects affected / exposed	4 / 289 (1.38%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	5 / 5	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza Like Illness			
subjects affected / exposed	1 / 289 (0.35%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multiple Organ Dysfunction Syndrome			
subjects affected / exposed	2 / 289 (0.69%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 2	0 / 1	
Oedema Peripheral			
subjects affected / exposed	1 / 289 (0.35%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain			
subjects affected / exposed	0 / 289 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	9 / 289 (3.11%)	3 / 287 (1.05%)	
occurrences causally related to treatment / all	5 / 9	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Pelvic Fluid Collection			
subjects affected / exposed	0 / 289 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Acute Respiratory Failure			

subjects affected / exposed	1 / 289 (0.35%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic Obstructive Pulmonary Disease			
subjects affected / exposed	1 / 289 (0.35%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cough			
subjects affected / exposed	1 / 289 (0.35%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	1 / 289 (0.35%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epistaxis			
subjects affected / exposed	1 / 289 (0.35%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoxia			
subjects affected / exposed	2 / 289 (0.69%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Interstitial Lung Disease			
subjects affected / exposed	0 / 289 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural Effusion			
subjects affected / exposed	4 / 289 (1.38%)	2 / 287 (0.70%)	
occurrences causally related to treatment / all	1 / 5	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleurisy			

subjects affected / exposed	2 / 289 (0.69%)	2 / 287 (0.70%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary Embolism			
subjects affected / exposed	6 / 289 (2.08%)	2 / 287 (0.70%)	
occurrences causally related to treatment / all	2 / 6	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Product issues			
Device Malfunction			
subjects affected / exposed	0 / 289 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Alanine Aminotransferase Increased			
subjects affected / exposed	14 / 289 (4.84%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	16 / 16	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspartate Aminotransferase Increased			
subjects affected / exposed	9 / 289 (3.11%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	11 / 11	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood Creatine Phosphokinase Increased			
subjects affected / exposed	1 / 289 (0.35%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood Creatinine Increased			
subjects affected / exposed	1 / 289 (0.35%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ejection Fraction Decreased			
subjects affected / exposed	2 / 289 (0.69%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	2 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Gamma-Glutamyltransferase Increased			
subjects affected / exposed	1 / 289 (0.35%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutrophil Count Decreased			
subjects affected / exposed	5 / 289 (1.73%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	5 / 5	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Platelet Count Decreased			
subjects affected / exposed	3 / 289 (1.04%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	3 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transaminases Increased			
subjects affected / exposed	1 / 289 (0.35%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Weight Decreased			
subjects affected / exposed	1 / 289 (0.35%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
White Blood Cell Count Decreased			
subjects affected / exposed	4 / 289 (1.38%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	4 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Anastomotic Ulcer			
subjects affected / exposed	1 / 289 (0.35%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal Stoma Complication			
subjects affected / exposed	1 / 289 (0.35%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Head Injury			
subjects affected / exposed	0 / 289 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hip Fracture			
subjects affected / exposed	1 / 289 (0.35%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infusion Related Reaction			
subjects affected / exposed	0 / 289 (0.00%)	2 / 287 (0.70%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Joint Dislocation			
subjects affected / exposed	0 / 289 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal Compression Fracture			
subjects affected / exposed	1 / 289 (0.35%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Atrial Fibrillation			
subjects affected / exposed	1 / 289 (0.35%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac Failure Congestive			
subjects affected / exposed	1 / 289 (0.35%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiopulmonary Failure			
subjects affected / exposed	1 / 289 (0.35%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Tachycardia			

subjects affected / exposed	1 / 289 (0.35%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 289 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lethargy			
subjects affected / exposed	1 / 289 (0.35%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			
subjects affected / exposed	1 / 289 (0.35%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	1 / 289 (0.35%)	0 / 287 (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			
Anaemia			
subjects affected / exposed	9 / 289 (3.11%)	2 / 287 (0.70%)	
occurrences causally related to treatment / all	17 / 17	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile Neutropenia			
subjects affected / exposed	14 / 289 (4.84%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	16 / 16	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukopenia			
subjects affected / exposed	3 / 289 (1.04%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	6 / 6	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			

subjects affected / exposed	12 / 289 (4.15%)	4 / 287 (1.39%)	
occurrences causally related to treatment / all	15 / 15	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	10 / 289 (3.46%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	13 / 13	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal Pain			
subjects affected / exposed	6 / 289 (2.08%)	3 / 287 (1.05%)	
occurrences causally related to treatment / all	3 / 7	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal Pain Lower			
subjects affected / exposed	0 / 289 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal Pain Upper			
subjects affected / exposed	1 / 289 (0.35%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ascites			
subjects affected / exposed	3 / 289 (1.04%)	8 / 287 (2.79%)	
occurrences causally related to treatment / all	0 / 3	0 / 9	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	5 / 289 (1.73%)	2 / 287 (0.70%)	
occurrences causally related to treatment / all	3 / 6	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	2 / 289 (0.69%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspepsia			

subjects affected / exposed	1 / 289 (0.35%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enteritis			
subjects affected / exposed	1 / 289 (0.35%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal Haemorrhage			
subjects affected / exposed	1 / 289 (0.35%)	0 / 287 (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 / 289 (0.35%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrooesophageal Reflux Disease			
subjects affected / exposed	0 / 289 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus			
subjects affected / exposed	0 / 289 (0.00%)	3 / 287 (1.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal Obstruction			
subjects affected / exposed	3 / 289 (1.04%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	8 / 289 (2.77%)	3 / 287 (1.05%)	
occurrences causally related to treatment / all	8 / 8	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenic Colitis			

subjects affected / exposed	0 / 289 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oral Pain			
subjects affected / exposed	0 / 289 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oral Pruritus			
subjects affected / exposed	0 / 289 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			
subjects affected / exposed	1 / 289 (0.35%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal Haemorrhage			
subjects affected / exposed	1 / 289 (0.35%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small Intestinal Obstruction			
subjects affected / exposed	4 / 289 (1.38%)	14 / 287 (4.88%)	
occurrences causally related to treatment / all	0 / 4	0 / 19	
deaths causally related to treatment / all	0 / 0	0 / 1	
Stomatitis			
subjects affected / exposed	0 / 289 (0.00%)	2 / 287 (0.70%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subileus			
subjects affected / exposed	1 / 289 (0.35%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper Gastrointestinal Haemorrhage			

subjects affected / exposed	1 / 289 (0.35%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	10 / 289 (3.46%)	7 / 287 (2.44%)	
occurrences causally related to treatment / all	10 / 13	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Drug-Induced Liver Injury			
subjects affected / exposed	1 / 289 (0.35%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatitis Toxic			
subjects affected / exposed	2 / 289 (0.69%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Palmar-Plantar Erythrodysaesthesia Syndrome			
subjects affected / exposed	0 / 289 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute Kidney Injury			
subjects affected / exposed	4 / 289 (1.38%)	2 / 287 (0.70%)	
occurrences causally related to treatment / all	2 / 4	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Renal Failure			
subjects affected / exposed	1 / 289 (0.35%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Urinary Retention			
subjects affected / exposed	0 / 289 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Endocrine disorders			
Inappropriate Antidiuretic Hormone Secretion			
subjects affected / exposed	1 / 289 (0.35%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Back Pain			
subjects affected / exposed	1 / 289 (0.35%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Abdominal Wall Abscess			
subjects affected / exposed	0 / 289 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Catheter Site Infection			
subjects affected / exposed	0 / 289 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	2 / 289 (0.69%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device Related Infection			
subjects affected / exposed	3 / 289 (1.04%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device Related Sepsis			
subjects affected / exposed	1 / 289 (0.35%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterobacter Bacteraemia			

subjects affected / exposed	1 / 289 (0.35%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	0 / 289 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection			
subjects affected / exposed	1 / 289 (0.35%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenic Sepsis			
subjects affected / exposed	2 / 289 (0.69%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	2 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oral Candidiasis			
subjects affected / exposed	0 / 289 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritonitis			
subjects affected / exposed	2 / 289 (0.69%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Peritonitis Bacterial			
subjects affected / exposed	1 / 289 (0.35%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumocystis Jirovecii Pneumonia			
subjects affected / exposed	2 / 289 (0.69%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	2 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			

subjects affected / exposed	4 / 289 (1.38%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	2 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pseudomonal Sepsis			
subjects affected / exposed	1 / 289 (0.35%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis Acute			
subjects affected / exposed	0 / 289 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	4 / 289 (1.38%)	2 / 287 (0.70%)	
occurrences causally related to treatment / all	1 / 4	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic Shock			
subjects affected / exposed	1 / 289 (0.35%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Soft Tissue Infection			
subjects affected / exposed	1 / 289 (0.35%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal Bacteraemia			
subjects affected / exposed	1 / 289 (0.35%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper Respiratory Tract Infection			
subjects affected / exposed	1 / 289 (0.35%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary Tract Infection			

subjects affected / exposed	5 / 289 (1.73%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	2 / 5	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	6 / 289 (2.08%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	4 / 6	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fluid Overload			
subjects affected / exposed	1 / 289 (0.35%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperkalaemia			
subjects affected / exposed	1 / 289 (0.35%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			
subjects affected / exposed	1 / 289 (0.35%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	1 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	2 / 289 (0.69%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypophagia			
subjects affected / exposed	0 / 289 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Trabectedin + DOXIL	DOXIL	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	282 / 289 (97.58%)	270 / 287 (94.08%)	
Investigations			
Alanine Aminotransferase Increased			
subjects affected / exposed	151 / 289 (52.25%)	12 / 287 (4.18%)	
occurrences (all)	486	16	
Aspartate Aminotransferase Increased			
subjects affected / exposed	100 / 289 (34.60%)	11 / 287 (3.83%)	
occurrences (all)	234	17	
Bilirubin Conjugated Increased			
subjects affected / exposed	24 / 289 (8.30%)	2 / 287 (0.70%)	
occurrences (all)	32	3	
Blood Alkaline Phosphatase Increased			
subjects affected / exposed	73 / 289 (25.26%)	16 / 287 (5.57%)	
occurrences (all)	163	35	
Blood Creatinine Increased			
subjects affected / exposed	20 / 289 (6.92%)	21 / 287 (7.32%)	
occurrences (all)	35	39	
Blood Bilirubin Increased			
subjects affected / exposed	24 / 289 (8.30%)	3 / 287 (1.05%)	
occurrences (all)	33	3	
Ejection Fraction Decreased			
subjects affected / exposed	20 / 289 (6.92%)	10 / 287 (3.48%)	
occurrences (all)	23	10	
Neutrophil Count Decreased			
subjects affected / exposed	52 / 289 (17.99%)	37 / 287 (12.89%)	
occurrences (all)	211	135	
Platelet Count Decreased			
subjects affected / exposed	52 / 289 (17.99%)	16 / 287 (5.57%)	
occurrences (all)	197	35	
Weight Decreased			
subjects affected / exposed	13 / 289 (4.50%)	16 / 287 (5.57%)	
occurrences (all)	21	18	
White Blood Cell Count Decreased			

subjects affected / exposed	33 / 289 (11.42%)	29 / 287 (10.10%)	
occurrences (all)	139	113	
Vascular disorders			
Hypertension			
subjects affected / exposed	22 / 289 (7.61%)	7 / 287 (2.44%)	
occurrences (all)	41	27	
Nervous system disorders			
Dysgeusia			
subjects affected / exposed	35 / 289 (12.11%)	20 / 287 (6.97%)	
occurrences (all)	46	23	
Headache			
subjects affected / exposed	38 / 289 (13.15%)	29 / 287 (10.10%)	
occurrences (all)	61	35	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	135 / 289 (46.71%)	70 / 287 (24.39%)	
occurrences (all)	417	194	
Leukopenia			
subjects affected / exposed	53 / 289 (18.34%)	38 / 287 (13.24%)	
occurrences (all)	275	157	
Neutropenia			
subjects affected / exposed	149 / 289 (51.56%)	104 / 287 (36.24%)	
occurrences (all)	948	424	
Thrombocytopenia			
subjects affected / exposed	63 / 289 (21.80%)	18 / 287 (6.27%)	
occurrences (all)	298	33	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	39 / 289 (13.49%)	16 / 287 (5.57%)	
occurrences (all)	146	30	
Mucosal Inflammation			
subjects affected / exposed	22 / 289 (7.61%)	33 / 287 (11.50%)	
occurrences (all)	28	81	
Fatigue			
subjects affected / exposed	171 / 289 (59.17%)	113 / 287 (39.37%)	
occurrences (all)	519	214	

Oedema Peripheral			
subjects affected / exposed	32 / 289 (11.07%)	22 / 287 (7.67%)	
occurrences (all)	52	31	
Pyrexia			
subjects affected / exposed	38 / 289 (13.15%)	26 / 287 (9.06%)	
occurrences (all)	51	38	
Gastrointestinal disorders			
Abdominal Distension			
subjects affected / exposed	20 / 289 (6.92%)	15 / 287 (5.23%)	
occurrences (all)	34	25	
Abdominal Pain			
subjects affected / exposed	54 / 289 (18.69%)	44 / 287 (15.33%)	
occurrences (all)	92	71	
Ascites			
subjects affected / exposed	12 / 289 (4.15%)	17 / 287 (5.92%)	
occurrences (all)	20	25	
Constipation			
subjects affected / exposed	82 / 289 (28.37%)	61 / 287 (21.25%)	
occurrences (all)	127	95	
Diarrhoea			
subjects affected / exposed	59 / 289 (20.42%)	47 / 287 (16.38%)	
occurrences (all)	91	80	
Gastrooesophageal Reflux Disease			
subjects affected / exposed	12 / 289 (4.15%)	15 / 287 (5.23%)	
occurrences (all)	12	19	
Dyspepsia			
subjects affected / exposed	23 / 289 (7.96%)	18 / 287 (6.27%)	
occurrences (all)	36	25	
Nausea			
subjects affected / exposed	212 / 289 (73.36%)	114 / 287 (39.72%)	
occurrences (all)	687	235	
Stomatitis			
subjects affected / exposed	52 / 289 (17.99%)	91 / 287 (31.71%)	
occurrences (all)	99	229	
Vomiting			

subjects affected / exposed	141 / 289 (48.79%)	54 / 287 (18.82%)	
occurrences (all)	276	86	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	41 / 289 (14.19%)	34 / 287 (11.85%)	
occurrences (all)	57	41	
Dyspnoea			
subjects affected / exposed	44 / 289 (15.22%)	28 / 287 (9.76%)	
occurrences (all)	69	37	
Oropharyngeal Pain			
subjects affected / exposed	16 / 289 (5.54%)	17 / 287 (5.92%)	
occurrences (all)	25	19	
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	32 / 289 (11.07%)	22 / 287 (7.67%)	
occurrences (all)	34	24	
Dry Skin			
subjects affected / exposed	22 / 289 (7.61%)	21 / 287 (7.32%)	
occurrences (all)	29	23	
Palmar-Plantar Erythrodysaesthesia Syndrome			
subjects affected / exposed	58 / 289 (20.07%)	117 / 287 (40.77%)	
occurrences (all)	124	313	
Rash			
subjects affected / exposed	22 / 289 (7.61%)	26 / 287 (9.06%)	
occurrences (all)	37	56	
Rash Maculo-Papular			
subjects affected / exposed	8 / 289 (2.77%)	24 / 287 (8.36%)	
occurrences (all)	15	46	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	18 / 289 (6.23%)	8 / 287 (2.79%)	
occurrences (all)	19	8	
Insomnia			
subjects affected / exposed	19 / 289 (6.57%)	16 / 287 (5.57%)	
occurrences (all)	23	20	
Musculoskeletal and connective tissue			

disorders			
Arthralgia			
subjects affected / exposed	25 / 289 (8.65%)	12 / 287 (4.18%)	
occurrences (all)	32	18	
Back Pain			
subjects affected / exposed	24 / 289 (8.30%)	15 / 287 (5.23%)	
occurrences (all)	29	19	
Muscular Weakness			
subjects affected / exposed	16 / 289 (5.54%)	9 / 287 (3.14%)	
occurrences (all)	21	15	
Myalgia			
subjects affected / exposed	16 / 289 (5.54%)	6 / 287 (2.09%)	
occurrences (all)	24	8	
Pain in Extremity			
subjects affected / exposed	8 / 289 (2.77%)	16 / 287 (5.57%)	
occurrences (all)	8	20	
Infections and infestations			
Urinary Tract Infection			
subjects affected / exposed	12 / 289 (4.15%)	15 / 287 (5.23%)	
occurrences (all)	12	24	
Metabolism and nutrition disorders			
Decreased Appetite			
subjects affected / exposed	83 / 289 (28.72%)	52 / 287 (18.12%)	
occurrences (all)	183	111	
Dehydration			
subjects affected / exposed	21 / 289 (7.27%)	9 / 287 (3.14%)	
occurrences (all)	33	14	
Hypoalbuminaemia			
subjects affected / exposed	21 / 289 (7.27%)	8 / 287 (2.79%)	
occurrences (all)	32	11	
Hypokalaemia			
subjects affected / exposed	22 / 289 (7.61%)	12 / 287 (4.18%)	
occurrences (all)	33	24	
Hypomagnesaemia			
subjects affected / exposed	19 / 289 (6.57%)	6 / 287 (2.09%)	
occurrences (all)	52	7	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
25 March 2013	The main reason of this amendment was to revise inclusion criterion.
29 August 2013	The overall reasons for the amendment are to extend the use of contraceptives from 3 months to 6 months after the study, to increase the creatinine clearance rate from greater than equal to (>=) 40 millilitres per minute/1.73 meter square (mL/min/1.73 m^2) to >=60 mL/min/1.73 m^2, and to add a prohibition regarding subjects receiving a yellow fever vaccine.
09 January 2018	The overall reason for the amendment was the sponsor's decision to amend the study protocol was based on the Independent Data Monitoring Committee (IDMC) recommendation to discontinue the study based on the results of a futility analysis of overall survival (OS), in which the prespecified futility threshold was crossed. In addition, the amendment will allow study subjects deriving clinical benefit to continue on single-agent DOXIL per local standard of care.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported