Clinical trial results:
A Randomized, Phase III, Open-Label Study of Oral Topotecan Plus Whole-Brain Radiation Therapy (WBRT) Compared with WBRT Alone in Patients with Brain Metastases from Non-Small Cell Lung Cancer.

Summary

EudraCT number	2006-002074-22
Trial protocol	HU SK
Global end of trial date	16 August 2013

Results information

Result version number	v1 (current)
This version publication date	02 May 2016
First version publication date	26 April 2015

Trial information

Trial identification

Sponsor protocol code	UM2005/00201/00

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	GlaxoSmithKline
Sponsor organisation address	980 Great West Road, Brentford, Middlesex, United Kingdom,
Public contact	GSK Response Center, GlaxoSmithKline, 1 866-435-7343,
Scientific contact	GSK Response Center, GlaxoSmithKline, 1 866-435-7343,

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	16 August 2013
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	16 August 2013
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study is to evaluate the efficacy of treatment with either oral topotecan plus WBRT or WBRT alone in patients with brain metastases due to NSCLC.

Protection of trial subjects:

Not applicable

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	06 December 2006
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	Canada: 45
Country: Number of subjects enrolled	Poland: 111
Country: Number of subjects enrolled	Russian Federation: 90
Country: Number of subjects enrolled	United States: 45
Country: Number of subjects enrolled	Hungary: 173
Country: Number of subjects enrolled	Slovakia: 8
Worldwide total number of subjects	472
EEA total number of subjects	292

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)	358
From 65 to 84 years	114
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Participants (par.) were randomly assigned to receive either topotecan capsules 1.1 mg/m2/day plus WBRT 3 Gy/day (experimental/chemoradiation arm) or WBRT alone 3 Gy/day over ten days. The randomization was stratified by the number of brain lesions and RPA Class.

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	Chemoradiation: Topotecan plus WBRT

Arm description:

Participants received topotecan 1.1 milligrams per meters squared per day (mg/m2/day), orally followed approximately 2 hours later by whole-brain radiation therapy (WBRT) 3 Gray (Gy)/day to midline over the course of 10 days. After a 2-week washout period, participants completing chemoradiation and willing to participate in the Continuation Phase of the study received oral topotecan 2.3 mg/m2/day for 5 days, every 21 days, as monotherapy provided the baseline hematologic requirements were met. Monotherapy continued until disease progression or discontinuation. Chemoradiation participants choosing not to participate in the Continuation Phase may have received other chemotherapies or best supportive care, as determined by the investigator.

Arm type	Experimental
Investigational medicinal product name	Topotecan
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

1.1 mg/m2/day

Investigational medicinal product name	whole-brain radiation therapy (WBRT)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Kit for radiopharmaceutical preparation
Routes of administration	Route of administration not applicable

Dosage and administration details:

3 Gy/day

Arm title	Radiation: WBRT Alone

Arm description:

Participants received WBRT 3 Gy/day for 10 days. Participants may have received other chemotherapies or best supportive care, as determined by the investigator.

Arm type	Active comparator

Investigational medicinal product name	whole-brain radiation therapy (WBRT)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Kit for radiopharmaceutical preparation
Routes of administration	Route of administration not applicable

Dosage and administration details:

3 Gy/day

Number of subjects in period 1	Chemoradiation: Topotecan plus WBRT	Radiation: WBRT Alone
Started	236	236
Completed	206	204
Not completed	30	32
Consent withdrawn by subject	12	15
Physician decision	-	1
Death	1	-
Ongoing	4	2
Investigator Decision	4	6
Lost to follow-up	7	6
Protocol deviation	2	2

Baseline characteristics

Reporting groups

Reporting group title	Chemoradiation: Topotecan plus WBRT

Reporting group description:

Participants received topotecan 1.1 milligrams per meters squared per day (mg/m2/day), orally followed approximately 2 hours later by whole-brain radiation therapy (WBRT) 3 Gray (Gy)/day to midline over the course of 10 days. After a 2-week washout period, participants completing chemoradiation and willing to participate in the Continuation Phase of the study received oral topotecan 2.3 mg/m2/day for 5 days, every 21 days, as monotherapy provided the baseline hematologic requirements were met. Monotherapy continued until disease progression or discontinuation. Chemoradiation participants choosing not to participate in the Continuation Phase may have received other chemotherapies or best supportive care, as determined by the investigator.

Reporting group title	Radiation: WBRT Alone

Reporting group description:

Participants received WBRT 3 Gy/day for 10 days. Participants may have received other chemotherapies or best supportive care, as determined by the investigator.

Reporting group values	Chemoradiation: Topotecan plus WBRT	Radiation: WBRT Alone	Total
Number of subjects	236	236	472
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	59.4	57.8	
standard deviation	± 8.56	± 8.65	-
Gender categorical Units: Subjects			
Female	84	78	162
Male	152	158	310
Race Units: Subjects			
African American/African Heritage (Her.)	3	1	4
Central/South Asian Heritage	1	0	1
Japanese/East Asian Heritage/South East Asian Her.	0	3	3
Native Hawaiian or other Pacific Islander	1	0	1
White	230	232	462
Asian & White	1	0	1
Race Units: Subjects			
African American/African Heritage (Her.)	3	1	4
Central/South Asian Heritage	1	0	1
Japanese/East Asian Heritage/South East Asian Her.	0	3	3
Native Hawaiian or other Pacific Islander	1	0	1

White	230	232	462
Asian & White	1	0	1

End points

End points reporting groups

Reporting group title	Chemoradiation: Topotecan plus WBRT

Reporting group description:

Participants received topotecan 1.1 milligrams per meters squared per day (mg/m2/day), orally followed approximately 2 hours later by whole-brain radiation therapy (WBRT) 3 Gray (Gy)/day to midline over the course of 10 days. After a 2-week washout period, participants completing chemoradiation and willing to participate in the Continuation Phase of the study received oral topotecan 2.3 mg/m2/day for 5 days, every 21 days, as monotherapy provided the baseline hematologic requirements were met. Monotherapy continued until disease progression or discontinuation. Chemoradiation participants choosing not to participate in the Continuation Phase may have received other chemotherapies or best supportive care, as determined by the investigator.

Reporting group title	Radiation: WBRT Alone

Reporting group description:

Participants received WBRT 3 Gy/day for 10 days. Participants may have received other chemotherapies or best supportive care, as determined by the investigator.

Primary: Overall Survival

End point title	Overall Survival

End point description:

Overall survival is defined as the time from randomization until the date of death due to any cause. The date of last contact was used for those participants who had not died or were lost to follow-up. These participants were classified as having been censored. Intent-to-Treat (ITT) Population: all randomized participants. Participants were analyzed by the treatment to which they were randomized, even if this differed from the treatment they actually received.

End point type	Primary

End point timeframe:

From the time of Randomization until the date of death due to any cause (up to 195 weeks)

End point values	Chemoradiation: Topotecan plus WBRT	Radiation: WBRT Alone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	236[1]	236[2]		
Units: months				
median (confidence interval 95%)	4 (3.4 to 4.8)	3.6 (3 to 4)		

Notes:

[1] - ITT Population

[2] - ITT Population

Statistical analyses

Statistical analysis title	Anaysis 1
Comparison groups	Chemoradiation: Topotecan plus WBRT v Radiation: WBRT Alone

Number of subjects included in analysis	472
Analysis specification	Pre-specified
Analysis type	superiority[3]
P-value	= 0.1862 [4]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.88
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.73
upper limit	1.07

Notes:

[3] - The hazard ratio is estimated using a Pike estimator. The hazard ratio from a stratified log-rank test is adjusted for RPA class and the number of brain lesions at Screening.

[4] - p-value from a stratified log-rank test is adjusted for Recursive Partitioning Analysis (RPA) class and the number of brain lesions at Screening.

Secondary: Six-month survival

End point title	Six-month survival

End point description:

Six-month survival is defined as the percentage of participants alive at 6 months following randomization. The date of last contact was used for those participants who had not died or were lost to follow-up. These participants were classified as having been censored.

End point type	Secondary

End point timeframe:

Month 6

End point values	Chemoradiation: Topotecan plus WBRT	Radiation: WBRT Alone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	236[5]	236[6]		
Units: percentage of participants	36	28		

Notes:

[5] - ITT Population

[6] - ITT Population

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with a complete response (CR) or a partial response (PR) (central nervous system [CNS]-radiologic)

End point title	Number of participants with a complete response (CR) or a partial response (PR) (central nervous system [CNS]-radiologic)

End point description:

The number of participants achieving either a CR or PR, per World Health Organization (WHO) Criteria, in the CNS was assessed. CR is defined as the complete disappearance of all known measurable (Must be accurately measured in >=1 dimension) and nonmeasurable disease, without clinical, laboratory, or radiological evidence of recurrence for at least 4 weeks. CR may have been defined in participants with measurable and/or non-measurable disease at Screening. PR is defined as at least a 50% decrease in

the sum of the products of the greatest length and perpendicular width of all measurable disease with no clear increase in nonmeasurable disease in participants without measurable disease. In both cases, there must have been no appearance of new disease, and no clinical, laboratory, or radiological evidence of disease progression for at least 4 weeks. Assessment of response was performed by the investigator and was based on unconfirmed responses.

End point type	Secondary

End point timeframe:

From the time of Randomization until the time of CR or PR (up to 75 weeks)

End point values	Chemoradiation: Topotecan plus WBRT	Radiation: WBRT Alone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	236[7]	236[8]		
Units: participants				
Complete response	23	11		
Partial response	63	61		

Notes:

[7] - ITT Population

[8] - ITT Population

Statistical analyses

No statistical analyses for this end point

Secondary: Time to response (TTR) (CNS-radiologic)

End point title	Time to response (TTR) (CNS-radiologic)

End point description:

TTR is defined as the time from Randomization until the first documented evidence of CR or PR in the CNS. CR is defined as the complete disappearance of all known measurable (Must be accurately measured in >=1 dimension) and nonmeasurable disease, without clinical, laboratory, or radiological evidence of recurrence for at least 4 weeks. CR may have been defined in participants with measurable and/or non-measurable disease at Screening. PR is defined as at least a 50% decrease in the sum of the products of the greatest length and perpendicular width of all measurable disease with no clear increase in nonmeasurable disease in participants without measurable disease. In both cases, there must have been no appearance of new disease, and no clinical, laboratory, or radiological evidence of disease progression for at least 4 weeks. Assessment of response was performed by the investigator and was based on unconfirmed responses.

End point type	Secondary

End point timeframe:

From the time of Randomization until the first documented evidence of CR or PR (up to 75 weeks)

End point values	Chemoradiation: Topotecan plus WBRT	Radiation: WBRT Alone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	173[9]	170[10]		
Units: weeks				
median (confidence interval 95%)	8 (7.7 to 8.1)	8.1 (6 to 8.1)		

Notes:

[9] - ITT Population. Only those participants with a CR, PR, or a missing response were assessed.

[10] - ITT Population. Only those participants with a CR, PR, or a missing response were assessed.

Statistical analyses

No statistical analyses for this end point

Secondary: Time to progression (TTP) (CNS-radiologic)

End point title	Time to progression (TTP) (CNS-radiologic)

End point description:

TTP is defined as the time from Randomization until the first documented sign of disease progression in the CNS. Progressive disease (PD) is defined as an increase >=25% in any measurable lesion or, in participants with non-measurable disease only, an estimation of an increase >=25%. In both cases, determination of progression included the appearance of any new lesions, or signification worsening of conditions presumed to be related to malignancy. Participants with clinical or laboratory evidence of possible disease progression were to be evaluated radiologically. TTP was analyzed with censoring for extended loss to follow-up to account for two or more missed assessments before a TTP event. The date of the last adequate CNS assessment before extended loss to follow-up was used for censored participants.

End point type	Secondary

End point timeframe:

From the time of Randomization until the first documented sign of disease progression (up to 75 weeks)

End point values	Chemoradiation: Topotecan plus WBRT	Radiation: WBRT Alone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	236[11]	236[12]		
Units: weeks				
median (confidence interval 95%)	9.7 (8.1 to 13.9)	9.7 (8.3 to 10.9)		

Notes:

[11] - ITT Population

[12] - ITT Population

Statistical analyses

No statistical analyses for this end point

Secondary: Time to progression (TTP) (all sites of disease-radiologic)

End point title	Time to progression (TTP) (all sites of disease-radiologic)

End point description:

TTP is defined as the time from Randomization until the first documented sign of disease progression in all sites of disease. Progressive disease (PD) is defined as an increase >=25% in any measurable lesion or, in participants with non-measurable disease only, an estimation of an increase >=25%. In both cases, determination of progression included the appearance of any new lesions, or signification worsening of conditions presumed to be related to malignancy. Participants with clinical or laboratory evidence of possible disease progression were to be evaluated radiologically. TTP was analyzed with censoring for extended loss to follow-up to account for two or more missed assessments before a TTP event. The date of the last adequate CNS assessment before extended loss to follow-up was used for censored participants.

End point type	Secondary

End point timeframe:

From the time of Randomization until the first documented sign of disease progression (up to 75 weeks)

End point values	Chemoradiation: Topotecan plus WBRT	Radiation: WBRT Alone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	236[13]	236[14]		
Units: weeks				
median (confidence interval 95%)	8 (6.7 to 8.7)	7.7 (6.1 to 8.1)		

Notes:

[13] - ITT Population

[14] - ITT Population

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants who ranked each individual indicated neurological sign and symptom as none, mild, moderate, or severe at Months 1 and 3

End point title	Number of participants who ranked each individual indicated neurological sign and symptom as none, mild, moderate, or severe at Months 1 and 3

End point description:

Neurological signs and symptoms data were derived from a participant-reported diary. The participants were asked to assess the following signs and symptoms on a scale of none, mild, moderate, or severe at Months 1 and 3: headache, problems with balance/coordination (PB/C), leg weakness, arm weakness, loss of feeling/numbness (LofF/N), speech difficulty (SD), confusion, loss of memory (LofM), drowsiness, nausea, vomiting, dizziness, visual problems (VP), seizures, leg/ankle swelling (L/AS), heart burn, difficulty sleeping (DS), tiredness, and appetite/weight gain (A/WG). Only those participants who were assessed for the indicated sign and symptom at the indicated time point were analyzed.

End point type	Secondary

End point timeframe:

Months 1 and 3

End point values	Chemoradiation: Topotecan plus WBRT	Radiation: WBRT Alone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	179[15]	189[16]		
Units: participants				
Headache, Month 1, none, n=179, 189	93	106		
Headache, Month 1, mild, n=179, 189	71	68		
Headache, Month 1, moderate, 179, 189	11	13		
Headache, Month 1, severe, 179, 189	4	2		
Headache, Month 3, none, n=109, 111	69	53		
Headache, Month 3, mild, n=109, 111	33	41		

Headache, Month 3, moderate, n=109, 111	5	14		
Headache, Month 3, severe, n=109, 111	2	3		
PB/C, Month 1, none, n=179, 188	84	79		
PB/C, Month 1, mild, n=179, 188	66	71		
PB/C, Month 1, moderate, n=179, 188	22	30		
PB/C, Month 1, severe, n=179, 188	7	8		
PB/C, Month 3, none, n=109, 111	69	46		
PB/C, Month 3, mild, n=109, 111	28	36		
PB/C, Month 3, moderate, n=109, 111	10	18		
PB/C, Month 3, severe, n=109, 111	2	11		
Leg weakness, Month 1, none, n=179, 188	47	59		
Leg weakness, Month 1, mild, n=179, 188	73	72		
Leg weakness, Month 1, moderate, n=179, 188	41	41		
Leg weakness, Month 1, severe, n=179, 188	18	16		
Leg weakness, Month 3, none, n=109, 111	28	34		
Leg weakness, Month 3, mild, n=109, 111	51	37		
Leg weakness, Month 3, moderate, n=109, 111	20	19		
Leg weakness, Month 3, severe, n=109, 111	10	21		
Arm weakness, Month 1, none, n=179, 188	96	97		
Arm weakness, Month 1, mild, n=179, 188	55	60		
Arm weakness, Month 1, moderate, n=179, 188	23	18		
Arm weakness, Month 1, severe, n=179, 188	5	13		
Arm weakness, Month 3, none, n=109, 111	60	53		
Arm weakness, Month 3, mild, n=109, 111	39	34		
Arm weakness, Month 3, molderate, n=109, 111	8	16		
Arm weakness, Month 3, severe, n=109, 111	2	8		
LofF/N, Month 1, none, n=179, 188	101	111		
LofF/N, Month 1, mild, n=179, 188	53	43		
LofF/N, Month 1, moderate, n=179, 188	17	25		
LofF/N, Month 1, severe, n=179, 188	8	9		
LofF/N, Month 3, none, n=109, 111	73	66		
LofF/N, Month 3, mild, n=109, 111	28	27		
LofF/N, Month 3, moderate, n=109, 111	3	11		
LofF/N, Month 3, severe, n=109, 111	5	7		
SD, Month 1, none, n=179, 188	151	137		
SD, Month 1, mild, n=179, 188	16	40		
SD, Month 1, moderate, n=179, 188	9	9		
SD, Month 1, severe, n=179, 188	3	2		
SD, Month 3, none, n=109, 110	94	78		
SD, Month 3, mild, n=109, 110	11	22		

SD, Month 3, moderate, n=109, 110	2	8		
SD, Month 3, severe, n=109, 110	2	2		
Confusion, Month 1, none, n=179, 188	150	148		
Confusion, Month 1, mild, n=179, 188	20	32		
Confusion, Month 1, moderate, n=179, 188	6	7		
Confusion, Month 1, severe, n=179, 188	3	1		
Confusion, Month 3, none, n=109, 110	99	71		
Confusion, Month 3, mild, n=109, 110	7	29		
Confusion, Month 3, moderate, n=109, 110	2	9		
Confusion, Month 3, severe, n=109, 110	1	1		
LofM, Month 1, none, n=179, 188	149	141		
LofM, Month 1, mild, n=179, 188	20	41		
LofM, Month 1, moderate, n=179, 188	8	5		
LofM, Month 1, severe, n=179, 188	2	1		
LofM, Month 3, none, n=109, 110	93	78		
LofM, Month 3, mild, n=109, 110	14	25		
LofM, Month 3, moderate, n=109, 110	1	6		
LofM, Month 3, severe, n=109, 110	1	1		
Drowsiness, Month 1, none, n=179, 188	90	96		
Drowsiness, Month 1, mild, n=179, 188	55	59		
Drowsiness, Month 1, moderate, n=179, 188	25	26		
Drowsiness, Month 1, severe, n=179, 188	9	7		
Drowsiness, Month 3, none, n=109, 111	50	44		
Drowsiness, Month 3, mild, n=109, 111	42	40		
Drowsiness, Month 3, moderate, n=109, 111	15	15		
Drowsiness, Month 3, severe, n=109, 111	2	12		
Nausea, Month 1, none, n=179, 188	125	142		
Nausea, Month 1, mild, n=179, 188	38	36		
Nausea, Month 1, moderate, n=179, 188	12	10		
Nausea, Month 1, severe, n=179, 188	4	0		
Nausea, Month 3, none, n=109, 111	70	73		
Nausea, Month 3, mild, n=109, 111	31	29		
Nausea, Month 3, moderate, n=109, 111	7	6		
Nausea, Month 3, severe, n=109, 111	1	3		
Vomiting, Month 1, none, n=179, 188	153	164		
Vomiting, Month 1, mild, n=179, 188	20	19		
Vomiting, Month 1, moderate, n=179, 188	4	4		
Vomiting, Month 1, severe, n=179, 188	2	1		
Vomiting, Month 3, none, n=109, 111	89	91		
Vomiting, Month 3, mild, n=109, 111	15	15		
Vomiting, Month 3, moderate, n=109, 111	4	3		
Vomiting, Month 3, severe=109, 111	1	2		
Dizziness, Month 1, none, n=179, 188	96	94		
Dizziness, Month 1, mild, n=179, 188	58	70		

Dizziness, Month 1, moderate, n=179, 188	22	21		
Dizziness, Month 1, severe, n=179, 188	3	3		
Dizziness, Month 3, none, n=109, 111	64	54		
Dizziness, Month 3, mild, n=109, 111	35	36		
Dizziness, Month 3, moderate, n=109, 111	7	14		
Dizziness, Month 3, severe, n=109, 111	3	7		
VP, Month 1, none, n=179, 188	103	117		
VP, Month 1, mild, n=179, 188	54	53		
VP, Month 1, moderate, n=179, 188	17	16		
VP, Month 1, severe, n=179, 188	5	2		
VP, Month 3, none, n=109, 111	72	69		
VP, Month 3, mild, n=109, 111	29	28		
VP, Month 3, moderate, n=109, 111	7	10		
VP, Month 3, severe, n=109, 111	1	4		
Seizures, Month 1, none, n=179, 188	173	179		
Seizures, Month 1, mild, n=179, 188	5	7		
Seizures, Month 1, moderate, n=179, 188	1	2		
Seizures, Month 1, severe, n=179, 188	0	0		
Seizures, Month 3, none, n=109, 110	108	102		
Seizures, Month 3, mild, n=109, 110	0	4		
Seizures, Month 3, moderate, n=109, 110	1	3		
Seizures, Month 3, severe, n=109, 110	0	1		
L/AS, Month 1, none, n=179, 188	141	138		
L/AS, Month 1, mild, n=179, 188	21	29		
L/AS, Month 1, moderate, n=179, 188	12	15		
L/AS, Month 1, severe, n=179, 188	5	6		
L/AS, Month 3, none, n=109, 111	86	85		
L/AS, Month 3, mild, n=109, 111	19	19		
L/AS, Month 3, moderate, n=109, 111	3	6		
L/AS, Month 3, severe, n=109, 111	1	1		
Heartburn, Month 1, none, n=179, 188	142	151		
Heartburn, Month 1, mild, n=179, 188	26	27		
Heartburn, Month 1, moderate, n=179, 188	9	9		
Heartburn, Month 1, severe, n=179, 188	2	1		
Heartburn, Month 3, none, n=109, 111	87	86		
Heartburn, Month 3, mild, n=109, 111	16	18		
Heartburn, Month 3, moderate, n=109, 111	4	6		
Heartburn, Month 3, severe, n=109, 111	2	1		
DS, Month 1, none, n=179, 188	112	109		
DS, Month 1, mild, n=179, 188	41	48		
DS, Month 1, moderate, n=179, 188	15	24		
DS, Month 1, severe, n=179, 188	11	7		
DS, Month 3, none, n=109, 110	78	71		
DS, Month 3, mild, n=109, 110	20	23		
DS, Month 3, moderate, n=109, 110	8	12		
DS, Month 3, severe, n=109, 110	3	4		

Tiredness, Month 1, none, n=179, 188	42	42		
Tiredness, Month 1, mild, n=179, 188	75	85		
Tiredness, Month 1, moderate, n=179, 188	46	44		
Tiredness, Month 1, severe, n=179, 188	16	17		
Tiredness, Month 3, none, n=109, 111	28	21		
Tiredness, Month 3, mild, n=109, 111	52	42		
Tiredness, Month 3, moderate, n=109, 111	19	32		
Tiredness, Month 3, severe, n=109, 111	10	16		
A/WG, Month 1, none, n=179, 188	107	113		
A/WG, Month 1, mild, n=179, 188	42	41		
A/WG, Month 1, moderate, n=179, 188	19	29		
A/WG, Month 1, severe, n=179, 188	11	5		
A/WG, Month 3, none, n=108, 111	71	73		
A/WG, Month 3, mild, n=108, 111	27	23		
A/WG, Month 3, moderate, n=108, 111	4	11		
A/WG, Month 3, severe, n=108, 111	6	4		

Notes:

[15] - ITT Population

[16] - ITT Population

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with the indicated investigator assessment for the neurological sign and symptom of level of consciousness at Baseline, Month 1, and Month 3

End point title	Number of participants with the indicated investigator assessment for the neurological sign and symptom of level of consciousness at Baseline, Month 1, and Month 3

End point description:

The investigator assessed participants for the neurological sign and symptom of level of consciousness and assigned each participant to one of the following categories: normal; somnolence or sedation not interfering with function (not intefering); somnolence or sedation interfering with function, but not activities of daily living (ADLs) (interfering); obtundation or stupor, difficult to arouse, inteferring with ADLs (obtundation or stupor); coma. If no data are presented for a particular status at a particular time point, then no participants had that status at that time point.

End point type	Secondary

End point timeframe:

Baseline, Month 1, and Month 3

End point values	Chemoradiation: Topotecan plus WBRT	Radiation: WBRT Alone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	230[17]	228[18]		
Units: participants				
Baseline, normal, n=230, 228	219	216		
Month 1, normal, n=178, 180	171	169		
Month 3, normal, n=109, 107	102	92		
Baseline, not interfering, n=230, 228	7	9		

Month 1, not interfering, n=178, 180	5	7		
Month 3, not interfering, n=109, 107	3	8		
Baseline, interfering, n=230, 228	3	3		
Month 1, interfering, n=178, 180	0	4		
Month 3, interfering, n=109, 107	3	5		
Baseline, obtundation and stupor, n=230, 228	1	0		
Month 1, obtundation and stupor, n=178, 180	2	0		
Month 3, obtundation and stupor, n=109, 107	1	2		

Notes:

[17] - ITT Population. Only those participants who were assessed at the indicated time point were analyzed.
[18] - ITT Population. Only those participants who were assessed at the indicated time point were analyzed.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with the indicated investigator assessment for the neurological sign and symptom of headache at Baseline, Month 1, and Month 3

End point title	Number of participants with the indicated investigator assessment for the neurological sign and symptom of headache at Baseline, Month 1, and Month 3

End point description:

The investigator (per Common Terminology Criteria for Adverse Events [CTCAE], version 3.0) assessed par. for headache and assigned each par. to one of the following categories:absent, Grade (G) 1, G 2, G 3, G 4, and G 5. Grade refers to the severity of the AE. The CTCAE displays G 1 through 5 with unique clinical descriptions of severity for each AE based on this general guideline: G 1: mild, asymptomatic or mild symptoms, clinical or diagnostic observations only, intervention not indicated; G 2: moderate, minimal, local or noninvasive intervention indicated, limiting age-appropriate instrumental ADL; G 3: severe or medically significant but not immediately life-threatening, hospitalization or prolongation of hospitalization indicated, disabling, limiting self care ADL; G 4: life-threatening consequences, urgent intervention indicated; G 5: death related to AE. If no data are presented for a particular grade and time point, then no par. had an event of that grade at that time point.

End point type	Secondary

End point timeframe:

Baseline, Month 1, and Month 3

End point values	Chemoradiation: Topotecan plus WBRT	Radiation: WBRT Alone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	230[19]	228[20]		
Units: participants				
Baseline, absent, n=230, 228	141	146		
Month 1, absent, n=178, 180	126	127		
Month 3, absent, n=109, 107	85	74		
Baseline, Grade 1, n=230, 228	62	55		
Month 1, Grade 1, n=178, 180	43	38		
Month 3, Grade 1, n=109, 107	17	23		
Baseline, Grade 2, n=230, 228	25	23		
Month 1, Grade 2, n=178, 180	9	14		

Month 3, Grade 2, n=109, 107	7	10		
Baseline, Grade 3, n=230, 228	2	4		
Month 1, Grade 3, n=178, 180	0	1		

Notes:

[19] - ITT Population. Only those participants who were assessed at the indicated time point were analyzed.
[20] - ITT Population. Only those participants who were assessed at the indicated time point were analyzed.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with the indicated investigator assessment for the neurological sign and symptom of dizziness/lightheadedness at Baseline, Month 1, and Month 3

End point title	Number of participants with the indicated investigator assessment for the neurological sign and symptom of dizziness/lightheadedness at Baseline, Month 1, and Month 3

End point description:

The investigator (per CTCAE, version 3.0) assessed participants for dizziness/lightheadedness and assigned each participant to one of the following categories: absent, G 1, G 2, G 3, G 4, and G 5. Grade refers to the severity of the AE. The CTCAE displays G 1 through 5 with unique clinical descriptions of severity for each AE based on this general guideline: G 1: mild, asymptomatic or mild symptoms, clinical or diagnostic observations only, intervention not indicated; G 2: moderate, minimal, local or noninvasive intervention indicated, limiting age-appropriate instrumental ADL; G 3: severe or medically significant but not immediately life-threatening, hospitalization or prolongation of hospitalization indicated, disabling, limiting self care ADL; G 4: life-threatening consequences, urgent intervention indicated; G 5: death related to AE. If no data are presented for a particular grade at a particular time point, then no participants had an event of that grade at that time point.

End point type	Secondary

End point timeframe:

Baseline, Month 1, and Month 3

End point values	Chemoradiation: Topotecan plus WBRT	Radiation: WBRT Alone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	230[21]	228[22]		
Units: participants				
Baseline, absent, n=230, 228	160	151		
Month 1, absent, n=178, 180	124	128		
Month 3, absent, n=109, 107	76	76		
Baseline, Grade 1, n=230, 228	45	47		
Month 1, Grade 1, n=178, 180	44	36		
Month 3, Grade 1, n=109, 107	21	20		
Baseline, Grade 2, n=230, 228	21	26		
Month 1, Grade 2, n=178, 180	7	14		
Month 3, Grade 2, n=109, 107	9	9		
Baseline, Grade 3, n=230, 228	4	4		
Month 1, Grade 3, n=178, 180	3	2		
Month 3, Grade 3, n=109, 107	3	2		

Notes:

[21] - ITT Population. Only those participants who were assessed at the indicated time point were analyzed.
[22] - ITT Population. Only those participants who were assessed at the indicated time point were analyzed.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with the indicated investigator assessment for the neurological sign and symptom of vertigo at Baseline, Month 1, and Month 3

End point title	Number of participants with the indicated investigator assessment for the neurological sign and symptom of vertigo at Baseline, Month 1, and Month 3

End point description:

The investigator (per CTCAE, version 3.0) assessed participants for vertigo and assigned each participant to one of the following categories: absent, G 1, G 2, G 3, G 4, and G 5. Grade refers to the severity of the AE. The CTCAE displays G 1 through 5 with unique clinical descriptions of severity for each AE based on this general guideline: G 1: mild, asymptomatic or mild symptoms, clinical or diagnostic observations only, intervention not indicated; G 2: moderate, minimal, local or noninvasive intervention indicated, limiting age-appropriate instrumental ADL; G 3: severe or medically significant but not immediately life-threatening, hospitalization or prolongation of hospitalization indicated, disabling, limiting self care ADL; G 4: life-threatening consequences, urgent intervention indicated; G 5: death related to AE. If no data are presented for a particular grade at a particular time point, then no participants had an event of that grade at that time point.

End point type	Secondary

End point timeframe:

Baseline, Month 1, and Month 3

End point values	Chemoradiation: Topotecan plus WBRT	Radiation: WBRT Alone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	230[23]	228[24]		
Units: participants				
Baseline, absent, n=230, 228	180	173		
Month 1, absent, n=178, 180	148	150		
Month 3, absent, n=109, 107	90	86		
Baseline, Grade 1, n=230, 228	26	30		
Month 1, Grade 1, n=178, 180	19	19		
Month 3, Grade 1, n=109, 107	14	13		
Baseline, Grade 2, n=230, 228	19	22		
Month 1, Grade 2, n=178, 180	7	9		
Month 3, Grade 2, n=109, 107	4	6		
Baseline, Grade 3, n=230, 228	5	3		
Month 1, Grade 3, n=178, 180	3	2		
Month 3, Grade 3, n=109, 107	1	2		
Month 1, Grade 4, n=178, 180	1	0		

Notes:

[23] - ITT Population. Only those participants who were assessed at the indicated time point were analyzed.
[24] - ITT Population. Only those participants who were assessed at the indicated time point were analyzed.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with the indicated investigator assessment for the neurological sign and symptom of nausea/vomiting at Baseline, Month 1, and Month 3

End point title	Number of participants with the indicated investigator assessment for the neurological sign and symptom of nausea/vomiting at Baseline, Month 1, and Month 3

End point description:

The investigator (per CTCAE, version 3.0) assessed participants for nausea/vomiting and assigned each participant to one of the following categories: absent, G 1, G 2, G 3, G 4, and G 5. Grade refers to the severity of the AE. The CTCAE displays G 1 through 5 with unique clinical descriptions of severity for each AE based on this general guideline: G 1: mild, asymptomatic or mild symptoms, clinical or diagnostic observations only, intervention not indicated; G 2: moderate, minimal, local or noninvasive intervention indicated, limiting age-appropriate instrumental ADL; G 3: severe or medically significant but not immediately life-threatening, hospitalization or prolongation of hospitalization indicated, disabling, limiting self care ADL; G 4: life-threatening consequences, urgent intervention indicated; G 5: death related to AE. If no data are presented for a particular grade at a particular time point, then no participants had an event of that grade at that time point.

End point type	Secondary

End point timeframe:

Baseline, Month 1, and Month 3

End point values	Chemoradiation: Topotecan plus WBRT	Radiation: WBRT Alone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	230[25]	228[26]		
Units: participants				
Baseline, absent, n=230, 228	203	192		
Month 1, absent, n=178, 180	151	162		
Month 3, absent, n=109, 107	88	93		
Baseline, Grade 1, n=230, 228	19	22		
Month 1, Grade 1, n=178, 180	20	15		
Month 3, Grade 1, n=109, 107	14	11		
Baseline, Grade 2, n=230, 228	7	10		
Month 1, Grade 2, n=178, 180	6	3		
Month 3, Grade 2, n=109, 107	6	3		
Baseline, Grade 3, n=230, 228	1	4		
Month 1, Grade 3, n=178, 180	1	0		
Month 3, Grade 5, n=109, 107	1	0		

Notes:

[25] - ITT Population. Only those participants who were assessed at the indicated time point were analyzed.

[26] - ITT Population. Only those participants who were assessed at the indicated time point were analyzed.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with the indicated investigator assessment for the neurological sign and symptom of visual problem at Baseline, Month 1, and Month 3

End point title	Number of participants with the indicated investigator assessment for the neurological sign and symptom of visual problem at Baseline, Month 1, and Month 3

End point description:

The investigator (per CTCAE, version 3.0) assessed participants for visual problem and assigned each participant to one of the following categories: absent, G 1, G 2, G 3, G 4, and G 5. Grade refers to the severity of the AE. The CTCAE displays G 1 through 5 with unique clinical descriptions of severity for each AE based on this general guideline: G 1: mild, asymptomatic or mild symptoms, clinical or diagnostic observations only, intervention not indicated; G 2: moderate, minimal, local or noninvasive intervention indicated, limiting age-appropriate instrumental ADL; G 3: severe or medically significant but not immediately life-threatening, hospitalization or prolongation of hospitalization indicated, disabling, limiting self care ADL; G 4: life-threatening consequences, urgent intervention indicated; G 5: death related to AE. If no data are presented for a particular grade at a particular time point, then no participants had an event of that grade at that time point.

End point type	Secondary

End point timeframe:

Baseline, Month 1, and Month 3

End point values	Chemoradiation: Topotecan plus WBRT	Radiation: WBRT Alone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	230[27]	228[28]		
Units: participants				
Baseline, absent, n=230, 228	181	189		
Month 1, absent, n=178, 180	148	154		
Month 3, absent, n=109, 107	93	93		
Baseline, Grade 1, n=230, 228	22	25		
Month 1, Grade 1, n=178, 180	16	19		
Month 3, Grade 1, n=109, 107	12	10		
Baseline, Grade 2, n=230, 228	20	13		
Month 1, Grade 2, n=178, 180	11	6		
Month 3, Grade 2, n=109, 107	4	3		
Baseline, Grade 3, n=230, 228	5	1		
Month 1, Grade 3, n=178, 180	2	1		
Month 3, Grade 3, n=109, 107	0	1		
Baseline, Grade 4, n=230, 228	2	0		
Month 1, Grade 4, n=178, 180	1	0		

Notes:

[27] - ITT Population. Only those participants who were assessed at the indicated time point were analyzed.
[28] - ITT Population. Only those participants who were assessed at the indicated time point were analyzed.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with the indicated investigator assessment for the neurological sign and symptom of seizure at Baseline, Month 1, and Month 3

End point title	Number of participants with the indicated investigator assessment for the neurological sign and symptom of seizure at Baseline, Month 1, and Month 3

End point description:

The investigator (per CTCAE, version 3.0) assessed participants for seizure and assigned each participant to one of the following categories: absent, G 1, G 2, G 3, G 4, and G 5. Grade refers to the severity of the AE. The CTCAE displays G 1 through 5 with unique clinical descriptions of severity for each AE based on this general guideline: G 1: mild, asymptomatic or mild symptoms, clinical or diagnostic observations only, intervention not indicated; G 2: moderate, minimal, local or noninvasive intervention indicated, limiting age-appropriate instrumental ADL; G 3: severe or medically significant but not immediately life-threatening, hospitalization or prolongation of hospitalization indicated, disabling, limiting self care ADL; G 4: life-threatening consequences, urgent intervention indicated; G 5: death related to AE. If no data are presented for a particular grade at a particular time point, then no participants had an event of that grade at that time point.

End point type	Secondary

End point timeframe:

Baseline, Month 1, and Month 3

End point values	Chemoradiation: Topotecan plus WBRT	Radiation: WBRT Alone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	230[29]	228[30]		
Units: participants				
Baseline, absent, n=230, 228	218	216		
Month 1, absent, n=178, 180	175	178		
Month 3, absent, n=109, 107	109	101		
Baseline, Grade 1, n=230, 228	4	6		
Month 1, Grade 1, n=178, 180	2	1		
Month 3, Grade 1, n=109, 107	0	4		
Baseline, Grade 2, n=230, 228	6	6		
Month 1, Grade 2, n=178, 180	1	1		
Month 3, Grade 2, n=109, 107	0	2		
Baseline, Grade 3, n=230, 228	1	0		
Baseline, Grade 4, n=230, 228	1	0		

Notes:

[29] - ITT Population. Only those participants who were assessed at the indicated time point were analyzed.
[30] - ITT Population. Only those participants who were assessed at the indicated time point were analyzed.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with the indicated investigator assessment for the neurological sign and symptom of other neurological symptoms at Baseline, Month 1, and Month 3

End point title	Number of participants with the indicated investigator assessment for the neurological sign and symptom of other neurological symptoms at Baseline, Month 1, and Month 3

End point description:

The investigator (per CTCAE, version 3.0) assessed participants for other neurological symptoms and assigned each participant to one of the following categories: absent, G 1, G 2, G 3, G 4, and G 5. Grade refers to the severity of the AE. The CTCAE displays G 1 through 5 with unique clinical descriptions of severity for each AE based on this general guideline: G 1: mild, asymptomatic or mild symptoms, clinical or diagnostic observations only, intervention not indicated; G 2: moderate, minimal, local or noninvasive intervention indicated, limiting age-appropriate instrumental ADL; G 3: severe or medically significant but not immediately life-threatening, hospitalization or prolongation of hospitalization indicated, disabling, limiting self care ADL; G 4: life-threatening consequences, urgent intervention indicated; G 5: death related to AE. If no data are presented for a particular grade at a particular time point, then no participants had an event of that grade at that time point.

End point type	Secondary

End point timeframe:

Baseline, Month 1, and Month 3

End point values	Chemoradiation: Topotecan plus WBRT	Radiation: WBRT Alone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	229[31]	228[32]		
Units: participants				
Baseline, absent, n=229, 228	219	214		
Month 1, absent, n=177, 180	165	171		
Month 3, absent, n=109, 107	99	101		
Baseline, Grade 1, n=229, 228	2	5		
Month 1, Grade 1, n=177, 180	2	6		
Month 3, Grade 1, n=109, 107	6	5		
Baseline, Grade 2, n=229, 228	7	8		
Month 1, Grade 2, n=177, 180	8	1		
Month 3, Grade 2, n=109, 107	3	1		
Baseline, Grade 3, n=229, 228	1	1		
Month 1, Grade 3, n=177, 180	2	1		
Month 1, Grade 4, n=177, 180	0	1		
Month 3, Grade 5, n=109, 107	1	0		

Notes:

[31] - ITT Population. Only those participants who were assessed at the indicated time point were analyzed.
[32] - ITT Population. Only those participants who were assessed at the indicated time point were analyzed.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with the indicated investigator assessment of cranial nerves II-XII at Baseline, Month 1, and Month 3

End point title	Number of participants with the indicated investigator assessment of cranial nerves II-XII at Baseline, Month 1, and Month 3

End point description:

The investigator assessed participants' status of cranial nerves II-XII and assigned each participant to one of the following categories: normal; present, not interfering with ADLs; present, interfering with ADLs; life threatening, disabling. If no data are presented for a particular grade at a particular time point, then no participants had an event of that grade at that time point.

End point type	Secondary

End point timeframe:

Baseline, Month 1, and Month 3

End point values	Chemoradiation: Topotecan plus WBRT	Radiation: WBRT Alone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	229[33]	225[34]		
Units: participants				
Baseline, normal, n=229, 225	218	211		
Month 1, normal, n=177, 179	172	169		
Month 3, normal, n=109, 107	106	102		
Baseline, present, not interfering, n=229, 225	11	10		
Month 1, present, not interfering, n=177, 179	4	6		
Month 3, present, not interfering, n=109, 107	3	2		
Baseline, present, interfering, n=229, 225	0	4		
Month 1, present, interfering, n=177, 179	1	4		
Month 3, present, interfering, n=109, 107	0	3		

Notes:

[33] - ITT Population. Only those participants who were assessed at the indicated time point were analyzed.
[34] - ITT Population. Only those participants who were assessed at the indicated time point were analyzed.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with the indicated investigator assessment of language (dysphasia or aphasia) at Baseline, Month 1, and Month 3

End point title	Number of participants with the indicated investigator assessment of language (dysphasia or aphasia) at Baseline, Month 1, and Month 3

End point description:

The investigator assessed participants' status of language (dysphasia or aphasia) and assigned each participant to one of the following categories: absent; awareness of receptive or expressive aphasia, not impairing ability to communicate (not impaired); receptive or expressive dysphasia, impairing ability to communicate (impaired); inability to communicate (unable). If no data are presented for a particular grade at a particular time point, then no participants had an event of that grade at that time point.

End point type	Secondary

End point timeframe:

Baseline, Month 1, and Month 3

End point values	Chemoradiation: Topotecan plus WBRT	Radiation: WBRT Alone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	230[35]	228[36]		
Units: participants				
Baseline, absent, n=230, 228	211	215		
Month 1, absent, n=178, 180	169	173		
Month 3, absent, n=109, 107	105	98		
Baseline, not impaired, n=230, 228	15	10		
Month 1, not impaired, n=178, 180	6	5		
Month 3, not impaired, n=109, 107	3	7		
Baseline, impaired, n=230, 228	3	3		
Month 1, impaired, n=178, 180	3	2		
Month 3, impaired, n=109, 107	1	0		
Baseline, unable, n=230, 228	1	0		
Month 3, unable, n=109, 107	0	2		

Notes:

[35] - ITT Population. Only those participants who were assessed at the indicated time point were analyzed.
[36] - ITT Population. Only those participants who were assessed at the indicated time point were analyzed.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with the indicated investigator assessment of strength (right upper extremity) at Baseline, Month 1, and Month 3

End point title	Number of participants with the indicated investigator assessment of strength (right upper extremity) at Baseline, Month 1, and Month 3

End point description:

The investigator assessed participants' status of strength (right upper extremity) and assigned each participant to one of the following categories: normal; Grade 1, asymptomatic with weakness on physical examination; Grade 2, symptomatic and interfering with function, but not interfering with ADLs; Grade 3, symptomatic and interfering with ADLs; Grade 4: bedridden or disabling. If no data are presented for a particular grade at a particular time point, then no participants had an event of that grade at that time point.

End point type	Secondary

End point timeframe:

Baseline, Month 1, and Month 3

End point values	Chemoradiation: Topotecan plus WBRT	Radiation: WBRT Alone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	230[37]	228[38]		
Units: participants				
Baseline, normal, n=230, 228	203	195		
Month 1, normal, n=178, 179	153	159		
Month 3, normal, n=109, 107	93	89		
Baseline, Grade 1, n=230, 228	15	16		
Month 1, Grade 1, n=178, 179	13	12		
Month 3, Grade 1, n=109, 107	10	10		
Baseline, Grade 2, n=230, 228	6	12		
Month 1, Grade 2, n=178, 179	6	5		
Month 3, Grade 2, n=109, 107	4	5		
Baseline, Grade 3, n=230, 228	5	5		
Month 1, Grade 3, n=178, 179	4	2		
Month 3, Grade 3, n=109, 107	2	3		
Baseline, Grade 4, n=230, 228	1	0		
Month 1, Grade 4, n=178, 179	2	1		

Notes:

[37] - ITT Population. Only those participants who were assessed at the indicated time point were analyzed.
[38] - ITT Population. Only those participants who were assessed at the indicated time point were analyzed.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with the indicated investigator assessment of strength (left upper extremity) at Baseline, Month 1, and Month 3

End point title	Number of participants with the indicated investigator assessment of strength (left upper extremity) at Baseline, Month 1, and Month 3

End point description:

The investigator assessed participants' status of strength (left upper extremity) and assigned each participant to one of the following categories: normal; Grade 1, asymptomatic with weakness on physical examination; Grade 2, symptomatic and interfering with function, but not interfering with ADLs; Grade 3, symptomatic and interfering with ADLs; Grade 4: bedridden or disabling. If no data are presented for a particular grade at a particular time point, then no participants had an event of that grade at that time point.

End point type	Secondary

End point timeframe:

Baseline, Month 1, and Month 3

End point values	Chemoradiation: Topotecan plus WBRT	Radiation: WBRT Alone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	230[39]	228[40]		
Units: participants				
Baseline, normal, n=230, 228	197	202		

Month 1, normal, n=178, 179	149	157		
Month 3, normal, n=109, 107	90	86		
Baseline, Grade 1, n=230, 228	16	13		
Month 1, Grade 1, n=178, 179	16	13		
Month 3, Grade 1, n=109, 107	10	11		
Baseline, Grade 2, n=230, 228	11	8		
Month 1, Grade 2, n=178, 179	8	5		
Month 3, Grade 2, n=109, 107	6	5		
Baseline, Grade 3, n=230, 228	6	4		
Month 1, Grade 3, n=178, 179	3	2		
Month 3, Grade 3, n=109, 107	3	4		
Baseline, Grade 4, n=230, 228	0	1		
Month 1, Grade 4, n=178, 179	2	2		
Month 3, Grade 4, n=109, 107	0	1		

Notes:

[39] - ITT Population. Only those participants who were assessed at the indicated time point were analyzed.
[40] - ITT Population. Only those participants who were assessed at the indicated time point were analyzed.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with the indicated investigator assessment of strength (right lower extremity) at Baseline, Month 1, and Month 3

End point title	Number of participants with the indicated investigator assessment of strength (right lower extremity) at Baseline, Month 1, and Month 3

End point description:

The investigator assessed participants' status of strength (right lower extremity) and assigned each participant to one of the following categories: normal; Grade 1, asymptomatic with weakness on physical examination; Grade 2, symptomatic and interfering with function, but not interfering with ADLs; Grade 3, symptomatic and interfering with ADLs; Grade 4: bedridden or disabling. If no data are presented for a particular grade at a particular time point, then no participants had an event of that grade at that time point.

End point type	Secondary

End point timeframe:

Baseline, Month 1, and Month 3

End point values	Chemoradiation: Topotecan plus WBRT	Radiation: WBRT Alone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	230[41]	228[42]		
Units: participants				
Baseline, normal, n=230, 228	196	189		
Month 1, normal, n=178, 180	137	145		
Month 3, normal, n=109, 107	81	80		
Baseline, Grade 1, n=230, 228	20	19		
Month 1, Grade 1, n=178, 180	17	15		
Month 3, Grade 1, n=109, 107	12	11		
Baseline, Grade 2, n=230, 228	9	16		

Month 1, Grade 2, n=178, 180	11	19		
Month 3, Grade 2, n=109, 107	11	11		
Baseline, Grade 3, n=230, 228	3	4		
Month 1, Grade 3, n=178, 180	9	0		
Month 3, Grade 3, n=109, 107	4	3		
Baseline, Grade 4, n=230, 228	2	0		
Month 1, Grade 4, n=178, 180	4	1		
Month 3, Grade 4, n=109, 107	1	2		

Notes:

[41] - ITT Population. Only those participants who were assessed at the indicated time point were analyzed.
[42] - ITT Population. Only those participants who were assessed at the indicated time point were analyzed.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with the indicated investigator assessment of strength (left lower extremity) at Baseline, Month 1, and Month 3

End point title	Number of participants with the indicated investigator assessment of strength (left lower extremity) at Baseline, Month 1, and Month 3

End point description:

The investigator assessed participants' status of strength (left lower extremity) and assigned each participant to one of the following categories: normal; Grade 1, asymptomatic with weakness on physical examination; Grade 2, symptomatic and interfering with function, but not interfering with ADLs; Grade 3, symptomatic and interfering with ADLs; Grade 4: bedridden or disabling. If no data are presented for a particular grade at a particular time point, then no participants had an event of that grade at that time point.

End point type	Secondary

End point timeframe:

Baseline, Month 1, and Month 3

End point values	Chemoradiation: Topotecan plus WBRT	Radiation: WBRT Alone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	230[43]	228[44]		
Units: participants				
Baseline, normal, n=230, 228	182	190		
Month 1, normal, n=178, 179	128	143		
Month 3, normal, n=109, 107	76	73		
Baseline, Grade 1, n=230, 228	28	18		
Month 1, Grade 1, n=178, 179	26	13		
Month 3, Grade 1, n=109, 107	11	11		
Baseline, Grade 2, n=230, 228	15	15		
Month 1, Grade 2, n=178, 179	11	17		
Month 3, Grade 2, n=109, 107	14	14		
Baseline, Grade 3, n=230, 228	4	3		
Month 1, Grade 3, n=178, 179	10	4		
Month 3, Grade 3, n=109, 107	6	5		
Baseline, Grade 4, n=230, 228	1	2		

Month 1, Grade 4, n=178, 179	3	2		
Month 3, Grade 4, n=109, 107	2	4		

Notes:

[43] - ITT Population. Only those participants who were assessed at the indicated time point were analyzed.
[44] - ITT Population. Only those participants who were assessed at the indicated time point were analyzed.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with the indicated investigator assessment of sensation at Baseline, Month 1, and Month 3

End point title	Number of participants with the indicated investigator assessment of sensation at Baseline, Month 1, and Month 3

End point description:

The investigator assessed participants' status of sensation and assigned each participant to one of the following categories: normal; loss of deep tendon reflexes or paresthesia, but not interfering with function (not interfering with function); objective sensory loss or paresthesia interfering with function, but not interfering with ADLs (interfering with function); sensory loss or paresthesia interfering with ADLs (intefering with ADLs); permanent sensory loss that interferes with function (permanent sensory loss). If no data are presented for a particular grade at a particular time point, then no participants had an event of that grade at that time point.

End point type	Secondary

End point timeframe:

Baseline, Month 1, and Month 3

End point values	Chemoradiation: Topotecan plus WBRT	Radiation: WBRT Alone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	230[45]	228[46]		
Units: participants				
Baseline (BL), normal, n=230, 228	197	192		
Month (M) 1, normal, n=178, 180	144	159		
Month 3, normal, n=109, 107	100	94		
BL, not interfering with function, n=230, 228	26	26		
M 1, not interfering with function, n=178, 180	22	15		
M 3, not interfering with function, n=109, 107	5	9		
BL, interfering with function, n=230, 228	3	6		
M 1, interfering with function, n=178, 180	7	4		
M 3, interfering with function, n=109, 107	2	2		
Baseline, interfering with ADLs, n=230, 228	4	3		
Month 1, interfering with ADLs, n=178, 180	5	2		
Month 3, interfering with ADLs, n=109, 107	2	2		

Baseline, permanent sensory loss, n=230, 228	0	1		

Notes:

[45] - ITT Population. Only those participants who were assessed at the indicated time point were analyzed.
[46] - ITT Population. Only those participants who were assessed at the indicated time point were analyzed.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with the indicated investigator assessment of ataxia (right upper extremity: finger to nose testing) at Baseline, Month 1, and Month 3

End point title	Number of participants with the indicated investigator assessment of ataxia (right upper extremity: finger to nose testing) at Baseline, Month 1, and Month 3

End point description:

The investigator assessed participants' status of ataxia (right upper extremity: finger to nose testing) and assigned each participant to one of the following categories: normal; Grade 1, asymptomatic but abnormal on physical examination, and not interfering with function; Grade 2, mild symptoms interfering with function, but not interfering with ADLs; Grade 3, moderate symptoms interfering with ADLs; Grade 4, bedridden or disabling. If no data are presented for a particular grade at a particular time point, then no participants had an event of that grade at that time point.

End point type	Secondary

End point timeframe:

Baseline, Month 1, and Month 3

End point values	Chemoradiation: Topotecan plus WBRT	Radiation: WBRT Alone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	229[47]	228[48]		
Units: participants				
Baseline, normal, n=229, 228	206	198		
Month 1, normal, n=178, 179	166	166		
Month 3, normal, n=109, 107	103	95		
Baseline, Grade 1, n=229, 228	13	17		
Month 1, Grade 1, n=178, 179	7	6		
Month 3, Grade 1, n=109, 107	6	5		
Baseline, Grade 2, n=229, 228	5	12		
Month 1, Grade 2, n=178, 179	3	6		
Month 3, Grade 2, n=109, 107	0	5		
Baseline, Grade 3, n=229, 228	3	1		
Month 3, Grade 3, n=109, 107	0	1		
Baseline, Grade 4, n=229, 228	2	0		
Month 1, Grade 4, n=178, 179	2	1		
Month 3, Grade 4, n=109, 107	0	1		

Notes:

[47] - ITT Population. Only those participants who were assessed at the indicated time point were analyzed.
[48] - ITT Population. Only those participants who were assessed at the indicated time point were

analyzed.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with the indicated investigator assessment of ataxia (left upper extremity: finger to nose testing) at Baseline, Month 1, and Month 3

End point title	Number of participants with the indicated investigator assessment of ataxia (left upper extremity: finger to nose testing) at Baseline, Month 1, and Month 3

End point description:

The investigator assessed participants' status of ataxia (left upper extremity: finger to nose testing) and assigned each participant to one of the following categories: normal; Grade 1, asymptomatic but abnormal on physical examination, and not interfering with function; Grade 2, mild symptoms interfering with function, but not interfering with ADLs; Grade 3, moderate symptoms interfering with ADLs; Grade 4, bedridden or disabling. If no data are presented for a particular grade at a particular time point, then no participants had an event of that grade at that time point.

End point type	Secondary

End point timeframe:

Baseline, Month 1, and Month 3

End point values	Chemoradiation: Topotecan plus WBRT	Radiation: WBRT Alone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	230[49]	227[50]		
Units: participants				
Baseline, normal, n=230, 227	199	201		
Month 1, normal, n=178, 178	156	162		
Month 3, normal, n=109, 107	97	94		
Baseline, Grade 1, n=230, 227	15	13		
Month 1, Grade 1, n=178, 178	14	9		
Month 3, Grade 1, n=109, 107	10	6		
Baseline, Grade 2, n=230, 227	8	7		
Month 1, Grade 2, n=178, 178	6	3		
Month 3, Grade 2, n=109, 107	2	3		
Baseline, Grade 3, n=230, 227	8	4		
Month 1, Grade 3, n=178, 178	0	3		
Month 3, Grade 3, n=109, 107	0	1		
Baseline, Grade 4, n=230, 227	0	2		
Month 1, Grade 4, n=178, 178	2	1		
Month 3, Grade 4, n=109, 107	0	3		

Notes:

[49] - ITT Population. Only those participants who were assessed at the indicated time point were analyzed.

[50] - ITT Population. Only those participants who were assessed at the indicated time point were analyzed.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with the indicated investigator assessment of ataxia (gait) at Baseline, Month 1, and Month 3

End point title	Number of participants with the indicated investigator assessment of ataxia (gait) at Baseline, Month 1, and Month 3

End point description:

The investigator assessed participants' status of ataxia (gait) and assigned each participant to one of the following categories: normal; Grade 1, asymptomatic but abnormal on physical examination, and not interfering with function; Grade 2, mild symptoms interfering with function, but not interfering with ADLs; Grade 3, moderate symptoms interfering with ADLs; Grade 4, bedridden or disabling. If no data are presented for a particular grade at a particular time point, then no participants had an event of that grade at that time point.

End point type	Secondary

End point timeframe:

Baseline, Month 1, and Month 3

End point values	Chemoradiation: Topotecan plus WBRT	Radiation: WBRT Alone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	230[51]	227[52]		
Units: participants				
Baseline, normal, n=230, 227	172	178		
Month 1, normal, n=178, 179	138	147		
Month 3, normal, n=108, 107	85	76		
Baseline, Grade 1, n=230, 227	13	22		
Month 1, Grade 1, n=178, 179	16	13		
Month 3, Grade 1, n=108, 107	9	10		
Baseline, Grade 2, n=230, 227	37	20		
Month 1, Grade 2, n=178, 179	14	14		
Month 3, Grade 2, n=108, 107	9	12		
Baseline, Grade 3, n=230, 227	6	6		
Month 1, Grade 3, n=178, 179	7	3		
Month 3, Grade 3, n=108, 107	4	5		
Baseline, Grade 4, n=230, 227	2	1		
Month 1, Grade 4, n=178, 179	3	2		
Month 3, Grade 4, n=108, 107	1	4		

Notes:

[51] - ITT Population. Only those participants who were assessed at the indicated time point were analyzed.
[52] - ITT Population. Only those participants who were assessed at the indicated time point were analyzed.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with the indicated investigator assessment of ataxia (balance) at Baseline, Month 1, and Month 3

End point title	Number of participants with the indicated investigator assessment of ataxia (balance) at Baseline, Month 1, and Month 3

End point description:

The investigator assessed participants' status of ataxia (balance) and assigned each participant to one of the following categories: normal; Grade 1, asymptomatic but abnormal on physical examination, and not interfering with function; Grade 2, mild symptoms interfering with function, but not interfering with ADLs; Grade 3, moderate symptoms interfering with ADLs; Grade 4, bedridden or disabling. If no data are presented for a particular grade at a particular time point, then no participants had an event of that grade at that time point.

End point type	Secondary

End point timeframe:

Baseline, Month 1, and Month 3

End point values	Chemoradiation: Topotecan plus WBRT	Radiation: WBRT Alone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	230[53]	228[54]		
Units: participants				
Baseline, normal, n=230, 228	153	152		
Month 1, normal, n=178, 178	131	128		
Month 3, normal, n=108, 107	78	75		
Baseline, Grade 1, n=230, 228	37	44		
Month 1, Grade 1, n=178, 178	23	28		
Month 3, Grade 1, n=108, 107	17	13		
Baseline, Grade 2, n=230, 228	27	23		
Month 1, Grade 2, n=178, 178	13	16		
Month 3, Grade 2, n=108, 107	8	9		
Baseline, Grade 3, n=230, 228	10	7		
Month 1, Grade 3, n=178, 178	8	5		
Month 3, Grade 3, n=108, 107	4	5		
Baseline, Grade 4, n=230, 228	3	2		
Month 1, Grade 4, n=178, 178	3	1		
Month 3, Grade 4, n=108, 107	1	5		

Notes:

[53] - ITT Population. Only those participants who were assessed at the indicated time point were analyzed.
[54] - ITT Population. Only those participants who were assessed at the indicated time point were analyzed.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with any adverse event (AE; both serious and non-serious) or serious adverse event (SAE)

End point title	Number of participants with any adverse event (AE; both serious and non-serious) or serious adverse event (SAE)

End point description:

An AE is defined as any untoward medical occurrence in a patient or clinical investigation subject, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. An SAE is defined as any untoward medical occurrence that, at any dose: results in death; is life threatening; requires hospitalization or prolongation of existing hospitalization; results in disability/incapacity; is a congenital anomaly/birth defect. For a list of all SAEs and AEs , see the SAE/AE module of this results summary. Participants were analyzed by the actual treatment received, even if this differed from the treatment to which they were randomized.

End point type	Secondary

End point timeframe:

From Randomization until the last clinic visit associated with the study, up until 35 days after the start of the last course of treatment (up to 75 weeks)

End point values	Chemoradiation: Topotecan plus WBRT	Radiation: WBRT Alone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	235[55]	233[56]		
Units: participants				
AE	204	148		
SAE	96	43		

Notes:

[55] - Modified ITT Population: all randomized par. who received at least one dose of randomized therapy.
[56] - Modified ITT Population: all randomized par. who received at least one dose of randomized therapy.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with the indicated worst-case change from Baseline in the indicated chemistry parameters with respect to the normal range

End point title	Number of participants with the indicated worst-case change from Baseline in the indicated chemistry parameters with respect to the normal range

End point description:

The worst-case change from Baseline in chemistry parameters was measured as decrease to low (DTL), change to normal or no change (CTN/NC), or increase to high (ITH). The worst-case change value could have been measured at any point during the on-therapy period. Participants are counted twice if the participant "Decreased to Low" and "Increased to High" during the on-therapy period. Modified ITT Population. Only those participants with available laboratory values (indicated by the "n" in the category titles) were analyzed. Different participants may have been analyzed for different parameters; therefore, the overall number of participants analyzed reflects everyone in the Modified ITT Population.

End point type	Secondary

End point timeframe:

From Randomization until the last clinic visit associated with the study, up until 35 days after the start of the last course of treatment (up to 75 weeks)

End point values	Chemoradiation: Topotecan plus WBRT	Radiation: WBRT Alone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	235[57]	233[58]		
Units: participants				
Chloride, DTL, n=169, 171	32	21		
Chloride, CTN/NC, n=169, 171	116	144		
Chloride, ITH, n=169, 171	22	6		
Creatinine clearance, DTL, n=159, 145	26	9		
Creatinine clearance, CTN/NC, n=159, 145	121	134		
Creatinine clearance, ITH, n=159, 145	15	2		
Lactate dehydrogenase, DTL, n=169, 168	8	1		
Lactate dehydrogenase, CTN/NC, n=169, 168	117	127		
Lactate dehydrogenase, ITH, n=169, 168	47	40		
Total protein, DTL, n=171, 175	48	36		
Total protein, CTN/NC, n=171, 175	119	137		
Total protein, ITH, n=171, 175	4	2		
Urea/blood urea nitrogen, DTL, n=178, 179	7	4		
Urea/blood urea nitrogen, CTN/NC, n=178, 179	139	152		
Urea/blood urea nitrogen, ITH, n=178, 179	33	24		
Uric acid, DTL, n=159, 152	21	12		
Uric acid, CTN/NC, n=159, 152	125	134		
Uric acid, ITH, n=159, 152	13	6		
Basophils, DTL, n=215, 211	7	1		
Basophils, CTN/NC, n=215, 211	186	200		
Basophils, ITH, n=215, 211	25	10		
Eosinophils, DTL, n=214, 211	28	12		
Eosinophils, CTN/NC, n=214, 211	182	191		
Eosinophils, ITH, n=214, 211	4	8		
Hematocrit, DTL, n=215, 212	98	38		
Hematocrit, CTN/NC, n=215, 212	117	169		
Hematocrit, ITH, n=215, 212	1	6		
Monocytes, DTL, n=216, 212	84	17		
Monocytes, CTN/NC, n=216, 212	119	161		
Monocytes, ITH, n=216, 212	54	37		
Red Blood Cell Count, DTL, n=216, 212	103	38		
Red Blood Cell Count, CTN/NC, n=216, 212	113	171		
Red Blood Cell Count, ITH, n=216, 212	0	4		

Notes:

[57] - Modified ITT Population

[58] - Modified ITT Population

Statistical analyses

No statistical analyses for this end point

Secondary: Lesion assessment and measurement

End point title	Lesion assessment and measurement

End point description:

Lesions were assessed per WHO criteria. For lesion assessment data, see the outcome measure entitled "Number of participants with a complete response (CR) or a partial response (PR) (central nervous system [CNS]-radiologic)."

End point type	Secondary

End point timeframe:

From the time of Randomization until the time of CR or PR (up to 75 weeks)

End point values	Chemoradiation: Topotecan plus WBRT	Radiation: WBRT Alone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[59]	0[60]		
Units: participants				

Notes:

[59] - ITT Population

[60] - ITT Population

Statistical analyses

No statistical analyses for this end point

Secondary: Brain symptoms

End point title	Brain symptoms

End point description:

Brain symptoms were assessed as the number of participants with neurological signs and symptoms. For brain symptom data, see the outcome measures entitled "Number of participants with the indicated investigator assessment for the neurological sign and symptom of X at Baseline, Month 1, and Month 3."

End point type	Secondary

End point timeframe:

Baseline, Month 1, and Month 3

End point values	Chemoradiation: Topotecan plus WBRT	Radiation: WBRT Alone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[61]	0[62]		
Units: participants				

Notes:

[61] - ITT Population

[62] - ITT Population

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants who died or progressed

End point title	Number of participants who died or progressed

End point description:

Disease-related events were measured as the number of participants who died or progressed. Progressive disease (PD) is defined as an increase >=25% in any measurable lesion or, in participants with non-measurable disease only, an estimation of an increase >=25%. In both cases, determination of progression included the appearance of any new lesions, or signification worsening of conditions presumed to be related to malignancy. Participants with clinical or laboratory evidence of possible disease progression were to be evaluated radiologically. Data were analyzed with censoring for extended loss to follow-up to account for two or more missed assessments before an event. The date of the last adequate CNS assessment before extended loss to follow-up was used for censored participants.

End point type	Secondary

End point timeframe:

From Randomization until the last clinic visit associated with the study, up until 35 days after the start of the last course of treatment (up to 75 weeks)

End point values	Chemoradiation: Topotecan plus WBRT	Radiation: WBRT Alone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	235[63]	233[64]		
Units: participants	179	161		

Notes:

[63] - mITT Population

[64] - mITT Population

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

On-treatment AEs

Adverse event reporting additional description:

Serious adverse events (SAEs) and non-serious AEs were collected in members of the Modified Intent-to-Treat Population, comprised of all randomized participants (par.) who received at least one dose of randomized therapy. Par. were analyzed by the actual treatment received, even if it differed from the treatment to which they were randomized.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	15.0

Reporting groups

Reporting group title	Chemoradiation: Topotecan plus WBRT

Reporting group description:

Participants received topotecan 1.1 milligrams per meters squared per day (mg/m2/day), orally followed approximately 2 hours later by whole-brain radiation therapy (WBRT) 3 Gray (Gy)/day to midline over the course of 10 days. After a 2-week washout period, participants completing chemoradiation and willing to participate in the Continuation Phase of the study received oral topotecan 2.3 mg/m2/day for 5 days, every 21 days, as monotherapy provided the baseline hematologic requirements were met. Monotherapy continued until disease progression or discontinuation. Chemoradiation participants choosing not to participate in the Continuation Phase may have received other chemotherapies or best supportive care, as determined by the investigator.

Reporting group title	Radiation: WBRT Alone

Reporting group description:

Participants received WBRT 3 Gy/day for 10 days. Participants may have received other chemotherapies or best supportive care, as determined by the investigator.

Serious adverse events	Chemoradiation: Topotecan plus WBRT	Radiation: WBRT Alone	
Total subjects affected by serious adverse events			
subjects affected / exposed	96 / 235 (40.85%)	43 / 233 (18.45%)	
number of deaths (all causes)	212	205	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Non-small cell lung cancer			
subjects affected / exposed	2 / 235 (0.85%)	0 / 233 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	1 / 2	0 / 0	
Vascular disorders			
Arterial thrombosis limb			

subjects affected / exposed	0 / 235 (0.00%)	1 / 233 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Jugular vein thrombosis			
subjects affected / exposed	1 / 235 (0.43%)	0 / 233 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Orthostatic hypotension			
subjects affected / exposed	1 / 235 (0.43%)	0 / 233 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Superior vena cava syndrome			
subjects affected / exposed	1 / 235 (0.43%)	0 / 233 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Venous thrombosis			
subjects affected / exposed	0 / 235 (0.00%)	1 / 233 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Deep vein thrombosis			
subjects affected / exposed	3 / 235 (1.28%)	1 / 233 (0.43%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Disease progression			
subjects affected / exposed	3 / 235 (1.28%)	0 / 233 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 3	0 / 0	
Performance status decreased			
subjects affected / exposed	2 / 235 (0.85%)	0 / 233 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 2	0 / 0	
Fatigue			

subjects affected / exposed	1 / 235 (0.43%)	0 / 233 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical health deterioration			
subjects affected / exposed	1 / 235 (0.43%)	0 / 233 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Non-cardiac chest pain			
subjects affected / exposed	0 / 235 (0.00%)	1 / 233 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oedema peripheral			
subjects affected / exposed	0 / 235 (0.00%)	1 / 233 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain			
subjects affected / exposed	0 / 235 (0.00%)	1 / 233 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Asthenia			
subjects affected / exposed	5 / 235 (2.13%)	1 / 233 (0.43%)	
occurrences causally related to treatment / all	1 / 5	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	5 / 235 (2.13%)	1 / 233 (0.43%)	
occurrences causally related to treatment / all	3 / 5	1 / 1	
deaths causally related to treatment / all	1 / 1	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Pulmonary embolism			
subjects affected / exposed	1 / 235 (0.43%)	4 / 233 (1.72%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 1	
Respiratory failure			

subjects affected / exposed	0 / 235 (0.00%)	3 / 233 (1.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 3	
Pulmonary haemorrhage			
subjects affected / exposed	0 / 235 (0.00%)	2 / 233 (0.86%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 2	
Aspiration			
subjects affected / exposed	0 / 235 (0.00%)	1 / 233 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Bronchial obstruction			
subjects affected / exposed	1 / 235 (0.43%)	0 / 233 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemoptysis			
subjects affected / exposed	1 / 235 (0.43%)	2 / 233 (0.86%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Hypoxia			
subjects affected / exposed	0 / 235 (0.00%)	1 / 233 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung infiltration			
subjects affected / exposed	0 / 235 (0.00%)	1 / 233 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Oropharyngeal pain			
subjects affected / exposed	1 / 235 (0.43%)	0 / 233 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleurisy			

subjects affected / exposed	0 / 235 (0.00%)	1 / 233 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonitis			
subjects affected / exposed	1 / 235 (0.43%)	1 / 233 (0.43%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic obstructive pulmonary disease			
subjects affected / exposed	3 / 235 (1.28%)	1 / 233 (0.43%)	
occurrences causally related to treatment / all	1 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	3 / 235 (1.28%)	1 / 233 (0.43%)	
occurrences causally related to treatment / all	1 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Confusional state			
subjects affected / exposed	2 / 235 (0.85%)	0 / 233 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mental status changes			
subjects affected / exposed	1 / 235 (0.43%)	0 / 233 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Blood bilirubin increased			
subjects affected / exposed	1 / 235 (0.43%)	0 / 233 (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 / 235 (0.43%)	0 / 233 (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 / 235 (0.43%)	0 / 233 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Accidental overdose			
subjects affected / exposed	2 / 235 (0.85%)	0 / 233 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Overdose			
subjects affected / exposed	2 / 235 (0.85%)	0 / 233 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Face injury			
subjects affected / exposed	1 / 235 (0.43%)	0 / 233 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femoral neck fracture			
subjects affected / exposed	0 / 235 (0.00%)	1 / 233 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femur fracture			
subjects affected / exposed	1 / 235 (0.43%)	0 / 233 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Radiation pneumonitis			
subjects affected / exposed	0 / 235 (0.00%)	1 / 233 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Cardiac failure acute			
subjects affected / exposed	2 / 235 (0.85%)	0 / 233 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 2	0 / 0	

Acute myocardial infarction			
subjects affected / exposed	1 / 235 (0.43%)	0 / 233 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiopulmonary failure			
subjects affected / exposed	0 / 235 (0.00%)	1 / 233 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Coronary artery insufficiency			
subjects affected / exposed	1 / 235 (0.43%)	0 / 233 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Myocardial infarction			
subjects affected / exposed	0 / 235 (0.00%)	1 / 233 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Myocardial ischaemia			
subjects affected / exposed	1 / 235 (0.43%)	0 / 233 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Atrial fibrillation			
subjects affected / exposed	1 / 235 (0.43%)	1 / 233 (0.43%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pericarditis			
subjects affected / exposed	1 / 235 (0.43%)	1 / 233 (0.43%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Brain oedema			
subjects affected / exposed	3 / 235 (1.28%)	0 / 233 (0.00%)	
occurrences causally related to treatment / all	1 / 3	0 / 0	
deaths causally related to treatment / all	1 / 2	0 / 0	
Cerebrovascular accident			

subjects affected / exposed	2 / 235 (0.85%)	0 / 233 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	1 / 2	0 / 0	
Syncope			
subjects affected / exposed	2 / 235 (0.85%)	0 / 233 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Convulsion			
subjects affected / exposed	1 / 235 (0.43%)	0 / 233 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Encephalopathy			
subjects affected / exposed	1 / 235 (0.43%)	0 / 233 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Grand mal convulsion			
subjects affected / exposed	0 / 235 (0.00%)	1 / 233 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache			
subjects affected / exposed	1 / 235 (0.43%)	0 / 233 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hydrocephalus			
subjects affected / exposed	1 / 235 (0.43%)	0 / 233 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Paraplegia			
subjects affected / exposed	1 / 235 (0.43%)	0 / 233 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Radiculopathy			

subjects affected / exposed	1 / 235 (0.43%)	0 / 233 (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	13 / 235 (5.53%)	0 / 233 (0.00%)	
occurrences causally related to treatment / all	13 / 13	0 / 0	
deaths causally related to treatment / all	2 / 2	0 / 0	
Pancytopenia			
subjects affected / exposed	6 / 235 (2.55%)	0 / 233 (0.00%)	
occurrences causally related to treatment / all	6 / 6	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Agranulocytosis			
subjects affected / exposed	1 / 235 (0.43%)	0 / 233 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphopenia			
subjects affected / exposed	1 / 235 (0.43%)	0 / 233 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukopenia			
subjects affected / exposed	8 / 235 (3.40%)	1 / 233 (0.43%)	
occurrences causally related to treatment / all	8 / 8	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anaemia			
subjects affected / exposed	16 / 235 (6.81%)	1 / 233 (0.43%)	
occurrences causally related to treatment / all	15 / 17	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	22 / 235 (9.36%)	2 / 233 (0.86%)	
occurrences causally related to treatment / all	23 / 23	1 / 2	
deaths causally related to treatment / all	1 / 1	0 / 0	
Thrombocytopenia			

subjects affected / exposed	22 / 235 (9.36%)	1 / 233 (0.43%)	
occurrences causally related to treatment / all	25 / 25	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	6 / 235 (2.55%)	0 / 233 (0.00%)	
occurrences causally related to treatment / all	5 / 6	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Nausea			
subjects affected / exposed	3 / 235 (1.28%)	0 / 233 (0.00%)	
occurrences causally related to treatment / all	1 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	3 / 235 (1.28%)	0 / 233 (0.00%)	
occurrences causally related to treatment / all	1 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	0 / 235 (0.00%)	2 / 233 (0.86%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal haemorrhage			
subjects affected / exposed	2 / 235 (0.85%)	0 / 233 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Intestinal obstruction			
subjects affected / exposed	0 / 235 (0.00%)	1 / 233 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Intestinal perforation			
subjects affected / exposed	1 / 235 (0.43%)	0 / 233 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Oesophageal stenosis			

subjects affected / exposed	0 / 235 (0.00%)	1 / 233 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			
subjects affected / exposed	0 / 235 (0.00%)	1 / 233 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Stevens-Johnson syndrome			
subjects affected / exposed	0 / 235 (0.00%)	1 / 233 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	0 / 235 (0.00%)	1 / 233 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			
subjects affected / exposed	0 / 235 (0.00%)	1 / 233 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary retention			
subjects affected / exposed	0 / 235 (0.00%)	1 / 233 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Adrenal insufficiency			
subjects affected / exposed	1 / 235 (0.43%)	0 / 233 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inappropriate antidiuretic hormone secretion			
subjects affected / exposed	1 / 235 (0.43%)	0 / 233 (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			
Back pain			
subjects affected / exposed	0 / 235 (0.00%)	1 / 233 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal chest pain			
subjects affected / exposed	1 / 235 (0.43%)	0 / 233 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscular weakness			
subjects affected / exposed	1 / 235 (0.43%)	1 / 233 (0.43%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Oropharyngitis fungal			
subjects affected / exposed	1 / 235 (0.43%)	0 / 233 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	1 / 235 (0.43%)	0 / 233 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	0 / 235 (0.00%)	1 / 233 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes zoster			
subjects affected / exposed	1 / 235 (0.43%)	0 / 233 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lobar pneumonia			
subjects affected / exposed	1 / 235 (0.43%)	0 / 233 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Lower respiratory tract infection			
subjects affected / exposed	0 / 235 (0.00%)	1 / 233 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung abscess			
subjects affected / exposed	1 / 235 (0.43%)	0 / 233 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peridiverticular abscess			
subjects affected / exposed	1 / 235 (0.43%)	0 / 233 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic shock			
subjects affected / exposed	1 / 235 (0.43%)	2 / 233 (0.86%)	
occurrences causally related to treatment / all	1 / 1	0 / 2	
deaths causally related to treatment / all	1 / 1	0 / 0	
Upper respiratory tract infection			
subjects affected / exposed	0 / 235 (0.00%)	1 / 233 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	7 / 235 (2.98%)	6 / 233 (2.58%)	
occurrences causally related to treatment / all	2 / 7	0 / 6	
deaths causally related to treatment / all	1 / 3	0 / 3	
Sepsis			
subjects affected / exposed	4 / 235 (1.70%)	1 / 233 (0.43%)	
occurrences causally related to treatment / all	1 / 4	0 / 1	
deaths causally related to treatment / all	1 / 2	0 / 0	
Metabolism and nutrition disorders			
Hyponatraemia			
subjects affected / exposed	1 / 235 (0.43%)	0 / 233 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Decreased appetite			

subjects affected / exposed	1 / 235 (0.43%)	0 / 233 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetes mellitus			
subjects affected / exposed	1 / 235 (0.43%)	0 / 233 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypernatraemia			
subjects affected / exposed	1 / 235 (0.43%)	0 / 233 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malnutrition			
subjects affected / exposed	1 / 235 (0.43%)	0 / 233 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemia			
subjects affected / exposed	1 / 235 (0.43%)	1 / 233 (0.43%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			
subjects affected / exposed	5 / 235 (2.13%)	3 / 233 (1.29%)	
occurrences causally related to treatment / all	2 / 6	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Chemoradiation: Topotecan plus WBRT	Radiation: WBRT Alone	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	192 / 235 (81.70%)	139 / 233 (59.66%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Cancer pain			
subjects affected / exposed	3 / 235 (1.28%)	3 / 233 (1.29%)	
occurrences (all)	3	3	

Tumour pain			
subjects affected / exposed	2 / 235 (0.85%)	1 / 233 (0.43%)	
occurrences (all)	2	1	
Non-small cell lung cancer			
subjects affected / exposed	1 / 235 (0.43%)	0 / 233 (0.00%)	
occurrences (all)	2	0	
Lung neoplasm malignant			
subjects affected / exposed	1 / 235 (0.43%)	0 / 233 (0.00%)	
occurrences (all)	1	0	
Metastases to skin			
subjects affected / exposed	1 / 235 (0.43%)	0 / 233 (0.00%)	
occurrences (all)	1	0	
Vascular disorders			
Hypotension			
subjects affected / exposed	6 / 235 (2.55%)	0 / 233 (0.00%)	
occurrences (all)	7	0	
Hypertension			
subjects affected / exposed	2 / 235 (0.85%)	1 / 233 (0.43%)	
occurrences (all)	2	1	
Flushing			
subjects affected / exposed	1 / 235 (0.43%)	1 / 233 (0.43%)	
occurrences (all)	1	1	
Phlebitis			
subjects affected / exposed	2 / 235 (0.85%)	0 / 233 (0.00%)	
occurrences (all)	2	0	
Haematoma			
subjects affected / exposed	0 / 235 (0.00%)	1 / 233 (0.43%)	
occurrences (all)	0	1	
Hot flush			
subjects affected / exposed	0 / 235 (0.00%)	1 / 233 (0.43%)	
occurrences (all)	0	1	
Orthostatic hypotension			
subjects affected / exposed	0 / 235 (0.00%)	1 / 233 (0.43%)	
occurrences (all)	0	1	
Thrombophlebitis superficial			

subjects affected / exposed	1 / 235 (0.43%)	0 / 233 (0.00%)	
occurrences (all)	1	0	
Deep vein thrombosis			
subjects affected / exposed	1 / 235 (0.43%)	2 / 233 (0.86%)	
occurrences (all)	1	2	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	39 / 235 (16.60%)	37 / 233 (15.88%)	
occurrences (all)	40	38	
Asthenia			
subjects affected / exposed	29 / 235 (12.34%)	19 / 233 (8.15%)	
occurrences (all)	29	21	
Oedema peripheral			
subjects affected / exposed	15 / 235 (6.38%)	15 / 233 (6.44%)	
occurrences (all)	16	16	
Pyrexia			
subjects affected / exposed	13 / 235 (5.53%)	5 / 233 (2.15%)	
occurrences (all)	14	5	
Mucosal inflammation			
subjects affected / exposed	7 / 235 (2.98%)	0 / 233 (0.00%)	
occurrences (all)	9	0	
Gait disturbance			
subjects affected / exposed	2 / 235 (0.85%)	4 / 233 (1.72%)	
occurrences (all)	2	4	
Chest pain			
subjects affected / exposed	1 / 235 (0.43%)	2 / 233 (0.86%)	
occurrences (all)	1	3	
Face oedema			
subjects affected / exposed	1 / 235 (0.43%)	3 / 233 (1.29%)	
occurrences (all)	1	3	
Pain			
subjects affected / exposed	1 / 235 (0.43%)	3 / 233 (1.29%)	
occurrences (all)	1	3	
Chills			

subjects affected / exposed	2 / 235 (0.85%)	1 / 233 (0.43%)	
occurrences (all)	2	1	
Non-cardiac chest pain			
subjects affected / exposed	2 / 235 (0.85%)	1 / 233 (0.43%)	
occurrences (all)	2	1	
Spinal pain			
subjects affected / exposed	1 / 235 (0.43%)	1 / 233 (0.43%)	
occurrences (all)	1	1	
Chest discomfort			
subjects affected / exposed	0 / 235 (0.00%)	1 / 233 (0.43%)	
occurrences (all)	0	1	
Early satiety			
subjects affected / exposed	1 / 235 (0.43%)	0 / 233 (0.00%)	
occurrences (all)	1	0	
Gravitational oedema			
subjects affected / exposed	1 / 235 (0.43%)	0 / 233 (0.00%)	
occurrences (all)	1	0	
Hyperthermia			
subjects affected / exposed	0 / 235 (0.00%)	1 / 233 (0.43%)	
occurrences (all)	0	1	
Influenza like illness			
subjects affected / exposed	1 / 235 (0.43%)	0 / 233 (0.00%)	
occurrences (all)	1	0	
Local swelling			
subjects affected / exposed	0 / 235 (0.00%)	1 / 233 (0.43%)	
occurrences (all)	0	1	
Localised oedema			
subjects affected / exposed	0 / 235 (0.00%)	1 / 233 (0.43%)	
occurrences (all)	0	1	
Malaise			
subjects affected / exposed	1 / 235 (0.43%)	0 / 233 (0.00%)	
occurrences (all)	1	0	
Mucosal erosion			
subjects affected / exposed	1 / 235 (0.43%)	0 / 233 (0.00%)	
occurrences (all)	1	0	
Oedema			

subjects affected / exposed	1 / 235 (0.43%)	0 / 233 (0.00%)	
occurrences (all)	1	0	
Swelling			
subjects affected / exposed	1 / 235 (0.43%)	0 / 233 (0.00%)	
occurrences (all)	1	0	
Reproductive system and breast disorders			
Epididymitis			
subjects affected / exposed	1 / 235 (0.43%)	0 / 233 (0.00%)	
occurrences (all)	1	0	
Prostatitis			
subjects affected / exposed	1 / 235 (0.43%)	0 / 233 (0.00%)	
occurrences (all)	1	0	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	31 / 235 (13.19%)	20 / 233 (8.58%)	
occurrences (all)	32	21	
Cough			
subjects affected / exposed	26 / 235 (11.06%)	17 / 233 (7.30%)	
occurrences (all)	29	18	
Epistaxis			
subjects affected / exposed	8 / 235 (3.40%)	2 / 233 (0.86%)	
occurrences (all)	9	2	
Haemoptysis			
subjects affected / exposed	3 / 235 (1.28%)	7 / 233 (3.00%)	
occurrences (all)	3	7	
Oropharyngeal pain			
subjects affected / exposed	5 / 235 (2.13%)	3 / 233 (1.29%)	
occurrences (all)	5	3	
Hiccups			
subjects affected / exposed	3 / 235 (1.28%)	2 / 233 (0.86%)	
occurrences (all)	3	2	
Dyspnoea exertional			
subjects affected / exposed	1 / 235 (0.43%)	3 / 233 (1.29%)	
occurrences (all)	1	3	
Hypoxia			

subjects affected / exposed	2 / 235 (0.85%)	1 / 233 (0.43%)		
occurrences (all)	3	1		
Productive cough				
subjects affected / exposed	1 / 235 (0.43%)	2 / 233 (0.86%)		
occurrences (all)	1	2		
Dysphonia				
subjects affected / exposed	1 / 235 (0.43%)	1 / 233 (0.43%)		
occurrences (all)	1	1		
Lung infiltration				
subjects affected / exposed	0 / 235 (0.00%)	2 / 233 (0.86%)		
occurrences (all)	0	2		
Pleural effusion				
subjects affected / exposed	1 / 235 (0.43%)	1 / 233 (0.43%)		
occurrences (all)	1	1		
Pulmonary embolism				
subjects affected / exposed	2 / 235 (0.85%)	0 / 233 (0.00%)		
occurrences (all)	2	0		
Upper-airway cough syndrome				
subjects affected / exposed	2 / 235 (0.85%)	0 / 233 (0.00%)		
occurrences (all)	2	0		
Wheezing				
subjects affected / exposed	2 / 235 (0.85%)	0 / 233 (0.00%)		
occurrences (all)	2	0		
Bronchitis chronic				
subjects affected / exposed	1 / 235 (0.43%)	0 / 233 (0.00%)		
occurrences (all)	1	0		
Chronic obstructive pulmonary disease				
subjects affected / exposed	1 / 235 (0.43%)	0 / 233 (0.00%)		
occurrences (all)	1	0		
Hydrothorax				
subjects affected / exposed	1 / 235 (0.43%)	0 / 233 (0.00%)		
occurrences (all)	1	0		
Increased upper airway secretion				
subjects affected / exposed	1 / 235 (0.43%)	0 / 233 (0.00%)		
occurrences (all)	1	0		

Laryngeal inflammation			
subjects affected / exposed	0 / 235 (0.00%)	1 / 233 (0.43%)	
occurrences (all)	0	1	
Pharyngeal inflammation			
subjects affected / exposed	0 / 235 (0.00%)	1 / 233 (0.43%)	
occurrences (all)	0	1	
Pneumothorax			
subjects affected / exposed	1 / 235 (0.43%)	0 / 233 (0.00%)	
occurrences (all)	1	0	
Pulmonary hypertension			
subjects affected / exposed	0 / 235 (0.00%)	1 / 233 (0.43%)	
occurrences (all)	0	1	
Rales			
subjects affected / exposed	0 / 235 (0.00%)	1 / 233 (0.43%)	
occurrences (all)	0	1	
Respiratory failure			
subjects affected / exposed	1 / 235 (0.43%)	0 / 233 (0.00%)	
occurrences (all)	1	0	
Respiratory tract congestion			
subjects affected / exposed	0 / 235 (0.00%)	1 / 233 (0.43%)	
occurrences (all)	0	1	
Rhinorrhoea			
subjects affected / exposed	1 / 235 (0.43%)	0 / 233 (0.00%)	
occurrences (all)	1	0	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	17 / 235 (7.23%)	19 / 233 (8.15%)	
occurrences (all)	17	20	
Confusional state			
subjects affected / exposed	7 / 235 (2.98%)	11 / 233 (4.72%)	
occurrences (all)	7	11	
Anxiety			
subjects affected / exposed	4 / 235 (1.70%)	1 / 233 (0.43%)	
occurrences (all)	4	1	
Depression			

subjects affected / exposed	2 / 235 (0.85%)	2 / 233 (0.86%)	
occurrences (all)	2	2	
Mood altered			
subjects affected / exposed	0 / 235 (0.00%)	2 / 233 (0.86%)	
occurrences (all)	0	2	
Nervousness			
subjects affected / exposed	0 / 235 (0.00%)	2 / 233 (0.86%)	
occurrences (all)	0	2	
Sleep disorder			
subjects affected / exposed	0 / 235 (0.00%)	1 / 233 (0.43%)	
occurrences (all)	0	2	
Delusion			
subjects affected / exposed	0 / 235 (0.00%)	1 / 233 (0.43%)	
occurrences (all)	0	1	
Depressed mood			
subjects affected / exposed	1 / 235 (0.43%)	0 / 233 (0.00%)	
occurrences (all)	1	0	
Disorientation			
subjects affected / exposed	0 / 235 (0.00%)	1 / 233 (0.43%)	
occurrences (all)	0	1	
Initial insomnia			
subjects affected / exposed	0 / 235 (0.00%)	1 / 233 (0.43%)	
occurrences (all)	0	1	
Mental disorder			
subjects affected / exposed	1 / 235 (0.43%)	0 / 233 (0.00%)	
occurrences (all)	1	0	
Staring			
subjects affected / exposed	0 / 235 (0.00%)	1 / 233 (0.43%)	
occurrences (all)	0	1	
Investigations			
Weight decreased			
subjects affected / exposed	18 / 235 (7.66%)	8 / 233 (3.43%)	
occurrences (all)	21	8	
Blood lactate dehydrogenase increased			

subjects affected / exposed	3 / 235 (1.28%)	2 / 233 (0.86%)	
occurrences (all)	3	2	
Platelet count decreased			
subjects affected / exposed	4 / 235 (1.70%)	1 / 233 (0.43%)	
occurrences (all)	4	1	
Haemoglobin decreased			
subjects affected / exposed	3 / 235 (1.28%)	1 / 233 (0.43%)	
occurrences (all)	3	1	
Alanine aminotransferase increased			
subjects affected / exposed	2 / 235 (0.85%)	1 / 233 (0.43%)	
occurrences (all)	2	1	
Weight increased			
subjects affected / exposed	2 / 235 (0.85%)	1 / 233 (0.43%)	
occurrences (all)	2	1	
Blood glucose increased			
subjects affected / exposed	0 / 235 (0.00%)	2 / 233 (0.86%)	
occurrences (all)	0	2	
Neutrophil count decreased			
subjects affected / exposed	2 / 235 (0.85%)	0 / 233 (0.00%)	
occurrences (all)	2	0	
White blood cell count decreased			
subjects affected / exposed	1 / 235 (0.43%)	1 / 233 (0.43%)	
occurrences (all)	1	1	
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 235 (0.00%)	1 / 233 (0.43%)	
occurrences (all)	0	1	
Bacterial test positive			
subjects affected / exposed	1 / 235 (0.43%)	0 / 233 (0.00%)	
occurrences (all)	1	0	
Blood alkaline phosphatase increased			
subjects affected / exposed	1 / 235 (0.43%)	0 / 233 (0.00%)	
occurrences (all)	1	0	
Blood bilirubin increased			
subjects affected / exposed	0 / 235 (0.00%)	1 / 233 (0.43%)	
occurrences (all)	0	1	

Blood creatinine increased			
subjects affected / exposed	0 / 235 (0.00%)	1 / 233 (0.43%)	
occurrences (all)	0	1	
Blood magnesium increased			
subjects affected / exposed	1 / 235 (0.43%)	0 / 233 (0.00%)	
occurrences (all)	1	0	
Blood phosphorus decreased			
subjects affected / exposed	0 / 235 (0.00%)	1 / 233 (0.43%)	
occurrences (all)	0	1	
Blood phosphorus increased			
subjects affected / exposed	1 / 235 (0.43%)	0 / 233 (0.00%)	
occurrences (all)	1	0	
Blood urea increased			
subjects affected / exposed	0 / 235 (0.00%)	1 / 233 (0.43%)	
occurrences (all)	0	1	
Blood uric acid increased			
subjects affected / exposed	0 / 235 (0.00%)	1 / 233 (0.43%)	
occurrences (all)	0	1	
Body temperature increased			
subjects affected / exposed	1 / 235 (0.43%)	0 / 233 (0.00%)	
occurrences (all)	1	0	
Breath sounds abnormal			
subjects affected / exposed	0 / 235 (0.00%)	1 / 233 (0.43%)	
occurrences (all)	0	1	
Gamma-glutamyltransferase increased			
subjects affected / exposed	0 / 235 (0.00%)	1 / 233 (0.43%)	
occurrences (all)	0	1	
International normalised ratio increased			
subjects affected / exposed	1 / 235 (0.43%)	0 / 233 (0.00%)	
occurrences (all)	1	0	
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	1 / 235 (0.43%)	1 / 233 (0.43%)	
occurrences (all)	1	1	
Thermal burn			

subjects affected / exposed	1 / 235 (0.43%)	1 / 233 (0.43%)	
occurrences (all)	1	1	
Contusion			
subjects affected / exposed	1 / 235 (0.43%)	0 / 233 (0.00%)	
occurrences (all)	1	0	
Incision site pain			
subjects affected / exposed	0 / 235 (0.00%)	1 / 233 (0.43%)	
occurrences (all)	0	1	
Overdose			
subjects affected / exposed	0 / 235 (0.00%)	1 / 233 (0.43%)	
occurrences (all)	0	1	
Radiation skin injury			
subjects affected / exposed	1 / 235 (0.43%)	0 / 233 (0.00%)	
occurrences (all)	1	0	
Skin wound			
subjects affected / exposed	1 / 235 (0.43%)	0 / 233 (0.00%)	
occurrences (all)	1	0	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	3 / 235 (1.28%)	2 / 233 (0.86%)	
occurrences (all)	3	2	
Tachycardia			
subjects affected / exposed	2 / 235 (0.85%)	3 / 233 (1.29%)	
occurrences (all)	2	3	
Cardiac failure			
subjects affected / exposed	1 / 235 (0.43%)	1 / 233 (0.43%)	
occurrences (all)	1	1	
Palpitations			
subjects affected / exposed	2 / 235 (0.85%)	0 / 233 (0.00%)	
occurrences (all)	2	0	
Angina pectoris			
subjects affected / exposed	1 / 235 (0.43%)	0 / 233 (0.00%)	
occurrences (all)	1	0	
Cardiac failure congestive			
subjects affected / exposed	0 / 235 (0.00%)	1 / 233 (0.43%)	
occurrences (all)	0	1	

Sinus tachycardia			
subjects affected / exposed	0 / 235 (0.00%)	1 / 233 (0.43%)	
occurrences (all)	0	1	
Supraventricular extrasystoles			
subjects affected / exposed	0 / 235 (0.00%)	1 / 233 (0.43%)	
occurrences (all)	0	1	
Nervous system disorders			
Headache			
subjects affected / exposed	27 / 235 (11.49%)	28 / 233 (12.02%)	
occurrences (all)	33	32	
Dizziness			
subjects affected / exposed	27 / 235 (11.49%)	19 / 233 (8.15%)	
occurrences (all)	29	22	
Somnolence			
subjects affected / exposed	14 / 235 (5.96%)	14 / 233 (6.01%)	
occurrences (all)	14	15	
Hypoaesthesia			
subjects affected / exposed	6 / 235 (2.55%)	11 / 233 (4.72%)	
occurrences (all)	6	12	
Ataxia			
subjects affected / exposed	8 / 235 (3.40%)	6 / 233 (2.58%)	
occurrences (all)	8	6	
Coordination abnormal			
subjects affected / exposed	7 / 235 (2.98%)	4 / 233 (1.72%)	
occurrences (all)	7	4	
Tremor			
subjects affected / exposed	6 / 235 (2.55%)	4 / 233 (1.72%)	
occurrences (all)	6	4	
Paraesthesia			
subjects affected / exposed	5 / 235 (2.13%)	4 / 233 (1.72%)	
occurrences (all)	5	4	
Amnesia			
subjects affected / exposed	2 / 235 (0.85%)	6 / 233 (2.58%)	
occurrences (all)	2	6	
Dysgeusia			

subjects affected / exposed	6 / 235 (2.55%)	2 / 233 (0.86%)	
occurrences (all)	6	2	
Aphasia			
subjects affected / exposed	1 / 235 (0.43%)	6 / 233 (2.58%)	
occurrences (all)	1	6	
Balance disorder			
subjects affected / exposed	0 / 235 (0.00%)	7 / 233 (3.00%)	
occurrences (all)	0	7	
Convulsion			
subjects affected / exposed	4 / 235 (1.70%)	1 / 233 (0.43%)	
occurrences (all)	5	2	
Epilepsy			
subjects affected / exposed	1 / 235 (0.43%)	3 / 233 (1.29%)	
occurrences (all)	1	6	
Neuropathy peripheral			
subjects affected / exposed	2 / 235 (0.85%)	2 / 233 (0.86%)	
occurrences (all)	2	2	
Peripheral sensory neuropathy			
subjects affected / exposed	2 / 235 (0.85%)	2 / 233 (0.86%)	
occurrences (all)	2	2	
Speech disorder			
subjects affected / exposed	1 / 235 (0.43%)	3 / 233 (1.29%)	
occurrences (all)	1	3	
Syncope			
subjects affected / exposed	2 / 235 (0.85%)	1 / 233 (0.43%)	
occurrences (all)	2	1	
Brain oedema			
subjects affected / exposed	1 / 235 (0.43%)	1 / 233 (0.43%)	
occurrences (all)	1	1	
Convulsions local			
subjects affected / exposed	2 / 235 (0.85%)	0 / 233 (0.00%)	
occurrences (all)	2	0	
Hemiparesis			
subjects affected / exposed	0 / 235 (0.00%)	2 / 233 (0.86%)	
occurrences (all)	0	2	
Hemiplegia			

subjects affected / exposed	1 / 235 (0.43%)	1 / 233 (0.43%)	
occurrences (all)	1	1	
Hypersomnia			
subjects affected / exposed	0 / 235 (0.00%)	1 / 233 (0.43%)	
occurrences (all)	0	2	
Loss of consciousness			
subjects affected / exposed	1 / 235 (0.43%)	1 / 233 (0.43%)	
occurrences (all)	1	1	
Memory impairment			
subjects affected / exposed	1 / 235 (0.43%)	1 / 233 (0.43%)	
occurrences (all)	1	1	
Psychomotor hyperactivity			
subjects affected / exposed	0 / 235 (0.00%)	2 / 233 (0.86%)	
occurrences (all)	0	2	
Ageusia			
subjects affected / exposed	0 / 235 (0.00%)	1 / 233 (0.43%)	
occurrences (all)	0	1	
Alcoholic seizure			
subjects affected / exposed	0 / 235 (0.00%)	1 / 233 (0.43%)	
occurrences (all)	0	1	
Burning sensation			
subjects affected / exposed	1 / 235 (0.43%)	0 / 233 (0.00%)	
occurrences (all)	1	0	
Cognitive disorder			
subjects affected / exposed	1 / 235 (0.43%)	0 / 233 (0.00%)	
occurrences (all)	1	0	
Dysarthria			
subjects affected / exposed	0 / 235 (0.00%)	1 / 233 (0.43%)	
occurrences (all)	0	1	
Facial paresis			
subjects affected / exposed	1 / 235 (0.43%)	0 / 233 (0.00%)	
occurrences (all)	1	0	
Hypotonia			
subjects affected / exposed	1 / 235 (0.43%)	0 / 233 (0.00%)	
occurrences (all)	1	0	
Mental impairment			

subjects affected / exposed	0 / 235 (0.00%)	1 / 233 (0.43%)	
occurrences (all)	0	1	
Monoplegia			
subjects affected / exposed	1 / 235 (0.43%)	0 / 233 (0.00%)	
occurrences (all)	1	0	
Neuritis			
subjects affected / exposed	0 / 235 (0.00%)	1 / 233 (0.43%)	
occurrences (all)	0	1	
Paresis			
subjects affected / exposed	1 / 235 (0.43%)	0 / 233 (0.00%)	
occurrences (all)	1	0	
Partial seizures			
subjects affected / exposed	1 / 235 (0.43%)	0 / 233 (0.00%)	
occurrences (all)	1	0	
Peripheral motor neuropathy			
subjects affected / exposed	1 / 235 (0.43%)	0 / 233 (0.00%)	
occurrences (all)	1	0	
Polyneuropathy			
subjects affected / exposed	0 / 235 (0.00%)	1 / 233 (0.43%)	
occurrences (all)	0	1	
Sciatica			
subjects affected / exposed	0 / 235 (0.00%)	1 / 233 (0.43%)	
occurrences (all)	0	1	
Visual field defect			
subjects affected / exposed	0 / 235 (0.00%)	1 / 233 (0.43%)	
occurrences (all)	0	1	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	7 / 235 (2.98%)	1 / 233 (0.43%)	
occurrences (all)	7	1	
Thrombocytopenia			
subjects affected / exposed	5 / 235 (2.13%)	1 / 233 (0.43%)	
occurrences (all)	5	1	
Neutropenia			
subjects affected / exposed	3 / 235 (1.28%)	0 / 233 (0.00%)	
occurrences (all)	4	0	

Leukopenia			
subjects affected / exposed	2 / 235 (0.85%)	0 / 233 (0.00%)	
occurrences (all)	2	0	
Coagulopathy			
subjects affected / exposed	0 / 235 (0.00%)	1 / 233 (0.43%)	
occurrences (all)	0	1	
Febrile neutropenia			
subjects affected / exposed	1 / 235 (0.43%)	0 / 233 (0.00%)	
occurrences (all)	1	0	
Pancytopenia			
subjects affected / exposed	1 / 235 (0.43%)	0 / 233 (0.00%)	
occurrences (all)	1	0	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	4 / 235 (1.70%)	3 / 233 (1.29%)	
occurrences (all)	4	3	
Tinnitus			
subjects affected / exposed	4 / 235 (1.70%)	0 / 233 (0.00%)	
occurrences (all)	4	0	
Ear pain			
subjects affected / exposed	2 / 235 (0.85%)	0 / 233 (0.00%)	
occurrences (all)	2	0	
Ear pruritus			
subjects affected / exposed	2 / 235 (0.85%)	0 / 233 (0.00%)	
occurrences (all)	2	0	
Auricular swelling			
subjects affected / exposed	0 / 235 (0.00%)	1 / 233 (0.43%)	
occurrences (all)	0	1	
Deafness			
subjects affected / exposed	0 / 235 (0.00%)	1 / 233 (0.43%)	
occurrences (all)	0	1	
Hearing impaired			
subjects affected / exposed	1 / 235 (0.43%)	0 / 233 (0.00%)	
occurrences (all)	1	0	
Hypoacusis			

subjects affected / exposed	1 / 235 (0.43%)	0 / 233 (0.00%)	
occurrences (all)	1	0	
Eye disorders			
Vision blurred			
subjects affected / exposed	4 / 235 (1.70%)	8 / 233 (3.43%)	
occurrences (all)	4	8	
Visual acuity reduced			
subjects affected / exposed	3 / 235 (1.28%)	2 / 233 (0.86%)	
occurrences (all)	3	2	
Visual impairment			
subjects affected / exposed	2 / 235 (0.85%)	2 / 233 (0.86%)	
occurrences (all)	2	3	
Asthenopia			
subjects affected / exposed	1 / 235 (0.43%)	0 / 233 (0.00%)	
occurrences (all)	1	0	
Blindness			
subjects affected / exposed	0 / 235 (0.00%)	1 / 233 (0.43%)	
occurrences (all)	0	1	
Conjunctivitis			
subjects affected / exposed	0 / 235 (0.00%)	1 / 233 (0.43%)	
occurrences (all)	0	1	
Eye inflammation			
subjects affected / exposed	1 / 235 (0.43%)	0 / 233 (0.00%)	
occurrences (all)	1	0	
Eye pain			
subjects affected / exposed	1 / 235 (0.43%)	0 / 233 (0.00%)	
occurrences (all)	1	0	
Myopia			
subjects affected / exposed	1 / 235 (0.43%)	0 / 233 (0.00%)	
occurrences (all)	1	0	
Retinal vascular disorder			
subjects affected / exposed	1 / 235 (0.43%)	0 / 233 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal disorders			
Nausea			

subjects affected / exposed	64 / 235 (27.23%)	30 / 233 (12.88%)	
occurrences (all)	84	32	
Vomiting			
subjects affected / exposed	37 / 235 (15.74%)	24 / 233 (10.30%)	
occurrences (all)	46	29	
Dyspepsia			
subjects affected / exposed	17 / 235 (7.23%)	10 / 233 (4.29%)	
occurrences (all)	17	11	
Diarrhoea			
subjects affected / exposed	19 / 235 (8.09%)	8 / 233 (3.43%)	
occurrences (all)	19	8	
Constipation			
subjects affected / exposed	8 / 235 (3.40%)	10 / 233 (4.29%)	
occurrences (all)	8	10	
Abdominal pain			
subjects affected / exposed	4 / 235 (1.70%)	6 / 233 (2.58%)	
occurrences (all)	5	6	
Stomatitis			
subjects affected / exposed	7 / 235 (2.98%)	1 / 233 (0.43%)	
occurrences (all)	7	1	
Abdominal pain upper			
subjects affected / exposed	2 / 235 (0.85%)	3 / 233 (1.29%)	
occurrences (all)	2	3	
Dysphagia			
subjects affected / exposed	2 / 235 (0.85%)	3 / 233 (1.29%)	
occurrences (all)	2	3	
Dry mouth			
subjects affected / exposed	2 / 235 (0.85%)	2 / 233 (0.86%)	
occurrences (all)	2	2	
Abdominal distension			
subjects affected / exposed	1 / 235 (0.43%)	1 / 233 (0.43%)	
occurrences (all)	2	1	
Flatulence			
subjects affected / exposed	2 / 235 (0.85%)	0 / 233 (0.00%)	
occurrences (all)	3	0	
Gastrooesophageal reflux disease			

subjects affected / exposed	3 / 235 (1.28%)	0 / 233 (0.00%)	
occurrences (all)	3	0	
Glossodynia			
subjects affected / exposed	1 / 235 (0.43%)	0 / 233 (0.00%)	
occurrences (all)	2	0	
Mouth ulceration			
subjects affected / exposed	2 / 235 (0.85%)	0 / 233 (0.00%)	
occurrences (all)	2	0	
Rectal haemorrhage			
subjects affected / exposed	1 / 235 (0.43%)	1 / 233 (0.43%)	
occurrences (all)	1	1	
Abdominal discomfort			
subjects affected / exposed	1 / 235 (0.43%)	0 / 233 (0.00%)	
occurrences (all)	1	0	
Aphthous stomatitis			
subjects affected / exposed	0 / 235 (0.00%)	1 / 233 (0.43%)	
occurrences (all)	0	1	
Ascites			
subjects affected / exposed	0 / 235 (0.00%)	1 / 233 (0.43%)	
occurrences (all)	0	1	
Breath odour			
subjects affected / exposed	0 / 235 (0.00%)	1 / 233 (0.43%)	
occurrences (all)	0	1	
Faecal incontinence			
subjects affected / exposed	1 / 235 (0.43%)	0 / 233 (0.00%)	
occurrences (all)	1	0	
Faeces discoloured			
subjects affected / exposed	1 / 235 (0.43%)	0 / 233 (0.00%)	
occurrences (all)	1	0	
Gastritis			
subjects affected / exposed	0 / 235 (0.00%)	1 / 233 (0.43%)	
occurrences (all)	0	1	
Gingival pain			
subjects affected / exposed	1 / 235 (0.43%)	0 / 233 (0.00%)	
occurrences (all)	1	0	
Haematochezia			

subjects affected / exposed	1 / 235 (0.43%)	0 / 233 (0.00%)	
occurrences (all)	1	0	
Haemorrhoids			
subjects affected / exposed	0 / 235 (0.00%)	1 / 233 (0.43%)	
occurrences (all)	0	1	
Hyperchlorhydria			
subjects affected / exposed	1 / 235 (0.43%)	0 / 233 (0.00%)	
occurrences (all)	1	0	
Oesophageal pain			
subjects affected / exposed	1 / 235 (0.43%)	0 / 233 (0.00%)	
occurrences (all)	1	0	
Oral pain			
subjects affected / exposed	0 / 235 (0.00%)	1 / 233 (0.43%)	
occurrences (all)	0	1	
Retching			
subjects affected / exposed	1 / 235 (0.43%)	0 / 233 (0.00%)	
occurrences (all)	1	0	
Hepatobiliary disorders			
Hepatic function abnormal			
subjects affected / exposed	1 / 235 (0.43%)	0 / 233 (0.00%)	
occurrences (all)	1	0	
Skin and subcutaneous tissue disorders			
Erythema			
subjects affected / exposed	4 / 235 (1.70%)	1 / 233 (0.43%)	
occurrences (all)	4	1	
Pruritus			
subjects affected / exposed	5 / 235 (2.13%)	0 / 233 (0.00%)	
occurrences (all)	5	0	
Rash			
subjects affected / exposed	2 / 235 (0.85%)	3 / 233 (1.29%)	
occurrences (all)	2	3	
Dry skin			
subjects affected / exposed	1 / 235 (0.43%)	2 / 233 (0.86%)	
occurrences (all)	1	2	
Ecchymosis			

subjects affected / exposed	1 / 235 (0.43%)	1 / 233 (0.43%)		
occurrences (all)	1	2		
Swelling face				
subjects affected / exposed	1 / 235 (0.43%)	2 / 233 (0.86%)		
occurrences (all)	1	2		
Acne				
subjects affected / exposed	1 / 235 (0.43%)	1 / 233 (0.43%)		
occurrences (all)	1	1		
Night sweats				
subjects affected / exposed	1 / 235 (0.43%)	1 / 233 (0.43%)		
occurrences (all)	1	1		
Skin disorder				
subjects affected / exposed	0 / 235 (0.00%)	2 / 233 (0.86%)		
occurrences (all)	0	2		
Skin ulcer				
subjects affected / exposed	1 / 235 (0.43%)	1 / 233 (0.43%)		
occurrences (all)	1	1		
Dermatitis allergic				
subjects affected / exposed	0 / 235 (0.00%)	1 / 233 (0.43%)		
occurrences (all)	0	1		
Haemorrhage subcutaneous				
subjects affected / exposed	1 / 235 (0.43%)	0 / 233 (0.00%)		
occurrences (all)	1	0		
Increased tendency to bruise				
subjects affected / exposed	0 / 235 (0.00%)	1 / 233 (0.43%)		
occurrences (all)	0	1		
Petechiae				
subjects affected / exposed	1 / 235 (0.43%)	0 / 233 (0.00%)		
occurrences (all)	1	0		
Rash papular				
subjects affected / exposed	1 / 235 (0.43%)	0 / 233 (0.00%)		
occurrences (all)	1	0		
Skin exfoliation				
subjects affected / exposed	0 / 235 (0.00%)	1 / 233 (0.43%)		
occurrences (all)	0	1		
Alopecia				

subjects affected / exposed	21 / 235 (8.94%)	17 / 233 (7.30%)	
occurrences (all)	21	17	
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	2 / 235 (0.85%)	1 / 233 (0.43%)	
occurrences (all)	2	1	
Dysuria			
subjects affected / exposed	2 / 235 (0.85%)	0 / 233 (0.00%)	
occurrences (all)	2	0	
Pollakiuria			
subjects affected / exposed	1 / 235 (0.43%)	1 / 233 (0.43%)	
occurrences (all)	1	1	
Chromaturia			
subjects affected / exposed	0 / 235 (0.00%)	1 / 233 (0.43%)	
occurrences (all)	0	1	
Incontinence			
subjects affected / exposed	0 / 235 (0.00%)	1 / 233 (0.43%)	
occurrences (all)	0	1	
Nephrolithiasis			
subjects affected / exposed	1 / 235 (0.43%)	0 / 233 (0.00%)	
occurrences (all)	1	0	
Proteinuria			
subjects affected / exposed	0 / 235 (0.00%)	1 / 233 (0.43%)	
occurrences (all)	0	1	
Urinary bladder haemorrhage			
subjects affected / exposed	0 / 235 (0.00%)	1 / 233 (0.43%)	
occurrences (all)	0	1	
Urinary incontinence			
subjects affected / exposed	1 / 235 (0.43%)	0 / 233 (0.00%)	
occurrences (all)	1	0	
Urinary retention			
subjects affected / exposed	1 / 235 (0.43%)	0 / 233 (0.00%)	
occurrences (all)	1	0	
Endocrine disorders			
Cushingoid			

subjects affected / exposed	1 / 235 (0.43%)	1 / 233 (0.43%)	
occurrences (all)	1	1	
Inappropriate antidiuretic hormone secretion			
subjects affected / exposed	1 / 235 (0.43%)	0 / 233 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal and connective tissue disorders			
Muscular weakness			
subjects affected / exposed	29 / 235 (12.34%)	22 / 233 (9.44%)	
occurrences (all)	41	29	
Pain in extremity			
subjects affected / exposed	8 / 235 (3.40%)	6 / 233 (2.58%)	
occurrences (all)	9	6	
Arthralgia			
subjects affected / exposed	6 / 235 (2.55%)	6 / 233 (2.58%)	
occurrences (all)	6	6	
Back pain			
subjects affected / exposed	4 / 235 (1.70%)	4 / 233 (1.72%)	
occurrences (all)	4	4	
Muscle spasms			
subjects affected / exposed	4 / 235 (1.70%)	2 / 233 (0.86%)	
occurrences (all)	5	2	
Musculoskeletal pain			
subjects affected / exposed	4 / 235 (1.70%)	1 / 233 (0.43%)	
occurrences (all)	4	1	
Myalgia			
subjects affected / exposed	2 / 235 (0.85%)	2 / 233 (0.86%)	
occurrences (all)	2	2	
Joint swelling			
subjects affected / exposed	0 / 235 (0.00%)	2 / 233 (0.86%)	
occurrences (all)	0	2	
Neck pain			
subjects affected / exposed	2 / 235 (0.85%)	0 / 233 (0.00%)	
occurrences (all)	2	0	
Bone pain			

subjects affected / exposed	1 / 235 (0.43%)	0 / 233 (0.00%)	
occurrences (all)	1	0	
Extremity contracture			
subjects affected / exposed	1 / 235 (0.43%)	0 / 233 (0.00%)	
occurrences (all)	1	0	
Groin pain			
subjects affected / exposed	0 / 235 (0.00%)	1 / 233 (0.43%)	
occurrences (all)	0	1	
Muscle atrophy			
subjects affected / exposed	0 / 235 (0.00%)	1 / 233 (0.43%)	
occurrences (all)	0	1	
Musculoskeletal chest pain			
subjects affected / exposed	1 / 235 (0.43%)	0 / 233 (0.00%)	
occurrences (all)	1	0	
Osteoarthritis			
subjects affected / exposed	1 / 235 (0.43%)	0 / 233 (0.00%)	
occurrences (all)	1	0	
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	3 / 235 (1.28%)	4 / 233 (1.72%)	
occurrences (all)	4	4	
Oral candidiasis			
subjects affected / exposed	5 / 235 (2.13%)	2 / 233 (0.86%)	
occurrences (all)	5	2	
Candidiasis			
subjects affected / exposed	3 / 235 (1.28%)	2 / 233 (0.86%)	
occurrences (all)	3	2	
Oral fungal infection			
subjects affected / exposed	2 / 235 (0.85%)	3 / 233 (1.29%)	
occurrences (all)	2	3	
Oropharyngitis fungal			
subjects affected / exposed	1 / 235 (0.43%)	3 / 233 (1.29%)	
occurrences (all)	1	3	
Upper respiratory tract infection			
subjects affected / exposed	3 / 235 (1.28%)	1 / 233 (0.43%)	
occurrences (all)	3	1	

Nasopharyngitis			
subjects affected / exposed	1 / 235 (0.43%)	2 / 233 (0.86%)	
occurrences (all)	1	2	
Rhinitis			
subjects affected / exposed	2 / 235 (0.85%)	1 / 233 (0.43%)	
occurrences (all)	2	1	
Bronchitis			
subjects affected / exposed	0 / 235 (0.00%)	2 / 233 (0.86%)	
occurrences (all)	0	2	
Cystitis			
subjects affected / exposed	0 / 235 (0.00%)	2 / 233 (0.86%)	
occurrences (all)	0	2	
Herpes zoster			
subjects affected / exposed	0 / 235 (0.00%)	2 / 233 (0.86%)	
occurrences (all)	0	2	
Influenza			
subjects affected / exposed	2 / 235 (0.85%)	0 / 233 (0.00%)	
occurrences (all)	2	0	
Oesophageal candidiasis			
subjects affected / exposed	2 / 235 (0.85%)	0 / 233 (0.00%)	
occurrences (all)	2	0	
Oral herpes			
subjects affected / exposed	2 / 235 (0.85%)	0 / 233 (0.00%)	
occurrences (all)	2	0	
Oropharyngeal candidiasis			
subjects affected / exposed	2 / 235 (0.85%)	0 / 233 (0.00%)	
occurrences (all)	2	0	
Pharyngitis			
subjects affected / exposed	2 / 235 (0.85%)	0 / 233 (0.00%)	
occurrences (all)	2	0	
Anal fungal infection			
subjects affected / exposed	1 / 235 (0.43%)	0 / 233 (0.00%)	
occurrences (all)	1	0	
Fungal infection			
subjects affected / exposed	0 / 235 (0.00%)	1 / 233 (0.43%)	
occurrences (all)	0	1	

Fungal oesophagitis			
subjects affected / exposed	0 / 235 (0.00%)	1 / 233 (0.43%)	
occurrences (all)	0	1	
Furuncle			
subjects affected / exposed	0 / 235 (0.00%)	1 / 233 (0.43%)	
occurrences (all)	0	1	
Herpes simplex			
subjects affected / exposed	1 / 235 (0.43%)	0 / 233 (0.00%)	
occurrences (all)	1	0	
Infection			
subjects affected / exposed	0 / 235 (0.00%)	1 / 233 (0.43%)	
occurrences (all)	0	1	
Mastoiditis			
subjects affected / exposed	0 / 235 (0.00%)	1 / 233 (0.43%)	
occurrences (all)	0	1	
Orchitis			
subjects affected / exposed	0 / 235 (0.00%)	1 / 233 (0.43%)	
occurrences (all)	0	1	
Otitis media			
subjects affected / exposed	0 / 235 (0.00%)	1 / 233 (0.43%)	
occurrences (all)	0	1	
Rash pustular			
subjects affected / exposed	1 / 235 (0.43%)	0 / 233 (0.00%)	
occurrences (all)	1	0	
Respiratory tract infection			
subjects affected / exposed	0 / 235 (0.00%)	1 / 233 (0.43%)	
occurrences (all)	0	1	
Soft tissue infection			
subjects affected / exposed	1 / 235 (0.43%)	0 / 233 (0.00%)	
occurrences (all)	1	0	
Tonsillitis			
subjects affected / exposed	1 / 235 (0.43%)	0 / 233 (0.00%)	
occurrences (all)	1	0	
Tracheobronchitis			
subjects affected / exposed	0 / 235 (0.00%)	1 / 233 (0.43%)	
occurrences (all)	0	1	

Vaginal infection			
subjects affected / exposed	1 / 235 (0.43%)	0 / 233 (0.00%)	
occurrences (all)	1	0	
Vulvovaginal mycotic infection			
subjects affected / exposed	1 / 235 (0.43%)	0 / 233 (0.00%)	
occurrences (all)	1	0	
Pneumonia			
subjects affected / exposed	4 / 235 (1.70%)	4 / 233 (1.72%)	
occurrences (all)	4	4	
Metabolism and nutrition disorders			
Hypokalaemia			
subjects affected / exposed	9 / 235 (3.83%)	3 / 233 (1.29%)	
occurrences (all)	9	4	
Increased appetite			
subjects affected / exposed	7 / 235 (2.98%)	6 / 233 (2.58%)	
occurrences (all)	7	6	
Hyperglycaemia			
subjects affected / exposed	4 / 235 (1.70%)	3 / 233 (1.29%)	
occurrences (all)	5	3	
Dehydration			
subjects affected / exposed	2 / 235 (0.85%)	4 / 233 (1.72%)	
occurrences (all)	2	4	
Hyponatraemia			
subjects affected / exposed	3 / 235 (1.28%)	1 / 233 (0.43%)	
occurrences (all)	3	1	
Cachexia			
subjects affected / exposed	2 / 235 (0.85%)	1 / 233 (0.43%)	
occurrences (all)	2	1	
Hypoalbuminaemia			
subjects affected / exposed	3 / 235 (1.28%)	0 / 233 (0.00%)	
occurrences (all)	3	0	
Hypomagnesaemia			
subjects affected / exposed	1 / 235 (0.43%)	2 / 233 (0.86%)	
occurrences (all)	1	2	
Hypocalcaemia			

subjects affected / exposed	1 / 235 (0.43%)	1 / 233 (0.43%)	
occurrences (all)	1	1	
Hyperkalaemia			
subjects affected / exposed	1 / 235 (0.43%)	0 / 233 (0.00%)	
occurrences (all)	1	0	
Malnutrition			
subjects affected / exposed	1 / 235 (0.43%)	0 / 233 (0.00%)	
occurrences (all)	1	0	
Polydipsia			
subjects affected / exposed	1 / 235 (0.43%)	0 / 233 (0.00%)	
occurrences (all)	1	0	
Decreased appetite			
subjects affected / exposed	28 / 235 (11.91%)	17 / 233 (7.30%)	
occurrences (all)	28	17	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported