



Clinical trial results:

A Randomized, Double-Blind, Placebo-Controlled, Phase 3 Study of Rovalpituzumab Tesirine as Maintenance Therapy Following First-Line Platinum-Based Chemotherapy in Subjects with Extensive Stage Small Cell Lung Cancer (MERU)

Summary

EudraCT number	2016-003503-64
Trial protocol	EE AT DK FI IE GB SE DE NL LV PT HU GR PL ES CZ BG LT BE
Global end of trial date	29 November 2019

Results information

Result version number	v2 (current)
This version publication date	06 January 2021
First version publication date	27 November 2020

Version creation reason	<ul style="list-style-type: none">• Correction of full data set Update to full data set.
-------------------------	--

Trial information

Trial identification

Sponsor protocol code	M16-298
-----------------------	---------

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03033511
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	AbbVie
Sponsor organisation address	AbbVie House, Vanwall Business Park, Vanwall Road, Maidenhead, Berkshire, United Kingdom, SL6 4UB
Public contact	Global Medical Services, AbbVie, 001 8006339110, abbvieclinicaltrials@abbvie.com
Scientific contact	Global Medical Services, AbbVie, 001 8006339110, abbvieclinicaltrials@abbvie.com

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	29 November 2019
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	29 November 2019
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The primary objective was to evaluate if rovalpituzumab tesirine improves progression-free survival (PFS), assessed by a central radiographic assessment committee, and overall survival (OS) in subjects with extensive stage disease small cell lung cancer (ED SCLC) tumors with a high level of delta-like protein 3 (DLL3) expression (DLL3^{high}) who have ongoing clinical benefit (stable disease [SD], partial response [PR], or complete response [CR]) following the completion of 4 cycles of first-line, platinum-based chemotherapy (cisplatin or carboplatin plus irinotecan or etoposide) compared to placebo.

Protection of trial subjects:

The study was conducted in accordance with the protocol, International Conference on Harmonization (ICH) guidelines applicable regulations and guidelines governing clinical study conduct and the ethical principles that have their origin in the Declaration of Helsinki. The investigator or his/her representative explained the nature of the study to the subject, and answered all questions regarding this study.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	07 February 2017
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	South Africa: 7
Country: Number of subjects enrolled	Spain: 47
Country: Number of subjects enrolled	Sweden: 9
Country: Number of subjects enrolled	Switzerland: 19
Country: Number of subjects enrolled	Taiwan: 18
Country: Number of subjects enrolled	Turkey: 44
Country: Number of subjects enrolled	Ukraine: 20
Country: Number of subjects enrolled	United Kingdom: 20
Country: Number of subjects enrolled	United States: 100
Country: Number of subjects enrolled	Australia: 16
Country: Number of subjects enrolled	Austria: 15
Country: Number of subjects enrolled	Belarus: 8
Country: Number of subjects enrolled	Belgium: 14
Country: Number of subjects enrolled	Brazil: 12
Country: Number of subjects enrolled	Canada: 13
Country: Number of subjects enrolled	China: 13

Country: Number of subjects enrolled	Croatia: 4
Country: Number of subjects enrolled	Czech Republic: 8
Country: Number of subjects enrolled	Denmark: 9
Country: Number of subjects enrolled	Estonia: 5
Country: Number of subjects enrolled	France: 32
Country: Number of subjects enrolled	Germany: 26
Country: Number of subjects enrolled	Greece: 17
Country: Number of subjects enrolled	Hong Kong: 3
Country: Number of subjects enrolled	Hungary: 10
Country: Number of subjects enrolled	Ireland: 8
Country: Number of subjects enrolled	Israel: 24
Country: Number of subjects enrolled	Italy: 11
Country: Number of subjects enrolled	Japan: 57
Country: Number of subjects enrolled	Korea, Republic of: 27
Country: Number of subjects enrolled	Latvia: 17
Country: Number of subjects enrolled	Lithuania: 13
Country: Number of subjects enrolled	Mexico: 2
Country: Number of subjects enrolled	Netherlands: 27
Country: Number of subjects enrolled	Norway: 23
Country: Number of subjects enrolled	Poland: 1
Country: Number of subjects enrolled	Portugal: 10
Country: Number of subjects enrolled	Russian Federation: 36
Country: Number of subjects enrolled	Serbia: 3
Worldwide total number of subjects	748
EEA total number of subjects	326

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)	388
From 65 to 84 years	356
85 years and over	4

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Screening procedures were performed within 21 days prior to randomization, with the exception of radiographic assessments (computed tomography [CT] scan or magnetic resonance imaging [MRI] including the head, chest, and abdomen) which may have been performed within 28 days prior to randomization.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Blinding implementation details:

AbbVie, the Investigator, the study site personnel, and subject remained blinded to each subject's treatment with rovalpituzumab tesirine or placebo and dexamethasone or placebo and throughout the course of the study.

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Placebo every 6 weeks (q6 wk); omitting every third cycle

Placebo for rovalpituzumab tesirine: Placebo for rovalpituzumab tesirine administered intravenously Day 1 of each 6-week cycle, omitting every third cycle

Placebo for dexamethasone: Placebo for dexamethasone administered orally twice daily on Day -1, Day 1 (the day of dosing), and Day 2 of each 6 week cycle, omitting every third cycle

Arm type	Placebo
Investigational medicinal product name	Placebo for rovalpituzumab tesirine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Placebo for rovalpituzumab tesirine administered intravenously Day 1 of each 6-week cycle, omitting every third cycle

Investigational medicinal product name	Placebo for dexamethasone
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Placebo for administered orally twice daily on Day -1, Day 1 (the day of dosing), and Day 2 of each 6 week cycle, omitting every third cycle

Arm title	Rovalpituzumab Tesirine/Dexamethasone
------------------	---------------------------------------

Arm description:

Rovalpituzumab tesirine/dexamethasone q6 wk; omitting every third cycle

Rovalpituzumab tesirine: Rovalpituzumab tesirine 0.3 mg/kg administered intravenously Day 1 of each

6-week cycle, omitting every third cycle

Dexamethasone: Dexamethasone 8 mg administered orally twice daily on Day -1, Day 1 (the day of dosing), and Day 2 of each 6 week cycle, omitting every third cycle

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

Dosage and administration details:

Roalpituzumab tesirine 0.3 mg/kg administered intravenously Day 1 of each 6-week cycle, omitting every third cycle

Investigational medicinal product name	Dexamethasone
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Dexamethasone 8 mg administered orally twice daily on Day -1, Day 1 (the day of dosing), and Day 2 of each 6 week cycle, omitting every third cycle

Number of subjects in period 1	Placebo	Roalpituzumab Tesirine/Dexamethasone
Started	376	372
Completed	376	372

Baseline characteristics

Reporting groups

Reporting group title	Placebo
Reporting group description:	
Placebo every 6 weeks (q6 wk); omitting every third cycle	
Placebo for rovalpituzumab tesirine: Placebo for rovalpituzumab tesirine administered intravenously Day 1 of each 6-week cycle, omitting every third cycle	
Placebo for dexamethasone: Placebo for dexamethasone administered orally twice daily on Day -1, Day 1 (the day of dosing), and Day 2 of each 6 week cycle, omitting every third cycle	
Reporting group title	Rovalpituzumab Tesirine/Dexamethasone
Reporting group description:	
Rovalpituzumab tesirine/dexamethasone q6 wk; omitting every third cycle	
Rovalpituzumab tesirine: Rovalpituzumab tesirine 0.3 mg/kg administered intravenously Day 1 of each 6-week cycle, omitting every third cycle	
Dexamethasone: Dexamethasone 8 mg administered orally twice daily on Day -1, Day 1 (the day of dosing), and Day 2 of each 6 week cycle, omitting every third cycle	

Reporting group values	Placebo	Rovalpituzumab Tesirine/Dexamethasone	Total
Number of subjects	376	372	748
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	63.8	64.1	-
standard deviation	± 8.20	± 8.40	
Gender categorical Units: Subjects			
Female	137	114	251
Male	239	258	497
Ethnicity Units: Subjects			
Hispanic or Latino	18	15	33
Not Hispanic or Latino	356	355	711
Missing	2	2	4
Race Units: Subjects			
White	301	314	615
Black or African American	7	2	9
Asian	66	55	121
American Indian or Alaska Native	2	0	2
Multiple Races	0	1	1

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description:	
Placebo every 6 weeks (q6 wk); omitting every third cycle	
Placebo for rovalpituzumab tesirine: Placebo for rovalpituzumab tesirine administered intravenously Day 1 of each 6-week cycle, omitting every third cycle	
Placebo for dexamethasone: Placebo for dexamethasone administered orally twice daily on Day -1, Day 1 (the day of dosing), and Day 2 of each 6 week cycle, omitting every third cycle	
Reporting group title	Rovalpituzumab Tesirine/Dexamethasone
Reporting group description:	
Rovalpituzumab tesirine/dexamethasone q6 wk; omitting every third cycle	
Rovalpituzumab tesirine: Rovalpituzumab tesirine 0.3 mg/kg administered intravenously Day 1 of each 6-week cycle, omitting every third cycle	
Dexamethasone: Dexamethasone 8 mg administered orally twice daily on Day -1, Day 1 (the day of dosing), and Day 2 of each 6 week cycle, omitting every third cycle	

Primary: Overall Survival (OS) in Participants With Extensive-Stage Small Cell Lung Cancer With Delta-Like Protein 3 High Expression in Tumor (DLL3high)

End point title	Overall Survival (OS) in Participants With Extensive-Stage Small Cell Lung Cancer With Delta-Like Protein 3 High Expression in Tumor (DLL3high)
End point description:	
OS is defined as the number of months from randomization to death of any cause. Calculated using the Kaplan-Meier methodology.	
DLL3 High Set: all randomized participants with extensive-stage small cell lung cancer with delta-like protein 3 high expression in tumor (DLL3high), defined as $\geq 75\%$ tumor cells staining positive according to the VENTANA DLL3 [SP347] immunohistochemistry [IHC] assay.	
End point type	Primary
End point timeframe:	
Survival follow-up continued until the endpoint of death, the subject was lost to follow-up or withdrew consent, or termination of the study by AbbVie, whichever occurred first. Median time on study overall was 11.9 months.	

End point values	Placebo	Rovalpituzumab Tesirine/Dexamethasone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	240	217		
Units: months				
median (confidence interval 95%)	9.79 (8.38 to 10.87)	8.48 (7.26 to 10.18)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo v Rovalpituzumab Tesirine/Dexamethasone
Number of subjects included in analysis	457
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.537 ^[1]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.07
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.84
upper limit	1.36

Notes:

[1] - stratified log-rank test

Secondary: OS in All Randomized Participants

End point title	OS in All Randomized Participants
-----------------	-----------------------------------

End point description:

OS is defined as the number of months from randomization to death of any cause. Calculated using the Kaplan-Meier methodology.

Randomized Set: all randomized participants, grouped according to the treatment arm to which they were randomized regardless the actual treatment received.

End point type	Secondary
----------------	-----------

End point timeframe:

Survival follow-up continued until the endpoint of death, the subject was lost to follow-up or withdrew consent, or termination of the study by AbbVie, whichever occurred first. Median time on study overall was 11.9 months.

End point values	Placebo	Rovalpituzumab Tesirine/Dexamethasone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	376	372		
Units: months				
median (confidence interval 95%)	9.89 (8.61 to 11.01)	8.80 (7.95 to 9.53)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Rovalpituzumab Tesirine/Dexamethasone v Placebo

Number of subjects included in analysis	748
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.237 ^[2]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.12
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.92
upper limit	1.36

Notes:

[2] - stratified log-rank test

Secondary: Change From Baseline in European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core (EORTC QLQ-C30) Physical Functioning Domain Over Time

End point title	Change From Baseline in European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core (EORTC QLQ-C30) Physical Functioning Domain Over Time
-----------------	---

End point description:

The EORTC QLQ-C30 is composed of global health status/QoL scale; five functional domains (physical, role, emotional, cognitive, and social); three symptom domains (fatigue, nausea and vomiting, and pain); and six single items (dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties).

The Physical Functioning domain includes 5 questions in which participants were asked to rate their overall health and overall quality of life as it relates to physical functioning during the past week on a scale from 1 (very poor) to 7 (excellent). The 5 scores were averaged and transformed to a scale from 0 to 100, where a high score represents a high QoL. A positive change from baseline indicates better quality of life.

Randomized Set: all randomized participants, grouped according to the treatment arm to which they were randomized regardless the actual treatment received. Participants with an assessment at given time point.

End point type	Secondary
----------------	-----------

End point timeframe:

Baseline, Weeks 6, 12, 18, 24, 30, 36, 42, 48, 54, 60, 66, 72, 78, Final Visit (up to Week 78)

End point values	Placebo	Rovalpituzumab Tesirine/Dexamethasone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	376 ^[3]	372 ^[4]		
Units: score on a scale				
least squares mean (standard error)				
Change at Week 6; n=287, 296	-3.97 (± 1.00)	-4.34 (± 0.95)		
Change at Week 12; n=104, 191	-1.70 (± 1.67)	-12.13 (± 1.27)		
Change at Week 18; n=9, 14	8.15 (± 4.02)	-19.52 (± 4.92)		

Change at Week 24; n=7, 11	-0.95 (± 7.32)	-19.39 (± 6.61)		
Change at Week 30; n=5, 10	5.33 (± 4.22)	-16.67 (± 6.78)		
Change at Week 36; n=2, 1	-13.33 (± 99999)	-13.33 (± 99999)		
Change at Week 42; n=1, 2	-6.67 (± 99999)	-3.33 (± 99999)		
Change at Week 48; n=3, 2	-6.67 (± 99999)	-63.33 (± 99999)		
Change at Week 54; n=1, 0	-6.67 (± 99999)	99999 (± 99999)		
Change at Week 60; n=1, 1	0.00 (± 99999)	0.00 (± 99999)		
Change at Week 66; n=2, 2	0.00 (± 99999)	0.00 (± 99999)		
Change at Week 72; n=1, 0	0.00 (± 99999)	99999 (± 99999)		
Change at Week 78; n=1, 1	0.00 (± 99999)	0.00 (± 99999)		
Change at Week Final Visit; n=298, 312	-4.14 (± 1.02)	-13.31 (± 1.12)		

Notes:

[3] - n=participants with assessment at given time point. 99999=not available

[4] - n=participants with assessment at given time point. 99999=not available

Attachments (see zip file)	EORTC QLQ-C30 Stat Analyses.docx
-----------------------------------	----------------------------------

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Day 1 of study treatment through 70 days after last treatment. Mean number of weeks on study treatment was 12.8 in the Placebo arm and 17.5 weeks in the Rovalpituzumab Tesirine Plus Dexamethasone arm.

Adverse event reporting additional description:

Safety Set: all subjects who were enrolled, randomized, and received at least 1 dose of study medication.

Assessment type	Systematic
-----------------	------------

Dictionary used

Dictionary name	MedDRA
-----------------	--------

Dictionary version	22.1
--------------------	------

Reporting groups

Reporting group title	Placebo
-----------------------	---------

Reporting group description:

Placebo q6 wk; omitting every third cycle

Placebo for rovalpituzumab tesirine: Placebo for rovalpituzumab tesirine administered intravenously Day 1 of each 6-week cycle, omitting every third cycle

Placebo for dexamethasone: Placebo for dexamethasone administered orally twice daily on Day -1, Day 1 (the day of dosing), and Day 2 of each 6 week cycle, omitting every third cycle

Reporting group title	Rovalpituzumab Tesirine/Dexamethasone
-----------------------	---------------------------------------

Reporting group description:

Rovalpituzumab tesirine/dexamethasone q6 wk; omitting every third cycle

Rovalpituzumab tesirine: Rovalpituzumab tesirine 0.3 mg/kg administered intravenously Day 1 of each 6-week cycle, omitting every third cycle

Dexamethasone: Dexamethasone 8 mg administered orally twice daily on Day -1, Day 1 (the day of dosing), and Day 2 of each 6 week cycle, omitting every third cycle

Serious adverse events	Placebo	Rovalpituzumab Tesirine/Dexamethasone	
Total subjects affected by serious adverse events			
subjects affected / exposed	87 / 373 (23.32%)	157 / 368 (42.66%)	
number of deaths (all causes)	198	223	
number of deaths resulting from adverse events	37	35	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
INFECTED NEOPLASM			
subjects affected / exposed	0 / 373 (0.00%)	1 / 368 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
ADENOCARCINOMA GASTRIC			

subjects affected / exposed	0 / 373 (0.00%)	1 / 368 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
LUNG NEOPLASM			
subjects affected / exposed	1 / 373 (0.27%)	1 / 368 (0.27%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
MALIGNANT NEOPLASM PROGRESSION			
subjects affected / exposed	21 / 373 (5.63%)	16 / 368 (4.35%)	
occurrences causally related to treatment / all	0 / 25	0 / 17	
deaths causally related to treatment / all	0 / 19	0 / 16	
METASTASES TO CENTRAL NERVOUS SYSTEM			
subjects affected / exposed	7 / 373 (1.88%)	7 / 368 (1.90%)	
occurrences causally related to treatment / all	0 / 10	0 / 8	
deaths causally related to treatment / all	0 / 2	0 / 0	
METASTASES TO LIVER			
subjects affected / exposed	1 / 373 (0.27%)	0 / 368 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
METASTATIC NEOPLASM			
subjects affected / exposed	1 / 373 (0.27%)	0 / 368 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
METASTASES TO MENINGES			
subjects affected / exposed	1 / 373 (0.27%)	2 / 368 (0.54%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 0	
NEOPLASM PROGRESSION			
subjects affected / exposed	1 / 373 (0.27%)	1 / 368 (0.27%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
NEUROENDOCRINE CARCINOMA			

subjects affected / exposed	1 / 373 (0.27%)	0 / 368 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
SINONASAL PAPILLOMA			
subjects affected / exposed	0 / 373 (0.00%)	1 / 368 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
SMALL CELL CARCINOMA			
subjects affected / exposed	1 / 373 (0.27%)	0 / 368 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
SMALL CELL LUNG CANCER METASTATIC			
subjects affected / exposed	1 / 373 (0.27%)	0 / 368 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
TUMOUR PAIN			
subjects affected / exposed	0 / 373 (0.00%)	1 / 368 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
HYPOTENSION			
subjects affected / exposed	0 / 373 (0.00%)	1 / 368 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
SHOCK			
subjects affected / exposed	0 / 373 (0.00%)	1 / 368 (0.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
JUGULAR VEIN THROMBOSIS			
subjects affected / exposed	0 / 373 (0.00%)	1 / 368 (0.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
SUPERIOR VENA CAVA SYNDROME			

subjects affected / exposed	3 / 373 (0.80%)	2 / 368 (0.54%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
VASCULAR COMPRESSION			
subjects affected / exposed	1 / 373 (0.27%)	0 / 368 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
VENA CAVA THROMBOSIS			
subjects affected / exposed	0 / 373 (0.00%)	1 / 368 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
General disorders and administration site conditions			
CHILLS			
subjects affected / exposed	0 / 373 (0.00%)	1 / 368 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
ASTHENIA			
subjects affected / exposed	1 / 373 (0.27%)	3 / 368 (0.82%)	
occurrences causally related to treatment / all	1 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
DISEASE PROGRESSION			
subjects affected / exposed	1 / 373 (0.27%)	0 / 368 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
DEATH			
subjects affected / exposed	1 / 373 (0.27%)	0 / 368 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
EUTHANASIA			
subjects affected / exposed	1 / 373 (0.27%)	0 / 368 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
FACE OEDEMA			

subjects affected / exposed	0 / 373 (0.00%)	1 / 368 (0.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
FATIGUE			
subjects affected / exposed	0 / 373 (0.00%)	2 / 368 (0.54%)	
occurrences causally related to treatment / all	0 / 0	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
GENERAL PHYSICAL HEALTH DETERIORATION			
subjects affected / exposed	8 / 373 (2.14%)	9 / 368 (2.45%)	
occurrences causally related to treatment / all	0 / 10	2 / 11	
deaths causally related to treatment / all	0 / 2	1 / 3	
GENERALISED OEDEMA			
subjects affected / exposed	0 / 373 (0.00%)	2 / 368 (0.54%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
HYPOTHERMIA			
subjects affected / exposed	1 / 373 (0.27%)	0 / 368 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
MALAISE			
subjects affected / exposed	2 / 373 (0.54%)	1 / 368 (0.27%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
MULTIPLE ORGAN DYSFUNCTION SYNDROME			
subjects affected / exposed	1 / 373 (0.27%)	0 / 368 (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	1 / 373 (0.27%)	0 / 368 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
OEDEMA PERIPHERAL			

subjects affected / exposed	0 / 373 (0.00%)	2 / 368 (0.54%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
SEROSITIS			
subjects affected / exposed	0 / 373 (0.00%)	1 / 368 (0.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PYREXIA			
subjects affected / exposed	2 / 373 (0.54%)	2 / 368 (0.54%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
SUDDEN DEATH			
subjects affected / exposed	0 / 373 (0.00%)	1 / 368 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
SWELLING FACE			
subjects affected / exposed	0 / 373 (0.00%)	1 / 368 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
ACUTE RESPIRATORY DISTRESS SYNDROME			
subjects affected / exposed	0 / 373 (0.00%)	3 / 368 (0.82%)	
occurrences causally related to treatment / all	0 / 0	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 2	
ACUTE RESPIRATORY FAILURE			
subjects affected / exposed	2 / 373 (0.54%)	0 / 368 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
BRONCHIAL OBSTRUCTION			
subjects affected / exposed	1 / 373 (0.27%)	0 / 368 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
CHRONIC OBSTRUCTIVE			

PULMONARY DISEASE			
subjects affected / exposed	2 / 373 (0.54%)	1 / 368 (0.27%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
COUGH			
subjects affected / exposed	1 / 373 (0.27%)	0 / 368 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
DYSпноEA			
subjects affected / exposed	4 / 373 (1.07%)	12 / 368 (3.26%)	
occurrences causally related to treatment / all	1 / 5	4 / 14	
deaths causally related to treatment / all	0 / 1	0 / 0	
DYSпноEA EXERTIONAL			
subjects affected / exposed	0 / 373 (0.00%)	1 / 368 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
EPISTAXIS			
subjects affected / exposed	0 / 373 (0.00%)	1 / 368 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
HYPOXIA			
subjects affected / exposed	1 / 373 (0.27%)	0 / 368 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
LUNG DISORDER			
subjects affected / exposed	0 / 373 (0.00%)	1 / 368 (0.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PLEURAL EFFUSION			
subjects affected / exposed	2 / 373 (0.54%)	22 / 368 (5.98%)	
occurrences causally related to treatment / all	0 / 2	18 / 23	
deaths causally related to treatment / all	0 / 0	0 / 0	
PNEUMONITIS			

subjects affected / exposed	0 / 373 (0.00%)	7 / 368 (1.90%)	
occurrences causally related to treatment / all	0 / 0	10 / 11	
deaths causally related to treatment / all	0 / 0	3 / 3	
PULMONARY ARTERY THROMBOSIS			
subjects affected / exposed	1 / 373 (0.27%)	0 / 368 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PULMONARY EMBOLISM			
subjects affected / exposed	1 / 373 (0.27%)	1 / 368 (0.27%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
RESPIRATORY DISORDER			
subjects affected / exposed	0 / 373 (0.00%)	1 / 368 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
RESPIRATORY DISTRESS			
subjects affected / exposed	0 / 373 (0.00%)	2 / 368 (0.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	
RESPIRATORY FAILURE			
subjects affected / exposed	1 / 373 (0.27%)	5 / 368 (1.36%)	
occurrences causally related to treatment / all	0 / 1	3 / 7	
deaths causally related to treatment / all	0 / 1	1 / 2	
Psychiatric disorders			
DELIRIUM			
subjects affected / exposed	0 / 373 (0.00%)	1 / 368 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
CONFUSIONAL STATE			
subjects affected / exposed	1 / 373 (0.27%)	1 / 368 (0.27%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
MENTAL STATUS CHANGES			

subjects affected / exposed	1 / 373 (0.27%)	1 / 368 (0.27%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
ASPARTATE AMINOTRANSFERASE INCREASED			
subjects affected / exposed	1 / 373 (0.27%)	0 / 368 (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	0 / 373 (0.00%)	1 / 368 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
BLOOD URIC ACID INCREASED			
subjects affected / exposed	0 / 373 (0.00%)	1 / 368 (0.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
C-REACTIVE PROTEIN INCREASED			
subjects affected / exposed	0 / 373 (0.00%)	1 / 368 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
OXYGEN SATURATION DECREASED			
subjects affected / exposed	1 / 373 (0.27%)	0 / 368 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
HEPATIC ENZYME INCREASED			
subjects affected / exposed	0 / 373 (0.00%)	3 / 368 (0.82%)	
occurrences causally related to treatment / all	0 / 0	4 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
PANCREATIC ENZYMES INCREASED			
subjects affected / exposed	1 / 373 (0.27%)	0 / 368 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PLATELET COUNT DECREASED			

subjects affected / exposed	1 / 373 (0.27%)	2 / 368 (0.54%)	
occurrences causally related to treatment / all	2 / 2	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
ANKLE FRACTURE			
subjects affected / exposed	0 / 373 (0.00%)	1 / 368 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
FALL			
subjects affected / exposed	1 / 373 (0.27%)	1 / 368 (0.27%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
HIP FRACTURE			
subjects affected / exposed	1 / 373 (0.27%)	0 / 368 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
HUMERUS FRACTURE			
subjects affected / exposed	0 / 373 (0.00%)	1 / 368 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
RADIATION PNEUMONITIS			
subjects affected / exposed	0 / 373 (0.00%)	1 / 368 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PELVIC FRACTURE			
subjects affected / exposed	0 / 373 (0.00%)	1 / 368 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
ACUTE MYOCARDIAL INFARCTION			
subjects affected / exposed	1 / 373 (0.27%)	0 / 368 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

ATRIAL FIBRILLATION			
subjects affected / exposed	1 / 373 (0.27%)	1 / 368 (0.27%)	
occurrences causally related to treatment / all	1 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
MYOCARDIAL INFARCTION			
subjects affected / exposed	1 / 373 (0.27%)	0 / 368 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
RIGHT VENTRICULAR FAILURE			
subjects affected / exposed	0 / 373 (0.00%)	1 / 368 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
PERICARDIAL EFFUSION			
subjects affected / exposed	2 / 373 (0.54%)	4 / 368 (1.09%)	
occurrences causally related to treatment / all	2 / 2	3 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
SUPRAVENTRICULAR TACHYCARDIA			
subjects affected / exposed	1 / 373 (0.27%)	1 / 368 (0.27%)	
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	0 / 373 (0.00%)	1 / 368 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
COGNITIVE DISORDER			
subjects affected / exposed	1 / 373 (0.27%)	0 / 368 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
DIZZINESS			
subjects affected / exposed	0 / 373 (0.00%)	2 / 368 (0.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
DYSMETRIA			

subjects affected / exposed	1 / 373 (0.27%)	0 / 368 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
EPILEPSY			
subjects affected / exposed	1 / 373 (0.27%)	2 / 368 (0.54%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
FACIAL PARESIS			
subjects affected / exposed	1 / 373 (0.27%)	0 / 368 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
HAEMORRHAGE INTRACRANIAL			
subjects affected / exposed	1 / 373 (0.27%)	0 / 368 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
HYPERAESTHESIA			
subjects affected / exposed	0 / 373 (0.00%)	1 / 368 (0.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
HYPOAESTHESIA			
subjects affected / exposed	1 / 373 (0.27%)	0 / 368 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
METABOLIC ENCEPHALOPATHY			
subjects affected / exposed	0 / 373 (0.00%)	1 / 368 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
NERVOUS SYSTEM DISORDER			
subjects affected / exposed	0 / 373 (0.00%)	1 / 368 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PARAPLEGIA			

subjects affected / exposed	0 / 373 (0.00%)	1 / 368 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
SEIZURE			
subjects affected / exposed	1 / 373 (0.27%)	1 / 368 (0.27%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
SPINAL CORD COMPRESSION			
subjects affected / exposed	1 / 373 (0.27%)	0 / 368 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
SYNCOPE			
subjects affected / exposed	1 / 373 (0.27%)	0 / 368 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
TRANSIENT ISCHAEMIC ATTACK			
subjects affected / exposed	0 / 373 (0.00%)	1 / 368 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
VOCAL CORD PARALYSIS			
subjects affected / exposed	0 / 373 (0.00%)	1 / 368 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
ANAEMIA			
subjects affected / exposed	1 / 373 (0.27%)	0 / 368 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
FEBRILE NEUTROPENIA			
subjects affected / exposed	3 / 373 (0.80%)	2 / 368 (0.54%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
LEUKOPENIA			

subjects affected / exposed	1 / 373 (0.27%)	0 / 368 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PANCYTOPENIA			
subjects affected / exposed	0 / 373 (0.00%)	2 / 368 (0.54%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
NEUTROPENIA			
subjects affected / exposed	0 / 373 (0.00%)	2 / 368 (0.54%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
THROMBOCYTOPENIA			
subjects affected / exposed	0 / 373 (0.00%)	8 / 368 (2.17%)	
occurrences causally related to treatment / all	0 / 0	9 / 9	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
VERTIGO			
subjects affected / exposed	1 / 373 (0.27%)	0 / 368 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
ANGLE CLOSURE GLAUCOMA			
subjects affected / exposed	0 / 373 (0.00%)	1 / 368 (0.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
EYELID OEDEMA			
subjects affected / exposed	0 / 373 (0.00%)	1 / 368 (0.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PERIORBITAL SWELLING			
subjects affected / exposed	0 / 373 (0.00%)	2 / 368 (0.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
VISUAL IMPAIRMENT			

subjects affected / exposed	1 / 373 (0.27%)	0 / 368 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
ABDOMINAL ADHESIONS			
subjects affected / exposed	0 / 373 (0.00%)	1 / 368 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
ABDOMINAL PAIN			
subjects affected / exposed	2 / 373 (0.54%)	6 / 368 (1.63%)	
occurrences causally related to treatment / all	0 / 2	1 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
ABDOMINAL PAIN UPPER			
subjects affected / exposed	0 / 373 (0.00%)	1 / 368 (0.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
ASCITES			
subjects affected / exposed	0 / 373 (0.00%)	2 / 368 (0.54%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
COLITIS			
subjects affected / exposed	0 / 373 (0.00%)	1 / 368 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
CONSTIPATION			
subjects affected / exposed	1 / 373 (0.27%)	1 / 368 (0.27%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
DIARRHOEA			
subjects affected / exposed	1 / 373 (0.27%)	0 / 368 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
DUODENAL OBSTRUCTION			

subjects affected / exposed	0 / 373 (0.00%)	1 / 368 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
DUODENAL ULCER			
subjects affected / exposed	0 / 373 (0.00%)	1 / 368 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
GASTRIC PERFORATION			
subjects affected / exposed	0 / 373 (0.00%)	1 / 368 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
GASTRITIS			
subjects affected / exposed	0 / 373 (0.00%)	1 / 368 (0.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
GASTROINTESTINAL HAEMORRHAGE			
subjects affected / exposed	1 / 373 (0.27%)	0 / 368 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
NAUSEA			
subjects affected / exposed	0 / 373 (0.00%)	3 / 368 (0.82%)	
occurrences causally related to treatment / all	0 / 0	3 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
INTESTINAL OBSTRUCTION			
subjects affected / exposed	0 / 373 (0.00%)	2 / 368 (0.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
PANCREATITIS			
subjects affected / exposed	0 / 373 (0.00%)	1 / 368 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
STOMATITIS			

subjects affected / exposed	2 / 373 (0.54%)	1 / 368 (0.27%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
UPPER GASTROINTESTINAL HAEMORRHAGE			
subjects affected / exposed	0 / 373 (0.00%)	2 / 368 (0.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
VOMITING			
subjects affected / exposed	2 / 373 (0.54%)	1 / 368 (0.27%)	
occurrences causally related to treatment / all	1 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
CHOLECYSTITIS ACUTE			
subjects affected / exposed	0 / 373 (0.00%)	1 / 368 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
DRUG-INDUCED LIVER INJURY			
subjects affected / exposed	0 / 373 (0.00%)	2 / 368 (0.54%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
HEPATIC FAILURE			
subjects affected / exposed	1 / 373 (0.27%)	0 / 368 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
HEPATIC FUNCTION ABNORMAL			
subjects affected / exposed	1 / 373 (0.27%)	2 / 368 (0.54%)	
occurrences causally related to treatment / all	0 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
HEPATITIS			
subjects affected / exposed	0 / 373 (0.00%)	1 / 368 (0.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
HEPATOTOXICITY			

subjects affected / exposed	0 / 373 (0.00%)	1 / 368 (0.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
HYPERBILIRUBINAEMIA			
subjects affected / exposed	1 / 373 (0.27%)	0 / 368 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
JAUNDICE CHOLESTATIC			
subjects affected / exposed	0 / 373 (0.00%)	1 / 368 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
LIVER DISORDER			
subjects affected / exposed	0 / 373 (0.00%)	1 / 368 (0.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
DERMATITIS BULLOUS			
subjects affected / exposed	0 / 373 (0.00%)	1 / 368 (0.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PHOTOSENSITIVITY REACTION			
subjects affected / exposed	0 / 373 (0.00%)	3 / 368 (0.82%)	
occurrences causally related to treatment / all	0 / 0	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
RASH ERYTHEMATOUS			
subjects affected / exposed	0 / 373 (0.00%)	1 / 368 (0.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
SKIN EXFOLIATION			
subjects affected / exposed	0 / 373 (0.00%)	1 / 368 (0.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			

ACUTE KIDNEY INJURY			
subjects affected / exposed	2 / 373 (0.54%)	1 / 368 (0.27%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
DYSURIA			
subjects affected / exposed	1 / 373 (0.27%)	0 / 368 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
RENAL FAILURE			
subjects affected / exposed	0 / 373 (0.00%)	1 / 368 (0.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
HYPERTHYROIDISM			
subjects affected / exposed	0 / 373 (0.00%)	1 / 368 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
INAPPROPRIATE ANTIDIURETIC HORMONE SECRETION			
subjects affected / exposed	1 / 373 (0.27%)	0 / 368 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
ARTHRALGIA			
subjects affected / exposed	0 / 373 (0.00%)	2 / 368 (0.54%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
BONE PAIN			
subjects affected / exposed	1 / 373 (0.27%)	0 / 368 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
FIBROMYALGIA			

subjects affected / exposed	0 / 373 (0.00%)	1 / 368 (0.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
MUSCULAR WEAKNESS			
subjects affected / exposed	0 / 373 (0.00%)	2 / 368 (0.54%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
MUSCULOSKELETAL PAIN			
subjects affected / exposed	0 / 373 (0.00%)	1 / 368 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
MYALGIA			
subjects affected / exposed	0 / 373 (0.00%)	1 / 368 (0.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
OSTEOLYSIS			
subjects affected / exposed	1 / 373 (0.27%)	0 / 368 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
BRONCHITIS			
subjects affected / exposed	0 / 373 (0.00%)	1 / 368 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
BILIARY TRACT INFECTION			
subjects affected / exposed	1 / 373 (0.27%)	0 / 368 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
CAMPYLOBACTER GASTROENTERITIS			
subjects affected / exposed	0 / 373 (0.00%)	1 / 368 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
CELLULITIS			

subjects affected / exposed	0 / 373 (0.00%)	1 / 368 (0.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
CORONA VIRUS INFECTION			
subjects affected / exposed	0 / 373 (0.00%)	1 / 368 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
CYTOMEGALOVIRUS CHORIORETINITIS			
subjects affected / exposed	0 / 373 (0.00%)	1 / 368 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
DIVERTICULITIS			
subjects affected / exposed	0 / 373 (0.00%)	2 / 368 (0.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
ERYSIPELAS			
subjects affected / exposed	0 / 373 (0.00%)	1 / 368 (0.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
GANGRENE			
subjects affected / exposed	0 / 373 (0.00%)	1 / 368 (0.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
ESCHERICHIA URINARY TRACT INFECTION			
subjects affected / exposed	0 / 373 (0.00%)	1 / 368 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
HAEMOPHILUS INFECTION			
subjects affected / exposed	0 / 373 (0.00%)	1 / 368 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
INFLUENZA			

subjects affected / exposed	0 / 373 (0.00%)	1 / 368 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
KLEBSIELLA INFECTION			
subjects affected / exposed	0 / 373 (0.00%)	1 / 368 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
LOWER RESPIRATORY TRACT INFECTION			
subjects affected / exposed	0 / 373 (0.00%)	3 / 368 (0.82%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
LUNG ABSCESS			
subjects affected / exposed	0 / 373 (0.00%)	1 / 368 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
METAPNEUMOVIRUS INFECTION			
subjects affected / exposed	0 / 373 (0.00%)	1 / 368 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PNEUMOCYSTIS JIROVECI PNEUMONIA			
subjects affected / exposed	0 / 373 (0.00%)	1 / 368 (0.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PNEUMONIA			
subjects affected / exposed	8 / 373 (2.14%)	14 / 368 (3.80%)	
occurrences causally related to treatment / all	0 / 8	5 / 16	
deaths causally related to treatment / all	0 / 0	1 / 1	
PNEUMONIA BACTERIAL			
subjects affected / exposed	1 / 373 (0.27%)	0 / 368 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PNEUMONIA PSEUDOMONAL			

subjects affected / exposed	1 / 373 (0.27%)	0 / 368 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PSEUDOMONAS INFECTION			
subjects affected / exposed	0 / 373 (0.00%)	1 / 368 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
RESPIRATORY TRACT INFECTION			
subjects affected / exposed	2 / 373 (0.54%)	2 / 368 (0.54%)	
occurrences causally related to treatment / all	1 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
RHINITIS			
subjects affected / exposed	0 / 373 (0.00%)	1 / 368 (0.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
SEPSIS			
subjects affected / exposed	2 / 373 (0.54%)	6 / 368 (1.63%)	
occurrences causally related to treatment / all	0 / 2	1 / 8	
deaths causally related to treatment / all	0 / 1	0 / 3	
SEPTIC SHOCK			
subjects affected / exposed	0 / 373 (0.00%)	1 / 368 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
SUBCUTANEOUS ABSCESS			
subjects affected / exposed	1 / 373 (0.27%)	0 / 368 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
URINARY TRACT INFECTION			
subjects affected / exposed	1 / 373 (0.27%)	3 / 368 (0.82%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
CACHEXIA			

subjects affected / exposed	1 / 373 (0.27%)	0 / 368 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
DECREASED APPETITE			
subjects affected / exposed	1 / 373 (0.27%)	3 / 368 (0.82%)	
occurrences causally related to treatment / all	0 / 2	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
DEHYDRATION			
subjects affected / exposed	0 / 373 (0.00%)	4 / 368 (1.09%)	
occurrences causally related to treatment / all	0 / 0	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
DIABETES MELLITUS			
subjects affected / exposed	1 / 373 (0.27%)	0 / 368 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
DIABETES MELLITUS INADEQUATE CONTROL			
subjects affected / exposed	0 / 373 (0.00%)	1 / 368 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
FAILURE TO THRIVE			
subjects affected / exposed	1 / 373 (0.27%)	0 / 368 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
HYPERCALCAEMIA			
subjects affected / exposed	1 / 373 (0.27%)	0 / 368 (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	0 / 373 (0.00%)	1 / 368 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
HYPOALBUMINAEMIA			

subjects affected / exposed	0 / 373 (0.00%)	3 / 368 (0.82%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
HYPOKALAEMIA			
subjects affected / exposed	0 / 373 (0.00%)	1 / 368 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
HYPONATRAEMIA			
subjects affected / exposed	5 / 373 (1.34%)	6 / 368 (1.63%)	
occurrences causally related to treatment / all	2 / 6	2 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
HYPOPROTEINAEMIA			
subjects affected / exposed	0 / 373 (0.00%)	1 / 368 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Placebo	Rovalpituzumab Tesirine/Dexamethasone	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	248 / 373 (66.49%)	315 / 368 (85.60%)	
Investigations			
ALANINE AMINOTRANSFERASE INCREASED			
subjects affected / exposed	8 / 373 (2.14%)	39 / 368 (10.60%)	
occurrences (all)	8	45	
ASPARTATE AMINOTRANSFERASE INCREASED			
subjects affected / exposed	12 / 373 (3.22%)	48 / 368 (13.04%)	
occurrences (all)	13	59	
BLOOD ALKALINE PHOSPHATASE INCREASED			
subjects affected / exposed	6 / 373 (1.61%)	29 / 368 (7.88%)	
occurrences (all)	7	44	
GAMMA-GLUTAMYLTRANSFERASE INCREASED			

subjects affected / exposed occurrences (all)	3 / 373 (0.80%) 3	19 / 368 (5.16%) 21	
WEIGHT DECREASED subjects affected / exposed occurrences (all)	16 / 373 (4.29%) 17	19 / 368 (5.16%) 22	
Cardiac disorders PERICARDIAL EFFUSION subjects affected / exposed occurrences (all)	6 / 373 (1.61%) 7	58 / 368 (15.76%) 63	
Nervous system disorders DIZZINESS subjects affected / exposed occurrences (all)	18 / 373 (4.83%) 18	30 / 368 (8.15%) 34	
HEADACHE subjects affected / exposed occurrences (all)	19 / 373 (5.09%) 19	31 / 368 (8.42%) 39	
Blood and lymphatic system disorders ANAEMIA subjects affected / exposed occurrences (all)	11 / 373 (2.95%) 18	45 / 368 (12.23%) 51	
NEUTROPENIA subjects affected / exposed occurrences (all)	10 / 373 (2.68%) 11	31 / 368 (8.42%) 37	
THROMBOCYTOPENIA subjects affected / exposed occurrences (all)	14 / 373 (3.75%) 19	61 / 368 (16.58%) 79	
General disorders and administration site conditions ASTHENIA subjects affected / exposed occurrences (all)	25 / 373 (6.70%) 27	34 / 368 (9.24%) 47	
FACE OEDEMA subjects affected / exposed occurrences (all)	5 / 373 (1.34%) 5	41 / 368 (11.14%) 48	
FATIGUE subjects affected / exposed occurrences (all)	60 / 373 (16.09%) 66	91 / 368 (24.73%) 112	

OEDEMA PERIPHERAL subjects affected / exposed occurrences (all)	28 / 373 (7.51%) 32	93 / 368 (25.27%) 130	
PYREXIA subjects affected / exposed occurrences (all)	12 / 373 (3.22%) 13	20 / 368 (5.43%) 24	
Gastrointestinal disorders			
ABDOMINAL PAIN subjects affected / exposed occurrences (all)	14 / 373 (3.75%) 14	21 / 368 (5.71%) 24	
CONSTIPATION subjects affected / exposed occurrences (all)	35 / 373 (9.38%) 37	48 / 368 (13.04%) 57	
DIARRHOEA subjects affected / exposed occurrences (all)	35 / 373 (9.38%) 39	30 / 368 (8.15%) 35	
DYSPEPSIA subjects affected / exposed occurrences (all)	4 / 373 (1.07%) 4	20 / 368 (5.43%) 22	
NAUSEA subjects affected / exposed occurrences (all)	51 / 373 (13.67%) 56	77 / 368 (20.92%) 86	
VOMITING subjects affected / exposed occurrences (all)	35 / 373 (9.38%) 40	35 / 368 (9.51%) 41	
Respiratory, thoracic and mediastinal disorders			
COUGH subjects affected / exposed occurrences (all)	43 / 373 (11.53%) 47	56 / 368 (15.22%) 69	
DYSPNOEA subjects affected / exposed occurrences (all)	39 / 373 (10.46%) 41	67 / 368 (18.21%) 82	
PLEURAL EFFUSION subjects affected / exposed occurrences (all)	11 / 373 (2.95%) 12	76 / 368 (20.65%) 91	
PRODUCTIVE COUGH			

subjects affected / exposed occurrences (all)	11 / 373 (2.95%) 12	23 / 368 (6.25%) 27	
Skin and subcutaneous tissue disorders			
DRY SKIN			
subjects affected / exposed	9 / 373 (2.41%)	21 / 368 (5.71%)	
occurrences (all)	9	21	
ERYTHEMA			
subjects affected / exposed	5 / 373 (1.34%)	22 / 368 (5.98%)	
occurrences (all)	6	36	
PHOTOSENSITIVITY REACTION			
subjects affected / exposed	5 / 373 (1.34%)	88 / 368 (23.91%)	
occurrences (all)	5	126	
PRURITUS			
subjects affected / exposed	17 / 373 (4.56%)	21 / 368 (5.71%)	
occurrences (all)	18	25	
RASH			
subjects affected / exposed	8 / 373 (2.14%)	24 / 368 (6.52%)	
occurrences (all)	9	28	
SKIN TOXICITY			
subjects affected / exposed	6 / 373 (1.61%)	22 / 368 (5.98%)	
occurrences (all)	6	24	
Psychiatric disorders			
INSOMNIA			
subjects affected / exposed	13 / 373 (3.49%)	33 / 368 (8.97%)	
occurrences (all)	13	33	
Musculoskeletal and connective tissue disorders			
ARTHRALGIA			
subjects affected / exposed	19 / 373 (5.09%)	30 / 368 (8.15%)	
occurrences (all)	20	33	
BACK PAIN			
subjects affected / exposed	29 / 373 (7.77%)	22 / 368 (5.98%)	
occurrences (all)	29	23	
Metabolism and nutrition disorders			
HYPERGLYCAEMIA			
subjects affected / exposed	3 / 373 (0.80%)	29 / 368 (7.88%)	
occurrences (all)	4	32	

DECREASED APPETITE			
subjects affected / exposed	49 / 373 (13.14%)	95 / 368 (25.82%)	
occurrences (all)	55	115	
HYPOALBUMINAEMIA			
subjects affected / exposed	3 / 373 (0.80%)	32 / 368 (8.70%)	
occurrences (all)	4	41	
HYPOKALAEMIA			
subjects affected / exposed	9 / 373 (2.41%)	27 / 368 (7.34%)	
occurrences (all)	10	34	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
03 February 2017	Amendment 1: clarification that best response at Screening is determined by RECIST v1.1; DLL3 ^{high} defined as > 75% tumor cells staining positive according to the VENTANA DLL3 (SP347) IHC Assay; allowed concomitant dose of prednisone reduced to < 10mg/day; clarification of 12 weeks of non-treatment after 2 dosing cycles; clarification that secondary variable of objective response rate (ORR) is per CRAC and investigator assessment.
20 April 2017	Amendment 2: exclude subjects with any history of capillary leak syndrome; exclude subjects with known hypersensitivity to pharmaceuticals produced in Chinese hamster ovary cells; strong inhibitors of cytochrome P450 3A4 (CYP3A4) prohibited.
09 May 2017	Amendment 3: addition of prospective testing for DLL3 and stratification factor of unknown versus 0% to < 25% versus 25% to < 75% versus 75% or above; clarification that clinical benefit is determined by RECIST v1.1; definition of disease progression clarified with respect to effusions; dose reduction guidelines for unacceptable toxicity included for edema; adverse event (AE) preferred terms (PTs) expected due to SCLC or progression of SCLC updated per Medical Dictionary for Regulatory Activities (MedDRA) v19.1.
05 March 2019	Amendment 4: primary efficacy endpoints clarified as progression-free survival (PFS) per CRAC and OS in subjects with DLL3 ^{high} ED SCLC; efficacy endpoints updated to include OS, PFS, and patient-reported outcomes (PROs; physical functioning) in all randomized subjects as secondary, and ORR, clinical benefit rate (CBR), duration of response (DOR), and PROs (except physical functioning) as exploratory; number of planned sites increased from 275 to 300; interim efficacy analysis removed and a futility analysis at 50% of the final OS endpoints added; ED SCLC definition per International Association for the Study of Lung Cancer/Veterans Association added; updated safety and toxicity management (per rovalpituzumab tesirine Investigator Brochure v7), including language around serosal effusions, pneumonitis, edema, and photosensitivity; updated language regarding rovalpituzumab tesirine classification as a hazardous drug.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported