Clinical trial results:
A Randomized, Open-label, Multicenter Phase 3 Study of the Combination of Rituximab, Cyclophosphamide, Doxorubicin, VELCADE, and Prednisone (VcR-CAP) or Rituximab, Cyclophosphamide, Doxorubicin, Vincristine, and Prednisone (R-CHOP) in Patients With Newly Diagnosed Mantle Cell Lymphoma who are not Eligible for a Bone Marrow Transplant

Summary

EudraCT number	2007-005669-37
Trial protocol	BE PT CZ AT IT HU DE ES FR
Global end of trial date	30 June 2017

Results information

Result version number	v1 (current)
This version publication date	15 July 2018
First version publication date	15 July 2018

Trial information

Trial identification

Sponsor protocol code	26866138LYM3002

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00722137
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Janssen-Cilag International N.V
Sponsor organisation address	Turnhoutseweg 30, Beerse, Belgium, B-2340
Public contact	Clinical Registry group, Janssen-Cilag International N.V, ClinicalTrialsEU@its.jnj.com
Scientific contact	Clinical Registry group, Janssen-Cilag International N.V, ClinicalTrialsEU@its.jnj.com

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	30 June 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	30 June 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the study was to determine which regimen of chemotherapy, VELCADE-rituximab-cyclophosphamide-doxorubicin-prednisone (VcR-CAP) or rituximab-cyclophosphamide-doxorubicin-prednisone-vincristine (R-CHOP), provided greater benefit in newly diagnosed mantle cell lymphoma (MCL) subjects with Stage II, III, or IV disease, as assessed by significant prolongation of progression-free survival (PFS).

Protection of trial subjects:

This study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with Good Clinical Practices and applicable regulatory requirements. Safety was evaluated throughout the study and included adverse events (AEs), Serious Adverse Events (SAEs), routine clinical laboratory tests (hematology, chemistry, and coagulation, Hepatitis B screening and Pregnancy test), vital signs, Electrocardiograms (ECGs).

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	20 May 2008
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	Austria: 10
Country: Number of subjects enrolled	Belgium: 26
Country: Number of subjects enrolled	Brazil: 22
Country: Number of subjects enrolled	Canada: 7
Country: Number of subjects enrolled	Chile: 3
Country: Number of subjects enrolled	China: 95
Country: Number of subjects enrolled	Colombia: 5
Country: Number of subjects enrolled	Czech Republic: 14
Country: Number of subjects enrolled	France: 3
Country: Number of subjects enrolled	Germany: 8
Country: Number of subjects enrolled	Hungary: 13
Country: Number of subjects enrolled	India: 12
Country: Number of subjects enrolled	Israel: 7
Country: Number of subjects enrolled	Italy: 9
Country: Number of subjects enrolled	Japan: 18
Country: Number of subjects enrolled	Poland: 19
Country: Number of subjects enrolled	Portugal: 7

Country: Number of subjects enrolled	Korea, Republic of: 5
Country: Number of subjects enrolled	Romania: 13
Country: Number of subjects enrolled	Russian Federation: 99
Country: Number of subjects enrolled	Singapore: 3
Country: Number of subjects enrolled	Spain: 14
Country: Number of subjects enrolled	Taiwan: 3
Country: Number of subjects enrolled	Thailand: 19
Country: Number of subjects enrolled	Tunisia: 6
Country: Number of subjects enrolled	Turkey: 6
Country: Number of subjects enrolled	Ukraine: 34
Country: Number of subjects enrolled	United States: 7
Worldwide total number of subjects	487
EEA total number of subjects	136

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)	241
From 65 to 84 years	246
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 487 subjects were randomized from 128 centers in 28 countries from 22 May 2008 to 05 December 2011; 244 to the R-CHOP treatment group and 243 to the VcR-CAP treatment group. Of the 487 randomized subjects, 242 in the R-CHOP group and 240 in the VcR-CAP group received at least 1 dose of study drug.

Period 1

Period 1 title	Open-Label
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	R-CHOP

Arm description:

Rituximab 375 milligram / meter^2 (mg/m^2) intravenous on Day 1 of a 21 day (3 week) cycle for 6 cycles; Cyclophosphamide 750 mg/m^2 intravenous on Day 1 of a 21 day (3 week) cycle for 6 cycles; Doxorubicin 50 mg/m^2 Intravenous on Day 1of a 21 day (3 week) cycle for 6 cycles; Prednisone 100 mg/m^2 orally on Day 1 to Day 5 of a 21 day (3 week) cycle for 6 cycles; Vincristine 1.4 mg/m^2 intravenous on Day 1of a 21 day (3 week) cycle for 6 cycles. Subjects entered to the short-term safety follow-up until PD/initiation of alternate therapy/withdrawal from study/death; and then to long term follow-up (extension) for survival assessment.

Arm type	Experimental
Investigational medicinal product name	Rituximab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Subjects received Rituximab 375 mg/m^2 intravenous on Day 1 of a 21 day (3 week) cycle for 6 cycles.

Investigational medicinal product name	Cyclophosphamide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

Dosage and administration details:

Subjects received Cyclophosphamide 750 mg/m^2 intravenous on Day 1 of a 21 day (3 week) cycle for 6 cycles.

Investigational medicinal product name	Vincristine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

Dosage and administration details:

Subjects received vincristine 1.4 mg/m^2 intravenous on Day 1 of a 21 day (3 week) cycle for 6 cycles.

Investigational medicinal product name	Prednisone
Investigational medicinal product code	
Other name	

Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received prednisone 100 mg/m^2 orally on Days 1 through 5 of each 21-day (3-week) cycle

Investigational medicinal product name	Doxorubicin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

Dosage and administration details:

Subjects received doxorubicin 50 mg/m^2 intravenous on Day 1 of a 21 day (3 week) cycle for 6 cycles.

Arm title	VcR-CAP

Arm description:

Rituximab 375 mg/m^2 intravenous on Day 1 of a 21 day (3 week) cycle for 6 cycles; Cyclophosphamide 750 mg/m^2 intravenous on Day 1 of a 21 day (3 week) cycle for 6 cycles; Doxorubicin 50 mg/m^2 Intravenous on Day 1 of a 21 day (3 week) cycle for 6 cycles; Velcade 1.3 mg/m^2 intravenous on Days 1, 4, 8, and 11 of a 21 day (3 week) cycle for 6 cycles; Prednisone 100 mg/m^2 orally on Day 1 to Day 5 of a 21 day (3 week) cycle for 6 cycles. Subjects entered to the short-term safety follow-up until PD/initiation of alternate therapy/withdrawal from study/death; and then to long term follow-up (extension) for survival assessment.

Arm type	Experimental
Investigational medicinal product name	Rituximab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

Subjects received rituximab 375 mg/m^2 IV on Day 1 of a 21-day (3-week) cycle of 6 cycles.

Investigational medicinal product name	Cyclophosphamide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

Dosage and administration details:

Subjects received Cyclophosphamide 750 mg/m^2 IV on Day 1 of a 21-day (3-week) cycle of 6 cycles.

Investigational medicinal product name	Doxorubicin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

Dosage and administration details:

Subjects received Doxorubicin 50 mg/m^2 IV on Day 1 of a 21-day (3-week) cycle of 6 cycles.

Investigational medicinal product name	Velcade
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

Dosage and administration details:

Subjects received Velcade 1.3 mg/m^2 IV on Days 1, 4, 8, and 11 of a 21-day (3-week) cycle of 6 cycles.

Investigational medicinal product name	Prednisone
Investigational medicinal product code	
Other name	

Pharmaceutical forms	Injection
Routes of administration	Intravenous use

Dosage and administration details:

Subjects received prednisone 100 mg/m^2 orally (PO) on Day 1 through Day 5 of a 21-day (3-week) cycle of 6 cycles.

Number of subjects in period 1	R-CHOP	VcR-CAP
Started	244	243
Treated	242	240
Completed	199	195
Not completed	45	48
Adverse Event	17	21
Randomized, Not treated	2	3
Death	12	7
Unspecified	3	4
Progressive disease	5	4
Withdrawal by subject	6	9

Period 2

Period 2 title	Extension Period
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Extension- R-CHOP

Arm description:

Rituximab 375 mg/m^2 intravenous on Day 1 of a 21 day (3 week) cycle for 6 cycles; Cyclophosphamide 750 mg/m^2 intravenous on Day 1 of a 21 day (3 week) cycle for 6 cycles; Doxorubicin 50 mg/m^2 Intravenous on Day 1of a 21 day (3 week) cycle for 6 cycles; Prednisone 100 mg/m^2 orally on Day 1 to Day 5 of a 21 day (3 week) cycle for 6 cycles; Vincristine 1.4 mg/m^2 intravenous on Day 1of a 21 day (3 week) cycle for 6 cycles. Subjects entered to the short term safety follow-up until PD/initiation of alternate therapy/withdrawal from study/death; and then to long term follow-up (extension) for survival assessment.

Arm type	Experimental
Investigational medicinal product name	Rituximab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

Subjects will receive Rituximab 375 mg/m^2 intravenous on Day 1 of a 21 day (3 week) cycle for 6 cycles.

Investigational medicinal product name	Cyclophosphamide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

Dosage and administration details:

Subjects received Cyclophosphamide 750 mg/m^2 intravenous on Day 1 of a 21 day (3 week) cycle for 6 cycles.

Investigational medicinal product name	Doxorubicin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

Dosage and administration details:

Subjects received doxorubicin 50 mg/m^2 intravenous on Day 1 of a 21 day (3 week) cycle for 6 cycles.

Investigational medicinal product name	Vincristine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

Dosage and administration details:

Subjects received vincristine 1.4 mg/m^2 intravenous on Day 1 of a 21 day (3 week) cycle for 6 cycles.

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

Dosage and administration details:

Subjects received prednisone 100 mg/m^2 orally on Days 1 through 5 of each 21-day (3-week) cycle

Arm title	Extension- VcR-CAP

Arm description:

Rituximab 375 mg/m^2 intravenous on Day 1 of a 21 day (3 week) cycle for 6 cycles; Cyclophosphamide 750 mg/m^2intravenous on Day 1 of a 21 day (3 week) cycle for 6 cycles; Doxorubicin 50 mg/m^2 Intravenous on Day 1of a 21 day (3 week) cycle for 6 cycles; Velcade 1.3 mg/m^2 intravenous on Days 1,4,8, and 11of a 21 day (3 week) cycle for 6 cycles; Prednisone orally on Day 1 to Day 5 of a 21 day (3 week) cycle for 6 cycles. Subjects entered to the short term safety follow-up until PD/initiation of alternate therapy/withdrawal from study/death; and then to long term follow-up (extension) for survival assessment.

Arm type	Experimental
Investigational medicinal product name	Rituximab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

Subjects received rituximab 375 mg/m^2 IV on Day 1 of a 21-day (3-week) cycle of 6 cycles.

Investigational medicinal product name	Cyclophosphamide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

Dosage and administration details:	
Subjects received Cyclophosphamide 750 mg/m^2 IV on Day 1 of a 21-day (3-week) cycle of 6 cycles.	
Investigational medicinal product name	Doxorubicin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intravenous use
Dosage and administration details:	
Subjects received Doxorubicin 50 mg/m^2 IV on Day 1 of a 21-day (3-week) cycle of 6 cycles.	
Investigational medicinal product name	Velcade
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intravenous use
Dosage and administration details:	
Subjects received VELCADE 1.3 mg/m^2 IV on Days 1, 4, 8, and 11 of a 21-day (3-week) cycle of 6 cycles.	
Investigational medicinal product name	Prednisone
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intravenous use
Dosage and administration details:	
Subjects received prednisone 100 mg/m^2 orally (PO) on Day 1 through Day 5 of a 21-day (3-week) cycle of 6 cycles.	

Number of subjects in period 2[1]	Extension- R-CHOP	Extension- VcR-CAP
Started	128	140
Completed	0	0
Not completed	128	140
Adverse event, serious fatal	51	32
Study closed by sponsor	62	89
Unspecified	2	4
Lost to follow-up	10	13
Withdrawal by subject	3	2

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.
Justification: Subjects who elected to continue with the follow-up were only continued for extension period.

Baseline characteristics

Reporting groups	
Reporting group title	R-CHOP
Reporting group description:	
Rituximab 375 milligram / meter^2 (mg/m^2) intravenous on Day 1 of a 21 day (3 week) cycle for 6 cycles; Cyclophosphamide 750 mg/m^2 intravenous on Day 1 of a 21 day (3 week) cycle for 6 cycles; Doxorubicin 50 mg/m^2 Intravenous on Day 1of a 21 day (3 week) cycle for 6 cycles; Prednisone 100 mg/m^2 orally on Day 1 to Day 5 of a 21 day (3 week) cycle for 6 cycles; Vincristine 1.4 mg/m^2 intravenous on Day 1of a 21 day (3 week) cycle for 6 cycles. Subjects entered to the short-term safety follow-up until PD/initiation of alternate therapy/withdrawal from study/death; and then to long term follow-up (extension) for survival assessment.	
Reporting group title	VcR-CAP
Reporting group description:	
Rituximab 375 mg/m^2 intravenous on Day 1 of a 21 day (3 week) cycle for 6 cycles; Cyclophosphamide 750 mg/m^2 intravenous on Day 1 of a 21 day (3 week) cycle for 6 cycles; Doxorubicin 50 mg/m^2 Intravenous on Day 1 of a 21 day (3 week) cycle for 6 cycles; Velcade 1.3 mg/m^2 intravenous on Days 1, 4, 8, and 11 of a 21 day (3 week) cycle for 6 cycles; Prednisone 100 mg/m^2 orally on Day 1 to Day 5 of a 21 day (3 week) cycle for 6 cycles. Subjects entered to the short-term safety follow-up until PD/initiation of alternate therapy/withdrawal from study/death; and then to long term follow-up (extension) for survival assessment.	

Reporting group values	R-CHOP	VcR-CAP	Total
Number of subjects	244	243	487
Title for AgeCategorical Units: subjects			
infants and toddlers(28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	117	124	241
From 65 to 84 years	127	119	246
85 years and over	0	0	0
Title for AgeContinuous Units: years			
arithmetic mean	64.4	64.2	
standard deviation	± 8.77	± 9.69	-
Title for Gender Units: subjects			
Female	62	65	127
Male	182	178	360

End points

End points reporting groups

Reporting group title	R-CHOP

Reporting group description:

Rituximab 375 milligram / meter^2 (mg/m^2) intravenous on Day 1 of a 21 day (3 week) cycle for 6 cycles; Cyclophosphamide 750 mg/m^2 intravenous on Day 1 of a 21 day (3 week) cycle for 6 cycles; Doxorubicin 50 mg/m^2 Intravenous on Day 1of a 21 day (3 week) cycle for 6 cycles; Prednisone 100 mg/m^2 orally on Day 1 to Day 5 of a 21 day (3 week) cycle for 6 cycles; Vincristine 1.4 mg/m^2 intravenous on Day 1of a 21 day (3 week) cycle for 6 cycles. Subjects entered to the short-term safety follow-up until PD/initiation of alternate therapy/withdrawal from study/death; and then to long term follow-up (extension) for survival assessment.

Reporting group title	VcR-CAP

Reporting group description:

Rituximab 375 mg/m^2 intravenous on Day 1 of a 21 day (3 week) cycle for 6 cycles; Cyclophosphamide 750 mg/m^2 intravenous on Day 1 of a 21 day (3 week) cycle for 6 cycles; Doxorubicin 50 mg/m^2 Intravenous on Day 1 of a 21 day (3 week) cycle for 6 cycles; Velcade 1.3 mg/m^2 intravenous on Days 1, 4, 8, and 11 of a 21 day (3 week) cycle for 6 cycles; Prednisone 100 mg/m^2 orally on Day 1 to Day 5 of a 21 day (3 week) cycle for 6 cycles. Subjects entered to the short-term safety follow-up until PD/initiation of alternate therapy/withdrawal from study/death; and then to long term follow-up (extension) for survival assessment.

Reporting group title	Extension- R-CHOP

Reporting group description:

Rituximab 375 mg/m^2 intravenous on Day 1 of a 21 day (3 week) cycle for 6 cycles; Cyclophosphamide 750 mg/m^2 intravenous on Day 1 of a 21 day (3 week) cycle for 6 cycles; Doxorubicin 50 mg/m^2 Intravenous on Day 1of a 21 day (3 week) cycle for 6 cycles; Prednisone 100 mg/m^2 orally on Day 1 to Day 5 of a 21 day (3 week) cycle for 6 cycles; Vincristine 1.4 mg/m^2 intravenous on Day 1of a 21 day (3 week) cycle for 6 cycles. Subjects entered to the short term safety follow-up until PD/initiation of alternate therapy/withdrawal from study/death; and then to long term follow-up (extension) for survival assessment.

Reporting group title	Extension- VcR-CAP

Reporting group description:

Rituximab 375 mg/m^2 intravenous on Day 1 of a 21 day (3 week) cycle for 6 cycles; Cyclophosphamide 750 mg/m^2intravenous on Day 1 of a 21 day (3 week) cycle for 6 cycles; Doxorubicin 50 mg/m^2 Intravenous on Day 1of a 21 day (3 week) cycle for 6 cycles; Velcade 1.3 mg/m^2 intravenous on Days 1,4,8, and 11of a 21 day (3 week) cycle for 6 cycles; Prednisone orally on Day 1 to Day 5 of a 21 day (3 week) cycle for 6 cycles. Subjects entered to the short term safety follow-up until PD/initiation of alternate therapy/withdrawal from study/death; and then to long term follow-up (extension) for survival assessment.

Primary: Progression Free Survival (PFS)

End point title	Progression Free Survival (PFS)

End point description:

PFS was defined as the interval between the date of randomization and the date of progressive disease (PD) or death, whichever occurred first. PD was based on the assessment of an Independent Review Committee. The population consisted of all randomized subjects.

End point type	Primary

End point timeframe:

Median duration of follow-up of 40 months

End point values	R-CHOP	VcR-CAP		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	244	243		
Units: Days				
median (confidence interval 95%)	437.0 (365.0 to 513.0)	751.0 (604.0 to 969.0)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Log Rank statistical method was based on the Log rank test stratified with IPI risk and stage of disease and Hazards ratio estimate was based on a Cox´s model stratified by IPI risk and stage of disease. A hazard ratio < 1 indicates an advantage for VcR-CAP.

Comparison groups	R-CHOP v VcR-CAP
Number of subjects included in analysis	487
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.63
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.5
upper limit	0.79

Secondary: Time to Progression (TTP)

End point title	Time to Progression (TTP)

End point description:

Time to progression was defined as the duration from the date of randomization until the date of first documented evidence of progressive disease (PD) or date of relapse for subjects who experienced complete response (CR) or complete response, unconfirmed (CRu). PD and response were based on the assessment of an Independent Review Committee. The population consisted of all randomized subjects.

End point type	Secondary

End point timeframe:

Median duration of follow-up of 40 months

End point values	R-CHOP	VcR-CAP		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	244	243		
Units: Days				
median (confidence interval 95%)	490.0 (417.0 to 550.0)	929.0 (696.0 to 1245.0)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Log Rank statistical method was based on the Log rank test stratified with IPI risk and stage of disease and Hazards ratio estimate was based on a Cox´s model stratified by IPI risk and stage of disease. A hazard ratio < 1 indicates an advantage for VcR-CAP.

Comparison groups	R-CHOP v VcR-CAP
Number of subjects included in analysis	487
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.58
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.45
upper limit	0.74

Secondary: Duration of Response

End point title	Duration of Response

End point description:

The duration of treatment response was defined as the time from the date of the first response to the date of PD or death due to PD for those subjects with a best response of CR, CRu, or PR as determined by the Independent Review Committee. The duration of response for complete responders was defined as the time from the date of the first response to the date of PD or death due to PD for those subjects with a best response of CR or CRu verified by bone marrow and lactate dehydrogenase (LDH). The response-evaluable population was defined as all subjects who received at least 1 dose of study drug, had >= 1 measurable tumor mass (>1.5 cm in the longest dimension and >1.0 cm in the short axis) at baseline and had at least 1 post-baseline tumor assessment by Independent Review Committee, before any subsequent anti-lymphoma treatment. Here 'n' signifies the number of subjects analyzed at this time point.

End point type	Secondary

End point timeframe:

Median duration of follow-up of 40 months

End point values	R-CHOP	VcR-CAP		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	228	229		
Units: Days				
median (confidence interval 95%)				
Duration of response (n=204, 211)	459.0 (379.0 to 518.0)	1110.0 (813.0 to 1320.0)		
Duration for Complete responders (n=95, 122)	563.0 (486.0 to 738.0)	1282.0 (933.0 to 1602.0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Next Anti-lymphoma Treatment (TTNT)

End point title	Time to Next Anti-lymphoma Treatment (TTNT)

End point description:

TTNT was measured from the date of initiation of study treatment as per protocol to the start date of new anti-lymphoma treatment. Death due to disease progression prior to subsequent therapy was considered as an event. Otherwise, time to next anti lymphoma treatment was censored at the date of death or the last date known to be alive. The population consisted of all randomized subjects. Here "99999" indicates data was not estimable.

End point type	Secondary

End point timeframe:

Median duration of follow-up of 40 months

End point values	R-CHOP	VcR-CAP		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	244	243		
Units: Days				
median (confidence interval 95%)	756.0 (674.0 to 837.0)	1353.0 (1180.0 to 99999)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Log Rank statistical method was based on the Log rank test stratified with IPI risk and stage of disease and Hazards ratio estimate is based on a Cox´s model stratified by IPI risk and stage of disease. A hazard ratio < 1 indicates an advantage for VcR-CAP.

Comparison groups	R-CHOP v VcR-CAP

Number of subjects included in analysis	487
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.38
upper limit	0.65

Secondary: Treatment-free Interval (TFI)

End point title	Treatment-free Interval (TFI)

End point description:

TFI was defined as the duration from the date of last dose plus 1 day to the start date of the new treatment. Death due to disease progression prior to subsequent therapy was considered as an event. Otherwise, treatment-free interval was censored at the date of death or the last date known to be alive. Population included all randomized subjects who received at least 1 dose of study medication. Here "99999" indicates data was not estimable.

End point type	Secondary

End point timeframe:

Median duration of follow-up of 40 months

End point values	R-CHOP	VcR-CAP		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	242	240		
Units: Days				
median (confidence interval 95%)	624.0 (542.0 to 693.0)	1236.0 (1023.0 to 99999)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Log Rank statistical method was based on the Log rank test stratified with IPI risk and stage of disease and Hazards ratio estimate was based on a Cox´s model stratified by IPI risk and stage of disease. A hazard ratio < 1 indicates an advantage for VcR-CAP.

Comparison groups	R-CHOP v VcR-CAP

Number of subjects included in analysis	482
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.38
upper limit	0.65

Secondary: Overall Response Rate (ORR)

End point title	Overall Response Rate (ORR)

End point description:

ORR was defined as complete response (CR) + complete response, unconfirmed (CRu) + partial response (PR) as determined by the Independent Review Committee. Response assessment was carried out every 6 weeks for 18 weeks; thereafter, every 8 weeks until PD/initiation of alternate therapy/withdrawal from study/death. The response-evaluable population was defined as all subjects who received >= 1 dose of study drug, had at least 1 measurable tumor mass (>1.5 cm in the longest dimension and >1.0 cm in the short axis) at baseline and had at least 1 post-baseline tumor assessment by Independent Review Committee, before any subsequent anti-lymphoma treatment.

End point type	Secondary

End point timeframe:

Median duration of follow-up of 40 months

End point values	R-CHOP	VcR-CAP		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	228	229		
Units: Subjects	209	219		

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Mantel-Haenszel estimate of the common odds ratio for stratified tables is used, with IPI risk and Stage of Disease as stratification factors. An odds ratio (OR) > 1 indicates an advantage for VcR-CAP.

Comparison groups	R-CHOP v VcR-CAP

Number of subjects included in analysis	457
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.275
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	1.428
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.749
upper limit	2.722

Secondary: Overall Complete Response (CR + CRu)

End point title	Overall Complete Response (CR + CRu)

End point description:

Overall complete response was defined as the number of subjects with complete response (CR) and those with unconfirmed complete response (CRu). Response assessment was carried out every 6 weeks for 18 weeks; thereafter, every 8 weeks until PD/initiation of alternate therapy/withdrawal from study/death. The response-evaluable population was defined as all subjects who received >= 1 dose of study drug, had at least 1 measurable tumor mass (>1.5 cm in the longest dimension and >1.0 cm in the short axis) at baseline and had at least 1 post-baseline tumor assessment by Independent Review Committee, before any subsequent anti-lymphoma treatment.

End point type	Secondary

End point timeframe:

Median duration of follow-up of 40 months

End point values	R-CHOP	VcR-CAP		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	228	229		
Units: Subjects				
Overall complete response	95	122		
CR	79	106		
CRu	16	16		

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Mantel-Haenszel estimate of the common odds ratio for stratified tables is used, with IPI risk and Stage of Disease as stratification factors. An odds ratio (OR) > 1 indicates an advantage for VcR-CAP.

Comparison groups	R-CHOP v VcR-CAP

Number of subjects included in analysis	457
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.007
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	1.688
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.148
upper limit	2.481

Secondary: Overall Survival (OS)

End point title	Overall Survival (OS)

End point description:

OS was measured from the date of randomization to the date of the subject's death. If the subject was alive or the vital status was unknown, OS was censored at the date that the subject was last known to be alive. The population consisted of all randomized subjects. Here "99999" indicates data was not estimable.

End point type	Secondary

End point timeframe:

Median duration of follow-up of approximately 82 months

End point values	R-CHOP	VcR-CAP		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	244	243		
Units: Days				
median (confidence interval 95%)	1695.0 (1436.0 to 2098.0)	2760.0 (2172.0 to 99999)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Log Rank statistical method was based on the Log rank test stratified with IPI risk and stage of disease and Hazards ratio estimate is based on a Cox´s model stratified by IPI risk and stage of disease. A hazard ratio < 1 indicates an advantage for VcR-CAP.

Comparison groups	R-CHOP v VcR-CAP

Number of subjects included in analysis	487
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.001
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.66
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.51
upper limit	0.85

Secondary: 18-Month Survival

End point title	18-Month Survival

End point description:

18-month survival was defined as the estimated probability of survival at 18 months (Kaplan-Meier estimate). The population consisted of all radmonized subjects.

End point type	Secondary

End point timeframe:

Up to month 18 from the time of randomization

End point values	R-CHOP	VcR-CAP		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	244	243		
Units: Percentage of Subjects				
arithmetic mean (confidence interval 95%)	83.8 (78.5 to 88.0)	85.0 (79.7 to 89.0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects Experiencing an Adverse Event (AE)

End point title	Number of Subjects Experiencing an Adverse Event (AE)

End point description:

An AE was defined as any untoward medical occurrence associated with the use of a drug, whether or not considered drug related. AEs were collected from the first dose of study drug through 30 days after the last dose of study drug. The safety population was defined as all randomized subjects who received at least 1 dose of study medication. For extension, Follow-up analysis set included subjects with data collected after 02 December 2013.

End point type	Secondary

End point timeframe:

Approximately 9 years

End point values	R-CHOP	Extension- R-CHOP	VcR-CAP	Extension-VcR-CAP
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	244	128	240	140
Units: Subjects	238	1	238	2

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Approximately 9 years

Adverse event reporting additional description:

The safety population was defined as all randomized subjects who received at least 1 dose of study medication. For extension, Follow-up analysis set included subjects with data collected after 02 December 2013.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	16.0

Reporting groups

Reporting group title	R-CHOP

Reporting group description:

Rituximab 375 milligram / meter^2 (mg/m^2) intravenous on Day 1 of a 21 day (3 week) cycle for 6 cycles; Cyclophosphamide 750 mg/m^2 intravenous on Day 1 of a 21 day (3 week) cycle for 6 cycles; Doxorubicin 50 mg/m^2 Intravenous on Day 1of a 21 day (3 week) cycle for 6 cycles; Prednisone 100 mg/m^2 orally on Day 1 to Day 5 of a 21 day (3 week) cycle for 6 cycles; Vincristine 1.4 mg/m^2 intravenous on Day 1of a 21 day (3 week) cycle for 6 cycles. Subjects entered to the short-term safety follow-up until PD/initiation of alternate therapy/withdrawal from study/death; and then to long term follow-up (extension) for survival assessment.

Reporting group title	Extension: R-CHOP

Reporting group description:

Rituximab 375 mg/m^2 intravenous on Day 1 of a 21 day (3 week) cycle for 6 cycles; Cyclophosphamide 750 mg/m^2 intravenous on Day 1 of a 21 day (3 week) cycle for 6 cycles; Doxorubicin 50 mg/m^2 Intravenous on Day 1of a 21 day (3 week) cycle for 6 cycles; Prednisone 100 mg/m^2 orally on Day 1 to Day 5 of a 21 day (3 week) cycle for 6 cycles; Vincristine 1.4 mg/m^2 intravenous on Day 1of a 21 day (3 week) cycle for 6 cycles. Subjects entered to the short-term safety follow-up until PD/initiation of alternate therapy/withdrawal from study/death; and then to long term follow-up (extension) for survival assessment.

Reporting group title	Extension: VcR-CAP

Reporting group description:

Rituximab 375 mg/m^2 intravenous on Day 1 of a 21 day (3 week) cycle for 6 cycles; Cyclophosphamide 750 mg/m^2intravenous on Day 1 of a 21 day (3 week) cycle for 6 cycles; Doxorubicin 50 mg/m^2 Intravenous on Day 1of a 21 day (3 week) cycle for 6 cycles; Velcade 1.3 mg/m^2 intravenous on Days 1,4,8, and 11of a 21 day (3 week) cycle for 6 cycles; Prednisone orally on Day 1 to Day 5 of a 21 day (3 week) cycle for 6 cycles. Subjects entered to the short-term safety follow-up until PD/initiation of alternate therapy/withdrawal from study/death; and then to long term follow-up (extension) for survival assessment.

Reporting group title	VcR-CAP

Reporting group description:

Rituximab 375 mg/m^2 intravenous on Day 1 of a 21 day (3 week) cycle for 6 cycles; Cyclophosphamide 750 mg/m^2 intravenous on Day 1 of a 21 day (3 week) cycle for 6 cycles; Doxorubicin 50 mg/m^2 Intravenous on Day 1 of a 21 day (3 week) cycle for 6 cycles; Velcade 1.3 mg/m^2 intravenous on Days 1, 4, 8, and 11 of a 21 day (3 week) cycle for 6 cycles; Prednisone 100 mg/m^2 orally on Day 1 to Day 5 of a 21 day (3 week) cycle for 6 cycles. Subjects entered to the short-term safety follow-up until PD/initiation of alternate therapy/withdrawal from study/death; and then to long term follow-up (extension) for survival assessment.

Serious adverse events	R-CHOP	Extension: R-CHOP	Extension: VcR-CAP
Total subjects affected by serious adverse events			
subjects affected / exposed	72 / 242 (29.75%)	0 / 128 (0.00%)	1 / 140 (0.71%)
number of deaths (all causes)	86	1	2
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Gastric cancer			
subjects affected / exposed	0 / 242 (0.00%)	0 / 128 (0.00%)	1 / 140 (0.71%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Malignant Melanoma			
subjects affected / exposed	1 / 242 (0.41%)	0 / 128 (0.00%)	0 / 140 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Deep Vein Thrombosis			
subjects affected / exposed	3 / 242 (1.24%)	0 / 128 (0.00%)	0 / 140 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertension			
subjects affected / exposed	0 / 242 (0.00%)	0 / 128 (0.00%)	0 / 140 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypotension			
subjects affected / exposed	1 / 242 (0.41%)	0 / 128 (0.00%)	0 / 140 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Orthostatic Hypotension			
subjects affected / exposed	0 / 242 (0.00%)	0 / 128 (0.00%)	0 / 140 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Poor Venous Access			

subjects affected / exposed	0 / 242 (0.00%)	0 / 128 (0.00%)	0 / 140 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Venous Thrombosis			
subjects affected / exposed	0 / 242 (0.00%)	0 / 128 (0.00%)	0 / 140 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Acute Phase Reaction			
subjects affected / exposed	0 / 242 (0.00%)	0 / 128 (0.00%)	0 / 140 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Asthenia			
subjects affected / exposed	0 / 242 (0.00%)	0 / 128 (0.00%)	0 / 140 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac Death			
subjects affected / exposed	1 / 242 (0.41%)	0 / 128 (0.00%)	0 / 140 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chest Pain			
subjects affected / exposed	1 / 242 (0.41%)	0 / 128 (0.00%)	0 / 140 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chills			
subjects affected / exposed	1 / 242 (0.41%)	0 / 128 (0.00%)	0 / 140 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Death			
subjects affected / exposed	0 / 242 (0.00%)	0 / 128 (0.00%)	0 / 140 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fatigue			

subjects affected / exposed	3 / 242 (1.24%)	0 / 128 (0.00%)	0 / 140 (0.00%)
occurrences causally related to treatment / all	3 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oedema Peripheral			
subjects affected / exposed	1 / 242 (0.41%)	0 / 128 (0.00%)	0 / 140 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia			
subjects affected / exposed	4 / 242 (1.65%)	0 / 128 (0.00%)	0 / 140 (0.00%)
occurrences causally related to treatment / all	3 / 4	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Acute Respiratory Distress Syndrome			
subjects affected / exposed	0 / 242 (0.00%)	0 / 128 (0.00%)	0 / 140 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute Respiratory Failure			
subjects affected / exposed	1 / 242 (0.41%)	0 / 128 (0.00%)	0 / 140 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aspiration			
subjects affected / exposed	0 / 242 (0.00%)	0 / 128 (0.00%)	0 / 140 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea			
subjects affected / exposed	5 / 242 (2.07%)	0 / 128 (0.00%)	0 / 140 (0.00%)
occurrences causally related to treatment / all	1 / 5	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Epistaxis			
subjects affected / exposed	1 / 242 (0.41%)	0 / 128 (0.00%)	0 / 140 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung Infiltration			

subjects affected / exposed	1 / 242 (0.41%)	0 / 128 (0.00%)	0 / 140 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleural Effusion			
subjects affected / exposed	1 / 242 (0.41%)	0 / 128 (0.00%)	0 / 140 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia Aspiration			
subjects affected / exposed	0 / 242 (0.00%)	0 / 128 (0.00%)	0 / 140 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary Embolism			
subjects affected / exposed	1 / 242 (0.41%)	0 / 128 (0.00%)	0 / 140 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary Hypertension			
subjects affected / exposed	0 / 242 (0.00%)	0 / 128 (0.00%)	0 / 140 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary Oedema			
subjects affected / exposed	0 / 242 (0.00%)	0 / 128 (0.00%)	0 / 140 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory Distress			
subjects affected / exposed	2 / 242 (0.83%)	0 / 128 (0.00%)	0 / 140 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory Failure			
subjects affected / exposed	0 / 242 (0.00%)	0 / 128 (0.00%)	0 / 140 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tonsillar Haemorrhage			

subjects affected / exposed	0 / 242 (0.00%)	0 / 128 (0.00%)	0 / 140 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Compression Fracture			
subjects affected / exposed	1 / 242 (0.41%)	0 / 128 (0.00%)	0 / 140 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Femur Fracture			
subjects affected / exposed	1 / 242 (0.41%)	0 / 128 (0.00%)	0 / 140 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Traumatic Lung Injury			
subjects affected / exposed	1 / 242 (0.41%)	0 / 128 (0.00%)	0 / 140 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Acute Left Ventricular Failure			
subjects affected / exposed	1 / 242 (0.41%)	0 / 128 (0.00%)	0 / 140 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute Myocardial Infarction			
subjects affected / exposed	1 / 242 (0.41%)	0 / 128 (0.00%)	0 / 140 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial Fibrillation			
subjects affected / exposed	2 / 242 (0.83%)	0 / 128 (0.00%)	0 / 140 (0.00%)
occurrences causally related to treatment / all	1 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac Arrest			
subjects affected / exposed	1 / 242 (0.41%)	0 / 128 (0.00%)	0 / 140 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Cardiac Failure			
subjects affected / exposed	0 / 242 (0.00%)	0 / 128 (0.00%)	0 / 140 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac Failure Acute			
subjects affected / exposed	1 / 242 (0.41%)	0 / 128 (0.00%)	0 / 140 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac Failure Congestive			
subjects affected / exposed	0 / 242 (0.00%)	0 / 128 (0.00%)	0 / 140 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardio-Respiratory Arrest			
subjects affected / exposed	2 / 242 (0.83%)	0 / 128 (0.00%)	0 / 140 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiogenic Shock			
subjects affected / exposed	0 / 242 (0.00%)	0 / 128 (0.00%)	0 / 140 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiomyopathy			
subjects affected / exposed	1 / 242 (0.41%)	0 / 128 (0.00%)	0 / 140 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiopulmonary Failure			
subjects affected / exposed	1 / 242 (0.41%)	0 / 128 (0.00%)	0 / 140 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Left Ventricular Dysfunction			
subjects affected / exposed	0 / 242 (0.00%)	0 / 128 (0.00%)	0 / 140 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Left Ventricular Failure			

subjects affected / exposed	1 / 242 (0.41%)	0 / 128 (0.00%)	0 / 140 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial Infarction			
subjects affected / exposed	2 / 242 (0.83%)	0 / 128 (0.00%)	0 / 140 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial Ischaemia			
subjects affected / exposed	1 / 242 (0.41%)	0 / 128 (0.00%)	0 / 140 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sinus Tachycardia			
subjects affected / exposed	0 / 242 (0.00%)	0 / 128 (0.00%)	0 / 140 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Supraventricular Extrasystoles			
subjects affected / exposed	0 / 242 (0.00%)	0 / 128 (0.00%)	0 / 140 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tachycardia			
subjects affected / exposed	2 / 242 (0.83%)	0 / 128 (0.00%)	0 / 140 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Autonomic Neuropathy			
subjects affected / exposed	0 / 242 (0.00%)	0 / 128 (0.00%)	0 / 140 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebral Ischaemia			
subjects affected / exposed	0 / 242 (0.00%)	0 / 128 (0.00%)	0 / 140 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebrovascular Accident			

subjects affected / exposed	1 / 242 (0.41%)	0 / 128 (0.00%)	0 / 140 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Convulsion			
subjects affected / exposed	1 / 242 (0.41%)	0 / 128 (0.00%)	0 / 140 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Depressed Level of Consciousness			
subjects affected / exposed	0 / 242 (0.00%)	0 / 128 (0.00%)	0 / 140 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Encephalitis			
subjects affected / exposed	0 / 242 (0.00%)	0 / 128 (0.00%)	0 / 140 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neuralgia			
subjects affected / exposed	0 / 242 (0.00%)	0 / 128 (0.00%)	0 / 140 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral Sensorimotor Neuropathy			
subjects affected / exposed	0 / 242 (0.00%)	0 / 128 (0.00%)	0 / 140 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral Sensory Neuropathy			
subjects affected / exposed	0 / 242 (0.00%)	0 / 128 (0.00%)	0 / 140 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			
subjects affected / exposed	0 / 242 (0.00%)	0 / 128 (0.00%)	0 / 140 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			

subjects affected / exposed	5 / 242 (2.07%)	0 / 128 (0.00%)	0 / 140 (0.00%)
occurrences causally related to treatment / all	6 / 7	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bone Marrow Failure			
subjects affected / exposed	1 / 242 (0.41%)	0 / 128 (0.00%)	0 / 140 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Febrile Neutropenia			
subjects affected / exposed	20 / 242 (8.26%)	0 / 128 (0.00%)	0 / 140 (0.00%)
occurrences causally related to treatment / all	27 / 28	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Leukopenia			
subjects affected / exposed	3 / 242 (1.24%)	0 / 128 (0.00%)	0 / 140 (0.00%)
occurrences causally related to treatment / all	2 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lymphopenia			
subjects affected / exposed	0 / 242 (0.00%)	0 / 128 (0.00%)	0 / 140 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutropenia			
subjects affected / exposed	13 / 242 (5.37%)	0 / 128 (0.00%)	0 / 140 (0.00%)
occurrences causally related to treatment / all	15 / 16	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombocytopenia			
subjects affected / exposed	1 / 242 (0.41%)	0 / 128 (0.00%)	0 / 140 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal Adhesions			
subjects affected / exposed	0 / 242 (0.00%)	0 / 128 (0.00%)	0 / 140 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anal Fissure			

subjects affected / exposed	1 / 242 (0.41%)	0 / 128 (0.00%)	0 / 140 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colitis			
subjects affected / exposed	1 / 242 (0.41%)	0 / 128 (0.00%)	0 / 140 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Constipation			
subjects affected / exposed	1 / 242 (0.41%)	0 / 128 (0.00%)	0 / 140 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	3 / 242 (1.24%)	0 / 128 (0.00%)	0 / 140 (0.00%)
occurrences causally related to treatment / all	2 / 4	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastritis			
subjects affected / exposed	0 / 242 (0.00%)	0 / 128 (0.00%)	0 / 140 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal Haemorrhage			
subjects affected / exposed	0 / 242 (0.00%)	0 / 128 (0.00%)	0 / 140 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematemesis			
subjects affected / exposed	1 / 242 (0.41%)	0 / 128 (0.00%)	0 / 140 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ileus Paralytic			
subjects affected / exposed	0 / 242 (0.00%)	0 / 128 (0.00%)	0 / 140 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Melaena			

subjects affected / exposed	1 / 242 (0.41%)	0 / 128 (0.00%)	0 / 140 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mouth Ulceration			
subjects affected / exposed	0 / 242 (0.00%)	0 / 128 (0.00%)	0 / 140 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oesophagitis			
subjects affected / exposed	0 / 242 (0.00%)	0 / 128 (0.00%)	0 / 140 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis			
subjects affected / exposed	1 / 242 (0.41%)	0 / 128 (0.00%)	0 / 140 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Periproctitis			
subjects affected / exposed	1 / 242 (0.41%)	0 / 128 (0.00%)	0 / 140 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Small Intestinal Obstruction			
subjects affected / exposed	1 / 242 (0.41%)	0 / 128 (0.00%)	0 / 140 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Stomatitis			
subjects affected / exposed	2 / 242 (0.83%)	0 / 128 (0.00%)	0 / 140 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	1 / 242 (0.41%)	0 / 128 (0.00%)	0 / 140 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Bile Duct Stone			

subjects affected / exposed	1 / 242 (0.41%)	0 / 128 (0.00%)	0 / 140 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic Failure			
subjects affected / exposed	0 / 242 (0.00%)	0 / 128 (0.00%)	0 / 140 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic Function Abnormal			
subjects affected / exposed	1 / 242 (0.41%)	0 / 128 (0.00%)	0 / 140 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Renal Failure			
subjects affected / exposed	1 / 242 (0.41%)	0 / 128 (0.00%)	0 / 140 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal Impairment			
subjects affected / exposed	1 / 242 (0.41%)	0 / 128 (0.00%)	0 / 140 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Soft Tissue Necrosis			
subjects affected / exposed	1 / 242 (0.41%)	0 / 128 (0.00%)	0 / 140 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Abscess Neck			
subjects affected / exposed	0 / 242 (0.00%)	0 / 128 (0.00%)	0 / 140 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anal Abscess			
subjects affected / exposed	1 / 242 (0.41%)	0 / 128 (0.00%)	0 / 140 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Bacterial Sepsis			
subjects affected / exposed	1 / 242 (0.41%)	0 / 128 (0.00%)	0 / 140 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchitis			
subjects affected / exposed	2 / 242 (0.83%)	0 / 128 (0.00%)	0 / 140 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchopneumonia			
subjects affected / exposed	1 / 242 (0.41%)	0 / 128 (0.00%)	0 / 140 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Candidiasis			
subjects affected / exposed	0 / 242 (0.00%)	0 / 128 (0.00%)	0 / 140 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis			
subjects affected / exposed	0 / 242 (0.00%)	0 / 128 (0.00%)	0 / 140 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Clostridium Difficile Infection			
subjects affected / exposed	1 / 242 (0.41%)	0 / 128 (0.00%)	0 / 140 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocarditis Bacterial			
subjects affected / exposed	1 / 242 (0.41%)	0 / 128 (0.00%)	0 / 140 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Erysipelas			
subjects affected / exposed	0 / 242 (0.00%)	0 / 128 (0.00%)	0 / 140 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Escherichia Urinary Tract Infection			

subjects affected / exposed	1 / 242 (0.41%)	0 / 128 (0.00%)	0 / 140 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis			
subjects affected / exposed	2 / 242 (0.83%)	0 / 128 (0.00%)	0 / 140 (0.00%)
occurrences causally related to treatment / all	3 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatitis B			
subjects affected / exposed	2 / 242 (0.83%)	0 / 128 (0.00%)	0 / 140 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Herpes Zoster			
subjects affected / exposed	1 / 242 (0.41%)	0 / 128 (0.00%)	0 / 140 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Klebsiella Sepsis			
subjects affected / exposed	0 / 242 (0.00%)	0 / 128 (0.00%)	0 / 140 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lobar Pneumonia			
subjects affected / exposed	1 / 242 (0.41%)	0 / 128 (0.00%)	0 / 140 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung Infection			
subjects affected / exposed	1 / 242 (0.41%)	0 / 128 (0.00%)	0 / 140 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nosocomial Infection			
subjects affected / exposed	0 / 242 (0.00%)	0 / 128 (0.00%)	0 / 140 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oral Fungal Infection			

subjects affected / exposed	1 / 242 (0.41%)	0 / 128 (0.00%)	0 / 140 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oral Herpes			
subjects affected / exposed	1 / 242 (0.41%)	0 / 128 (0.00%)	0 / 140 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oropharyngeal Candidiasis			
subjects affected / exposed	1 / 242 (0.41%)	0 / 128 (0.00%)	0 / 140 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Paronychia			
subjects affected / exposed	1 / 242 (0.41%)	0 / 128 (0.00%)	0 / 140 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Parotitis			
subjects affected / exposed	0 / 242 (0.00%)	0 / 128 (0.00%)	0 / 140 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peritonsillar Abscess			
subjects affected / exposed	1 / 242 (0.41%)	0 / 128 (0.00%)	0 / 140 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	7 / 242 (2.89%)	0 / 128 (0.00%)	0 / 140 (0.00%)
occurrences causally related to treatment / all	5 / 7	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia Bacterial			
subjects affected / exposed	0 / 242 (0.00%)	0 / 128 (0.00%)	0 / 140 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia Cytomegaloviral			

subjects affected / exposed	0 / 242 (0.00%)	0 / 128 (0.00%)	0 / 140 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia Streptococcal			
subjects affected / exposed	0 / 242 (0.00%)	0 / 128 (0.00%)	0 / 140 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Postoperative Abscess			
subjects affected / exposed	0 / 242 (0.00%)	0 / 128 (0.00%)	0 / 140 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary Mycosis			
subjects affected / exposed	0 / 242 (0.00%)	0 / 128 (0.00%)	0 / 140 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary Tuberculosis			
subjects affected / exposed	1 / 242 (0.41%)	0 / 128 (0.00%)	0 / 140 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rectal Abscess			
subjects affected / exposed	1 / 242 (0.41%)	0 / 128 (0.00%)	0 / 140 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory Tract Infection			
subjects affected / exposed	1 / 242 (0.41%)	0 / 128 (0.00%)	0 / 140 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Salmonellosis			
subjects affected / exposed	0 / 242 (0.00%)	0 / 128 (0.00%)	0 / 140 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			

subjects affected / exposed	1 / 242 (0.41%)	0 / 128 (0.00%)	0 / 140 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Septic Shock			
subjects affected / exposed	1 / 242 (0.41%)	0 / 128 (0.00%)	0 / 140 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tracheobronchitis			
subjects affected / exposed	1 / 242 (0.41%)	0 / 128 (0.00%)	0 / 140 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper Respiratory Tract Infection			
subjects affected / exposed	1 / 242 (0.41%)	0 / 128 (0.00%)	0 / 140 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary Tract Infection			
subjects affected / exposed	0 / 242 (0.00%)	0 / 128 (0.00%)	0 / 140 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Decreased Appetite			
subjects affected / exposed	0 / 242 (0.00%)	0 / 128 (0.00%)	0 / 140 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dehydration			
subjects affected / exposed	1 / 242 (0.41%)	0 / 128 (0.00%)	0 / 140 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diabetes Mellitus			
subjects affected / exposed	1 / 242 (0.41%)	0 / 128 (0.00%)	0 / 140 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fluid Retention			

subjects affected / exposed	0 / 242 (0.00%)	0 / 128 (0.00%)	0 / 140 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypokalaemia			
subjects affected / exposed	0 / 242 (0.00%)	0 / 128 (0.00%)	0 / 140 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyponatraemia			
subjects affected / exposed	0 / 242 (0.00%)	0 / 128 (0.00%)	0 / 140 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tumour Lysis Syndrome			
subjects affected / exposed	2 / 242 (0.83%)	0 / 128 (0.00%)	0 / 140 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	VcR-CAP		
Total subjects affected by serious adverse events			
subjects affected / exposed	90 / 240 (37.50%)		
number of deaths (all causes)	69		
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Gastric cancer			
subjects affected / exposed	0 / 240 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Malignant Melanoma			
subjects affected / exposed	0 / 240 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Deep Vein Thrombosis			

subjects affected / exposed	1 / 240 (0.42%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hypertension				
subjects affected / exposed	1 / 240 (0.42%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Hypotension				
subjects affected / exposed	3 / 240 (1.25%)			
occurrences causally related to treatment / all	3 / 3			
deaths causally related to treatment / all	0 / 0			
Orthostatic Hypotension				
subjects affected / exposed	2 / 240 (0.83%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Poor Venous Access				
subjects affected / exposed	2 / 240 (0.83%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Venous Thrombosis				
subjects affected / exposed	1 / 240 (0.42%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
General disorders and administration site conditions				
Acute Phase Reaction				
subjects affected / exposed	1 / 240 (0.42%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Asthenia				
subjects affected / exposed	1 / 240 (0.42%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Cardiac Death				

subjects affected / exposed	0 / 240 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Chest Pain				
subjects affected / exposed	0 / 240 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Chills				
subjects affected / exposed	1 / 240 (0.42%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Death				
subjects affected / exposed	1 / 240 (0.42%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Fatigue				
subjects affected / exposed	0 / 240 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Oedema Peripheral				
subjects affected / exposed	0 / 240 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pyrexia				
subjects affected / exposed	10 / 240 (4.17%)			
occurrences causally related to treatment / all	8 / 12			
deaths causally related to treatment / all	0 / 0			
Respiratory, thoracic and mediastinal disorders				
Acute Respiratory Distress Syndrome				
subjects affected / exposed	1 / 240 (0.42%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Acute Respiratory Failure				

subjects affected / exposed	0 / 240 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Aspiration				
subjects affected / exposed	1 / 240 (0.42%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Dyspnoea				
subjects affected / exposed	2 / 240 (0.83%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Epistaxis				
subjects affected / exposed	0 / 240 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Lung Infiltration				
subjects affected / exposed	0 / 240 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pleural Effusion				
subjects affected / exposed	3 / 240 (1.25%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Pneumonia Aspiration				
subjects affected / exposed	1 / 240 (0.42%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pulmonary Embolism				
subjects affected / exposed	4 / 240 (1.67%)			
occurrences causally related to treatment / all	1 / 4			
deaths causally related to treatment / all	0 / 0			
Pulmonary Hypertension				

subjects affected / exposed	1 / 240 (0.42%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Pulmonary Oedema				
subjects affected / exposed	1 / 240 (0.42%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Respiratory Distress				
subjects affected / exposed	0 / 240 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Respiratory Failure				
subjects affected / exposed	1 / 240 (0.42%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Tonsillar Haemorrhage				
subjects affected / exposed	1 / 240 (0.42%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Injury, poisoning and procedural complications				
Compression Fracture				
subjects affected / exposed	0 / 240 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Femur Fracture				
subjects affected / exposed	1 / 240 (0.42%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Traumatic Lung Injury				
subjects affected / exposed	0 / 240 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cardiac disorders				

Acute Left Ventricular Failure				
subjects affected / exposed	0 / 240 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Acute Myocardial Infarction				
subjects affected / exposed	0 / 240 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Atrial Fibrillation				
subjects affected / exposed	1 / 240 (0.42%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Cardiac Arrest				
subjects affected / exposed	0 / 240 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cardiac Failure				
subjects affected / exposed	2 / 240 (0.83%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Cardiac Failure Acute				
subjects affected / exposed	0 / 240 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cardiac Failure Congestive				
subjects affected / exposed	1 / 240 (0.42%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Cardio-Respiratory Arrest				
subjects affected / exposed	0 / 240 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cardiogenic Shock				

subjects affected / exposed	1 / 240 (0.42%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Cardiomyopathy				
subjects affected / exposed	0 / 240 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cardiopulmonary Failure				
subjects affected / exposed	0 / 240 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Left Ventricular Dysfunction				
subjects affected / exposed	3 / 240 (1.25%)			
occurrences causally related to treatment / all	3 / 4			
deaths causally related to treatment / all	0 / 0			
Left Ventricular Failure				
subjects affected / exposed	0 / 240 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Myocardial Infarction				
subjects affected / exposed	0 / 240 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Myocardial Ischaemia				
subjects affected / exposed	1 / 240 (0.42%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Sinus Tachycardia				
subjects affected / exposed	1 / 240 (0.42%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Supraventricular Extrasystoles				

subjects affected / exposed	1 / 240 (0.42%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Tachycardia				
subjects affected / exposed	0 / 240 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Nervous system disorders				
Autonomic Neuropathy				
subjects affected / exposed	1 / 240 (0.42%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Cerebral Ischaemia				
subjects affected / exposed	1 / 240 (0.42%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cerebrovascular Accident				
subjects affected / exposed	0 / 240 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Convulsion				
subjects affected / exposed	0 / 240 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Depressed Level of Consciousness				
subjects affected / exposed	1 / 240 (0.42%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Encephalitis				
subjects affected / exposed	1 / 240 (0.42%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Neuralgia				

subjects affected / exposed	2 / 240 (0.83%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Peripheral Sensorimotor Neuropathy				
subjects affected / exposed	1 / 240 (0.42%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Peripheral Sensory Neuropathy				
subjects affected / exposed	1 / 240 (0.42%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Syncope				
subjects affected / exposed	1 / 240 (0.42%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Blood and lymphatic system disorders				
Anaemia				
subjects affected / exposed	4 / 240 (1.67%)			
occurrences causally related to treatment / all	4 / 4			
deaths causally related to treatment / all	0 / 0			
Bone Marrow Failure				
subjects affected / exposed	0 / 240 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Febrile Neutropenia				
subjects affected / exposed	26 / 240 (10.83%)			
occurrences causally related to treatment / all	33 / 33			
deaths causally related to treatment / all	0 / 0			
Leukopenia				
subjects affected / exposed	6 / 240 (2.50%)			
occurrences causally related to treatment / all	26 / 26			
deaths causally related to treatment / all	0 / 0			
Lymphopenia				

subjects affected / exposed	1 / 240 (0.42%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Neutropenia				
subjects affected / exposed	12 / 240 (5.00%)			
occurrences causally related to treatment / all	17 / 17			
deaths causally related to treatment / all	0 / 0			
Thrombocytopenia				
subjects affected / exposed	8 / 240 (3.33%)			
occurrences causally related to treatment / all	11 / 11			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal disorders				
Abdominal Adhesions				
subjects affected / exposed	1 / 240 (0.42%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Anal Fissure				
subjects affected / exposed	0 / 240 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Colitis				
subjects affected / exposed	1 / 240 (0.42%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Constipation				
subjects affected / exposed	0 / 240 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Diarrhoea				
subjects affected / exposed	4 / 240 (1.67%)			
occurrences causally related to treatment / all	4 / 4			
deaths causally related to treatment / all	0 / 0			
Gastritis				

subjects affected / exposed	1 / 240 (0.42%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal Haemorrhage				
subjects affected / exposed	1 / 240 (0.42%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Haematemesis				
subjects affected / exposed	0 / 240 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Ileus Paralytic				
subjects affected / exposed	1 / 240 (0.42%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Melaena				
subjects affected / exposed	1 / 240 (0.42%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Mouth Ulceration				
subjects affected / exposed	1 / 240 (0.42%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Oesophagitis				
subjects affected / exposed	1 / 240 (0.42%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Pancreatitis				
subjects affected / exposed	0 / 240 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Periproctitis				

subjects affected / exposed	0 / 240 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Small Intestinal Obstruction				
subjects affected / exposed	0 / 240 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Stomatitis				
subjects affected / exposed	1 / 240 (0.42%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Vomiting				
subjects affected / exposed	2 / 240 (0.83%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Hepatobiliary disorders				
Bile Duct Stone				
subjects affected / exposed	0 / 240 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hepatic Failure				
subjects affected / exposed	1 / 240 (0.42%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Hepatic Function Abnormal				
subjects affected / exposed	0 / 240 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Renal and urinary disorders				
Renal Failure				
subjects affected / exposed	0 / 240 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Renal Impairment				

subjects affected / exposed	0 / 240 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Soft Tissue Necrosis			
subjects affected / exposed	0 / 240 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Abscess Neck			
subjects affected / exposed	1 / 240 (0.42%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Anal Abscess			
subjects affected / exposed	0 / 240 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Bacterial Sepsis			
subjects affected / exposed	0 / 240 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Bronchitis			
subjects affected / exposed	2 / 240 (0.83%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Bronchopneumonia			
subjects affected / exposed	1 / 240 (0.42%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Candidiasis			
subjects affected / exposed	1 / 240 (0.42%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Cellulitis			
subjects affected / exposed	1 / 240 (0.42%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Clostridium Difficile Infection			
subjects affected / exposed	0 / 240 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Endocarditis Bacterial			
subjects affected / exposed	0 / 240 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Erysipelas			
subjects affected / exposed	1 / 240 (0.42%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Escherichia Urinary Tract Infection			
subjects affected / exposed	0 / 240 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastroenteritis			
subjects affected / exposed	0 / 240 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hepatitis B			
subjects affected / exposed	1 / 240 (0.42%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Herpes Zoster			
subjects affected / exposed	1 / 240 (0.42%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Klebsiella Sepsis			

subjects affected / exposed	1 / 240 (0.42%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Lobar Pneumonia				
subjects affected / exposed	2 / 240 (0.83%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Lung Infection				
subjects affected / exposed	2 / 240 (0.83%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Nosocomial Infection				
subjects affected / exposed	1 / 240 (0.42%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Oral Fungal Infection				
subjects affected / exposed	0 / 240 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Oral Herpes				
subjects affected / exposed	0 / 240 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Oropharyngeal Candidiasis				
subjects affected / exposed	0 / 240 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Paronychia				
subjects affected / exposed	0 / 240 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Parotitis				

subjects affected / exposed	1 / 240 (0.42%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Peritonsillar Abscess				
subjects affected / exposed	0 / 240 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pneumonia				
subjects affected / exposed	19 / 240 (7.92%)			
occurrences causally related to treatment / all	14 / 22			
deaths causally related to treatment / all	0 / 0			
Pneumonia Bacterial				
subjects affected / exposed	1 / 240 (0.42%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumonia Cytomegaloviral				
subjects affected / exposed	1 / 240 (0.42%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumonia Streptococcal				
subjects affected / exposed	2 / 240 (0.83%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Postoperative Abscess				
subjects affected / exposed	1 / 240 (0.42%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pulmonary Mycosis				
subjects affected / exposed	1 / 240 (0.42%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Pulmonary Tuberculosis				

subjects affected / exposed	0 / 240 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Rectal Abscess				
subjects affected / exposed	0 / 240 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Respiratory Tract Infection				
subjects affected / exposed	1 / 240 (0.42%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Salmonellosis				
subjects affected / exposed	1 / 240 (0.42%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Sepsis				
subjects affected / exposed	4 / 240 (1.67%)			
occurrences causally related to treatment / all	3 / 4			
deaths causally related to treatment / all	0 / 0			
Septic Shock				
subjects affected / exposed	2 / 240 (0.83%)			
occurrences causally related to treatment / all	1 / 3			
deaths causally related to treatment / all	0 / 0			
Tracheobronchitis				
subjects affected / exposed	0 / 240 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Upper Respiratory Tract Infection				
subjects affected / exposed	1 / 240 (0.42%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Urinary Tract Infection				

subjects affected / exposed	1 / 240 (0.42%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Decreased Appetite			
subjects affected / exposed	1 / 240 (0.42%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Dehydration			
subjects affected / exposed	0 / 240 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Diabetes Mellitus			
subjects affected / exposed	0 / 240 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Fluid Retention			
subjects affected / exposed	1 / 240 (0.42%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Hypokalaemia			
subjects affected / exposed	2 / 240 (0.83%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Hyponatraemia			
subjects affected / exposed	1 / 240 (0.42%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Tumour Lysis Syndrome			
subjects affected / exposed	1 / 240 (0.42%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	R-CHOP	Extension: R-CHOP	Extension: VcR-CAP
Total subjects affected by non-serious adverse events			
subjects affected / exposed	228 / 242 (94.21%)	0 / 128 (0.00%)	0 / 140 (0.00%)
Vascular disorders			
Hypertension			
subjects affected / exposed	9 / 242 (3.72%)	0 / 128 (0.00%)	0 / 140 (0.00%)
occurrences (all)	15	0	0
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	26 / 242 (10.74%)	0 / 128 (0.00%)	0 / 140 (0.00%)
occurrences (all)	45	0	0
Chills			
subjects affected / exposed	4 / 242 (1.65%)	0 / 128 (0.00%)	0 / 140 (0.00%)
occurrences (all)	4	0	0
Fatigue			
subjects affected / exposed	45 / 242 (18.60%)	0 / 128 (0.00%)	0 / 140 (0.00%)
occurrences (all)	90	0	0
Oedema Peripheral			
subjects affected / exposed	24 / 242 (9.92%)	0 / 128 (0.00%)	0 / 140 (0.00%)
occurrences (all)	38	0	0
Pyrexia			
subjects affected / exposed	34 / 242 (14.05%)	0 / 128 (0.00%)	0 / 140 (0.00%)
occurrences (all)	53	0	0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	20 / 242 (8.26%)	0 / 128 (0.00%)	0 / 140 (0.00%)
occurrences (all)	24	0	0
Dyspnoea			
subjects affected / exposed	11 / 242 (4.55%)	0 / 128 (0.00%)	0 / 140 (0.00%)
occurrences (all)	14	0	0
Oropharyngeal Pain			
subjects affected / exposed	10 / 242 (4.13%)	0 / 128 (0.00%)	0 / 140 (0.00%)
occurrences (all)	15	0	0
Psychiatric disorders			

Insomnia			
subjects affected / exposed	18 / 242 (7.44%)	0 / 128 (0.00%)	0 / 140 (0.00%)
occurrences (all)	22	0	0
Investigations			
Weight Decreased			
subjects affected / exposed	10 / 242 (4.13%)	0 / 128 (0.00%)	0 / 140 (0.00%)
occurrences (all)	16	0	0
Nervous system disorders			
Dizziness			
subjects affected / exposed	9 / 242 (3.72%)	0 / 128 (0.00%)	0 / 140 (0.00%)
occurrences (all)	11	0	0
Headache			
subjects affected / exposed	11 / 242 (4.55%)	0 / 128 (0.00%)	0 / 140 (0.00%)
occurrences (all)	12	0	0
Hypoaesthesia			
subjects affected / exposed	15 / 242 (6.20%)	0 / 128 (0.00%)	0 / 140 (0.00%)
occurrences (all)	20	0	0
Neuralgia			
subjects affected / exposed	2 / 242 (0.83%)	0 / 128 (0.00%)	0 / 140 (0.00%)
occurrences (all)	3	0	0
Neuropathy Peripheral			
subjects affected / exposed	19 / 242 (7.85%)	0 / 128 (0.00%)	0 / 140 (0.00%)
occurrences (all)	26	0	0
Paraesthesia			
subjects affected / exposed	12 / 242 (4.96%)	0 / 128 (0.00%)	0 / 140 (0.00%)
occurrences (all)	18	0	0
Peripheral Sensory Neuropathy			
subjects affected / exposed	48 / 242 (19.83%)	0 / 128 (0.00%)	0 / 140 (0.00%)
occurrences (all)	73	0	0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	88 / 242 (36.36%)	0 / 128 (0.00%)	0 / 140 (0.00%)
occurrences (all)	276	0	0
Febrile Neutropenia			
subjects affected / exposed	16 / 242 (6.61%)	0 / 128 (0.00%)	0 / 140 (0.00%)
occurrences (all)	19	0	0
Leukopenia			

subjects affected / exposed	91 / 242 (37.60%)	0 / 128 (0.00%)	0 / 140 (0.00%)
occurrences (all)	455	0	0
Lymphopenia			
subjects affected / exposed	32 / 242 (13.22%)	0 / 128 (0.00%)	0 / 140 (0.00%)
occurrences (all)	175	0	0
Neutropenia			
subjects affected / exposed	174 / 242 (71.90%)	0 / 128 (0.00%)	0 / 140 (0.00%)
occurrences (all)	725	0	0
Thrombocytopenia			
subjects affected / exposed	46 / 242 (19.01%)	0 / 128 (0.00%)	0 / 140 (0.00%)
occurrences (all)	141	0	0
Gastrointestinal disorders			
Abdominal Distension			
subjects affected / exposed	5 / 242 (2.07%)	0 / 128 (0.00%)	0 / 140 (0.00%)
occurrences (all)	6	0	0
Abdominal Pain			
subjects affected / exposed	9 / 242 (3.72%)	0 / 128 (0.00%)	0 / 140 (0.00%)
occurrences (all)	12	0	0
Abdominal Pain Upper			
subjects affected / exposed	11 / 242 (4.55%)	0 / 128 (0.00%)	0 / 140 (0.00%)
occurrences (all)	11	0	0
Constipation			
subjects affected / exposed	38 / 242 (15.70%)	0 / 128 (0.00%)	0 / 140 (0.00%)
occurrences (all)	50	0	0
Diarrhoea			
subjects affected / exposed	22 / 242 (9.09%)	0 / 128 (0.00%)	0 / 140 (0.00%)
occurrences (all)	38	0	0
Dyspepsia			
subjects affected / exposed	14 / 242 (5.79%)	0 / 128 (0.00%)	0 / 140 (0.00%)
occurrences (all)	15	0	0
Nausea			
subjects affected / exposed	33 / 242 (13.64%)	0 / 128 (0.00%)	0 / 140 (0.00%)
occurrences (all)	46	0	0
Stomatitis			
subjects affected / exposed	20 / 242 (8.26%)	0 / 128 (0.00%)	0 / 140 (0.00%)
occurrences (all)	33	0	0

Vomiting			
subjects affected / exposed	12 / 242 (4.96%)	0 / 128 (0.00%)	0 / 140 (0.00%)
occurrences (all)	23	0	0
Hepatobiliary disorders			
Hepatic Function Abnormal			
subjects affected / exposed	12 / 242 (4.96%)	0 / 128 (0.00%)	0 / 140 (0.00%)
occurrences (all)	25	0	0
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	33 / 242 (13.64%)	0 / 128 (0.00%)	0 / 140 (0.00%)
occurrences (all)	42	0	0
Rash			
subjects affected / exposed	8 / 242 (3.31%)	0 / 128 (0.00%)	0 / 140 (0.00%)
occurrences (all)	10	0	0
Musculoskeletal and connective tissue disorders			
Back Pain			
subjects affected / exposed	15 / 242 (6.20%)	0 / 128 (0.00%)	0 / 140 (0.00%)
occurrences (all)	17	0	0
Pain in Extremity			
subjects affected / exposed	5 / 242 (2.07%)	0 / 128 (0.00%)	0 / 140 (0.00%)
occurrences (all)	5	0	0
Infections and infestations			
Bronchitis			
subjects affected / exposed	9 / 242 (3.72%)	0 / 128 (0.00%)	0 / 140 (0.00%)
occurrences (all)	9	0	0
Herpes Zoster			
subjects affected / exposed	2 / 242 (0.83%)	0 / 128 (0.00%)	0 / 140 (0.00%)
occurrences (all)	2	0	0
Pneumonia			
subjects affected / exposed	9 / 242 (3.72%)	0 / 128 (0.00%)	0 / 140 (0.00%)
occurrences (all)	10	0	0
Upper Respiratory Tract Infection			
subjects affected / exposed	8 / 242 (3.31%)	0 / 128 (0.00%)	0 / 140 (0.00%)
occurrences (all)	15	0	0
Metabolism and nutrition disorders			

Decreased Appetite			
subjects affected / exposed	23 / 242 (9.50%)	0 / 128 (0.00%)	0 / 140 (0.00%)
occurrences (all)	32	0	0
Hyperglycaemia			
subjects affected / exposed	20 / 242 (8.26%)	0 / 128 (0.00%)	0 / 140 (0.00%)
occurrences (all)	74	0	0
Hypoalbuminaemia			
subjects affected / exposed	11 / 242 (4.55%)	0 / 128 (0.00%)	0 / 140 (0.00%)
occurrences (all)	15	0	0
Hypokalaemia			
subjects affected / exposed	15 / 242 (6.20%)	0 / 128 (0.00%)	0 / 140 (0.00%)
occurrences (all)	16	0	0

Non-serious adverse events	VcR-CAP		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	235 / 240 (97.92%)		
Vascular disorders			
Hypertension			
subjects affected / exposed	21 / 240 (8.75%)		
occurrences (all)	39		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	38 / 240 (15.83%)		
occurrences (all)	85		
Chills			
subjects affected / exposed	12 / 240 (5.00%)		
occurrences (all)	14		
Fatigue			
subjects affected / exposed	56 / 240 (23.33%)		
occurrences (all)	114		
Oedema Peripheral			
subjects affected / exposed	37 / 240 (15.42%)		
occurrences (all)	64		
Pyrexia			
subjects affected / exposed	66 / 240 (27.50%)		
occurrences (all)	127		
Respiratory, thoracic and mediastinal			

disorders			
Cough			
subjects affected / exposed	49 / 240 (20.42%)		
occurrences (all)	78		
Dyspnoea			
subjects affected / exposed	18 / 240 (7.50%)		
occurrences (all)	25		
Oropharyngeal Pain			
subjects affected / exposed	14 / 240 (5.83%)		
occurrences (all)	20		
Psychiatric disorders			
Insomnia			
subjects affected / exposed	27 / 240 (11.25%)		
occurrences (all)	31		
Investigations			
Weight Decreased			
subjects affected / exposed	14 / 240 (5.83%)		
occurrences (all)	24		
Nervous system disorders			
Dizziness			
subjects affected / exposed	15 / 240 (6.25%)		
occurrences (all)	27		
Headache			
subjects affected / exposed	13 / 240 (5.42%)		
occurrences (all)	23		
Hypoaesthesia			
subjects affected / exposed	15 / 240 (6.25%)		
occurrences (all)	22		
Neuralgia			
subjects affected / exposed	24 / 240 (10.00%)		
occurrences (all)	42		
Neuropathy Peripheral			
subjects affected / exposed	19 / 240 (7.92%)		
occurrences (all)	30		
Paraesthesia			
subjects affected / exposed	16 / 240 (6.67%)		
occurrences (all)	32		

Peripheral Sensory Neuropathy subjects affected / exposed occurrences (all)	54 / 240 (22.50%) 99		
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all)	122 / 240 (50.83%) 596		
Febrile Neutropenia subjects affected / exposed occurrences (all)	16 / 240 (6.67%) 19		
Leukopenia subjects affected / exposed occurrences (all)	120 / 240 (50.00%) 1135		
Lymphopenia subjects affected / exposed occurrences (all)	73 / 240 (30.42%) 736		
Neutropenia subjects affected / exposed occurrences (all)	211 / 240 (87.92%) 1297		
Thrombocytopenia subjects affected / exposed occurrences (all)	172 / 240 (71.67%) 1223		
Gastrointestinal disorders Abdominal Distension subjects affected / exposed occurrences (all)	22 / 240 (9.17%) 29		
Abdominal Pain subjects affected / exposed occurrences (all)	18 / 240 (7.50%) 20		
Abdominal Pain Upper subjects affected / exposed occurrences (all)	16 / 240 (6.67%) 26		
Constipation subjects affected / exposed occurrences (all)	60 / 240 (25.00%) 95		
Diarrhoea			

subjects affected / exposed occurrences (all) Dyspepsia subjects affected / exposed occurrences (all) Nausea subjects affected / exposed occurrences (all) Stomatitis subjects affected / exposed occurrences (all) Vomiting subjects affected / exposed occurrences (all)	72 / 240 (30.00%) 170 13 / 240 (5.42%) 14 59 / 240 (24.58%) 110 26 / 240 (10.83%) 36 28 / 240 (11.67%) 46		
Hepatobiliary disorders Hepatic Function Abnormal subjects affected / exposed occurrences (all)	 14 / 240 (5.83%) 52		
Skin and subcutaneous tissue disorders Alopecia subjects affected / exposed occurrences (all) Rash subjects affected / exposed occurrences (all)	 33 / 240 (13.75%) 39 13 / 240 (5.42%) 18		
Musculoskeletal and connective tissue disorders Back Pain subjects affected / exposed occurrences (all) Pain in Extremity subjects affected / exposed occurrences (all)	 15 / 240 (6.25%) 20 20 / 240 (8.33%) 39		
Infections and infestations Bronchitis subjects affected / exposed occurrences (all)	 17 / 240 (7.08%) 20		

Herpes Zoster			
subjects affected / exposed	16 / 240 (6.67%)		
occurrences (all)	22		
Pneumonia			
subjects affected / exposed	12 / 240 (5.00%)		
occurrences (all)	17		
Upper Respiratory Tract Infection			
subjects affected / exposed	19 / 240 (7.92%)		
occurrences (all)	25		
Metabolism and nutrition disorders			
Decreased Appetite			
subjects affected / exposed	45 / 240 (18.75%)		
occurrences (all)	83		
Hyperglycaemia			
subjects affected / exposed	18 / 240 (7.50%)		
occurrences (all)	31		
Hypoalbuminaemia			
subjects affected / exposed	14 / 240 (5.83%)		
occurrences (all)	25		
Hypokalaemia			
subjects affected / exposed	20 / 240 (8.33%)		
occurrences (all)	42		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
01 October 2008	The main reason of this amendment was to provide the clarification was added that the IDMC would review data for interim analyses of safety, efficacy and the concordance rate of histological review; TFI added as a secondary objective; MRU added as an exploratory objective; subjects who withdrew could agree to provide information (ie, outcome of adverse events and survival status); subjects with initial response documented in Cycle 6 could receive 2 further cycles of therapy; central radiology review and assessments based on modified IWRC criteria; clarifications to definition of PFS, TTP. OS, TTNT, TFI; clarifications to definitions of measureable and assessable disease, criteria for response categories; ECG/ECHO/MUGA scans added to document baseline abnormalities; clarification that carriers of hepatitis B were allowed, but those with active hepatitis B or human immunodeficiency virus (HIV) were excluded; guidance on management of study drug toxicities added; defined minimum laboratory requirements at the beginning of each cycle (other than Cycle 1) before study drug administration; clarification was added that patients for whom bone marrow transplantation was not available and patients who refused a transplant as frontline treatment were eligible for the study; additional clarifications were made to other subject inclusion/exclusion criteria, dose adjustments, and statistical analyses.
26 February 2009	The main reason of this amendment was to do the modification of inclusion criterion restricting enrollment to patients who are truly not eligible for transplantation and the criterion for platelet counts was modified to include patients with lower baseline platelet counts secondary to mantle cell lymphoma. Exclusion criterion regarding serious medical conditions was clarified. Criteria for efficacy response were modified to make measurements operationally feasible and to comply with modified IWRC recommendations. Some laboratory tests considered not to be mandatory were eliminated. Adverse event collection wording was clarified to ensure the capture of adverse events relevant to the study.
16 September 2009	The IDMC recommendation for an additional interim analysis on safety. To ensure the potential for feedback to the investigator regarding the quality of the samples sent for central review and whether they will be adequate for analysis. Provide clarity on what constitutes central MCL diagnosis. Changes to inclusion and exclusion criteria to include that a check of the quality of the lymph node sample be performed before the patient can be randomized and added in the potential to use steroids if they are waiting for the quality check of sample, and the patient has high burden disease.
23 September 2010	The main reason for this amendment in the protocol was to provide clarification that randomization could occur only after central confirmation of the diagnosis of MCL, except for potential patients in China where central confirmation of sample adequacy on lymph node tissue was required; mandatory hepatitis B screening added as per IDMC, with additional safety monitoring for subjects at risk for hepatitis B reactivation and recommendation to prophylactically treat hepatitis B surface antigen positive subjects with lamivudine or equivalent agent; subjects with moderate/severe hepatic impairment (total bilirubin =<1.5x the upper limit of normal [ULN]) excluded; reconstitution of VELCADE added as per SmPC.
09 August 2011	The main reason for this amendment in protocol was to add a futility stopping guideline for the prospectively planned interim analysis.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

A limitation of this study is that current recommendations for rituximab maintenance therapy were not established when this study was initiated.

Notes: