Clinical trial results:
A Phase III, randomized, double-blind, controlled, multicenter study of intravenous PI3K inhibitor copanlisib in combination with standard immunochemotherapy versus standard immunochemotherapy in patients with relapsed indolent non-Hodgkin's lymphoma (iNHL) - CHRONOS-4

Summary

EudraCT number	2015-001088-38
Trial protocol	FI DE BE CZ DK ES GB FR PL IE AT PT HU SK GR BG IT RO
Global end of trial date	10 November 2023

Results information

Result version number	v1 (current)
This version publication date	27 September 2024
First version publication date	27 September 2024

Trial information

Trial identification

Sponsor protocol code	BAY 80-6946/17833

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02626455
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Bayer AG
Sponsor organisation address	Kaiser Wilhelm Allee, Leverkusen, Germany, D-51368
Public contact	Therapeutic Area Head, Bayer AG, 49 30 300139003, clinical-trials-contact@bayer.com
Scientific contact	Therapeutic Area Head, Bayer AG, 49 30 300139003, clinical-trials-contact@bayer.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	15 September 2023
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	10 November 2023
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the safety run-in (SRI) was to determine the recommended phase 3 dose (RP3D) of copanlisib in combination with standard immunochemotherapy [rituximab and bendamustine (R-B) or rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP)] to be used in the subsequent Phase 3 part of the study. The primary objective of the Phase 3 part was to evaluate whether copanlisib in combination with standard immunochemotherapy is superior to standard immunochemotherapy in prolonging PFS in patients with relapsed iNHL, who have received at least 1, but at most 3 lines of treatment, including rituximab, and/or rituximab biosimilars, and/or anti-CD20 monoclonal antibody(MAb)-based immunochemotherapy and alkylating agents, and for whom the combination of rituximab with either bendamustine or CHOP represents a valid therapeutic option.

Protection of trial subjects:

The conduct of this clinical study met all local legal and regulatory requirements. The study was conducted in accordance with ethical principles that have their origin in the Declaration of Helsinki and the International Council for Harmonization guideline E6: Good Clinical Practice. Before entering the study, the informed consent was read by and explained to all the subjects (or their legally authorized representative according to local legislation). Participating subjects (or their legally authorized representative according to local legislation) signed informed consent form and could withdraw from the study at any time without any disadvantage and without having to provide a reason for this decision. Only investigators qualified by training and experience were selected as appropriate experts to investigate the study drug.

Background therapy:

R-B and R-CHOP

Evidence for comparator: -

Actual start date of recruitment	06 January 2016
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	7 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Australia: 21
Country: Number of subjects enrolled	Belgium: 6
Country: Number of subjects enrolled	Brazil: 39
Country: Number of subjects enrolled	Bulgaria: 12
Country: Number of subjects enrolled	Canada: 16
Country: Number of subjects enrolled	Chile: 22
Country: Number of subjects enrolled	China: 130
Country: Number of subjects enrolled	Czechia: 10

Country: Number of subjects enrolled	Denmark: 4
Country: Number of subjects enrolled	Finland: 13
Country: Number of subjects enrolled	France: 33
Country: Number of subjects enrolled	Germany: 19
Country: Number of subjects enrolled	Greece: 17
Country: Number of subjects enrolled	Hong Kong: 4
Country: Number of subjects enrolled	Hungary: 18
Country: Number of subjects enrolled	Ireland: 3
Country: Number of subjects enrolled	Israel: 12
Country: Number of subjects enrolled	Italy: 15
Country: Number of subjects enrolled	Japan: 41
Country: Number of subjects enrolled	Mexico: 12
Country: Number of subjects enrolled	Poland: 7
Country: Number of subjects enrolled	Portugal: 15
Country: Number of subjects enrolled	Romania: 29
Country: Number of subjects enrolled	Russian Federation: 30
Country: Number of subjects enrolled	Singapore: 5
Country: Number of subjects enrolled	Slovakia: 5
Country: Number of subjects enrolled	South Africa: 14
Country: Number of subjects enrolled	Korea, Republic of: 30
Country: Number of subjects enrolled	Spain: 23
Country: Number of subjects enrolled	Taiwan: 14
Country: Number of subjects enrolled	Thailand: 7
Country: Number of subjects enrolled	Türkiye: 36
Country: Number of subjects enrolled	Ukraine: 25
Country: Number of subjects enrolled	United Kingdom: 8
Country: Number of subjects enrolled	United States: 19
Worldwide total number of subjects	714
EEA total number of subjects	229

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)	438
From 65 to 84 years	270
85 years and over	6

Subject disposition

Recruitment

Recruitment details:

SRI part enrolled 42 subjects from 12 countries, between 06-Jan-2016 (first subject first visit [FPFV]) and 31-Oct-2019 (last subject first visit [LPFV]). LPLV is 28-Aug-2023. Phase 3 part enrolled 672 participants from 35 countries/regions, between 06-Feb-2017 (FPFV) and 31-Mar-2020(LPFV), study terminated on 10-Nov-2023,

Pre-assignment

Screening details:

SRI: 42 subjects were screened, 15 subjects discontinued screening, 27 subjects were assigned to treatment and administered. Phase 3: 672 subjects were screened, 148 discontinued screening. 4 subjects were randomized to treatment but never administered, 520 subjects randomized treatment.

Period 1

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

Blinding implementation details:

SRI part is not randomised, not controlled, not blind. Phase 2 part is randomised-controlled, double blind.

Arms

Are arms mutually exclusive?	Yes
Arm title	SRI: Copa+R-B 45 mg

Arm description:

In SRI part, subjects received copanlisib at dose level of 45 mg in combination with R-B.

Arm type	Experimental
Investigational medicinal product name	Copanlisib
Investigational medicinal product code	BAY 80-6946
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

Dosage and administration details:

Copanlisib 45 mg on Days 1, 8 and 15 of each cycle, one cycle is 28 days, the maximum duration of treatment is 12 months.

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

Dosage and administration details:

90 mg/m^2 body surface on D1 and D2 of each cycle, from C1 to C6, one cycle is 28 days

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

Dosage and administration details:

375 mg/m^2 body surface on Day 1 (D1), from Cycle 1 (C1) to C6, one cycle is 28 days

Arm title	SRI: Copa+R-B 60 mg (excluding subjects from Japan)

Arm description:

In SRI part, subjects received copanlisib at dose level of 60 mg in combination with R-B.

Arm type	Experimental
Investigational medicinal product name	Copanlisib
Investigational medicinal product code	BAY 80-6946
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

Dosage and administration details:

Copanlisib 60 mg on Days 1, 8 and 15 of each 28-day cycle, the maximum duration of treatment is 12 months.

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

Dosage and administration details:

90 mg/m^2 body surface on D1 and D2 of each cycle, from C1 to C6, one cycle is 28 days

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

Dosage and administration details:

375 mg/m^2 body surface on D1, from C1 to C6, one cycle is 28 days

Arm title	SRI: Copa+R-CHOP 45 mg

Arm description:

In SRI part, subjects received copanlisib at dose level of 45 mg in combination with R-CHOP.

Arm type	Experimental
Investigational medicinal product name	Copanlisib
Investigational medicinal product code	BAY 80-6946
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

Dosage and administration details:

Copanlisib 45 mg on Days 1, 8 and 15 of each cycle, from C1 to C6, one cycle is 21 days, from C7 onward, one cycle is 28 days, the maximum duration of treatment is 12 months

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

Dosage and administration details:

375 mg/m^2 body surface on D2, from C1 to C6, one cycle is 21 days

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

Dosage and administration details:

750 mg/m^2 body surface on D2, from C1 to C6, one cycle is 21 days

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

Dosage and administration details:

50 mg/m^2 body surface on D2, from C1 to C6, one cycle is 21 days

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

Dosage and administration details:

1.4 mg/m^2 body surface (maximum dose 2.0 mg) on D2, from C1 to C6, one cycle is 21 days

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

Dosage and administration details:

100 mg daily orally (PO) from D2 to D6, from C1 to C6, one cycle is 21 days

Arm title	SRI: Copa+R-CHOP 60 mg

Arm description:

In SRI part, subjects received copanlisib at dose level of 60 mg in combination with R-CHOP.

Arm type	Experimental
Investigational medicinal product name	Copanlisib
Investigational medicinal product code	BAY 80-6946
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

Dosage and administration details:

Copanlisib 60 mg on Days 1, 8 and 15 of each cycle, from C1 to C6, one cycle is 21 days, from C7 onward, one cycle is 28 days, the maximum duration of treatment is 12 months

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

Dosage and administration details:

100 mg daily orally (PO) from D2 to D6, from C1 to C6, one cycle is 21 days

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

Dosage and administration details:

50 mg/m^2 body surface on D2, from C1 to C6, one cycle is 21 days

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

Dosage and administration details:

1.4 mg/m^2 body surface (maximum dose 2.0 mg) on D2, from C1 to C6, one cycle is 21 days

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

Dosage and administration details:

375 mg/m^2 body surface on D2, from C1 to C6, one cycle is 21 days

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

Dosage and administration details:

750 mg/m^2 body surface on D2, from C1 to C6, one cycle is 21 days

Arm title	SRI: Japan Copa+R-B 60 mg

Arm description:

In SRI part, subjects from Japan received copanlisib at dose level of 60 mg in combination with R-B.

Arm type	Experimental
Investigational medicinal product name	Copanlisib
Investigational medicinal product code	BAY 80-6946
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

Dosage and administration details:

Copanlisib 60 mg on Days 1, 8 and 15 of each cycle, one cycle is 28 days, the maximum duration of treatment is 12 months.

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

Dosage and administration details:

90 mg/m^2 body surface on D1 and D2 of each cycle, from C1 to C6, one cycle is 28 days

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

Dosage and administration details:

375 mg/m^2 body surface on D1, from C1 to C6, one cycle is 28 days

Arm title	Phase 3: Copa+R-B/R-CHOP

Arm description:

In Phase 3 part, subjects who never received R-B as a previous line of therapy were randomized to copanlisib + R-B. Subjects who received R-B as a previous line of therapy were randomized to copanlisib + R-CHOP or, if progression-free interval after the last R-B treatment was ≥ 24 months, to copanlisib + R-B.

Arm type	Experimental

Investigational medicinal product name	Copanlisib
Investigational medicinal product code	BAY 80-6946
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

Dosage and administration details:

Copanlisib 60 mg on Days 1, 8 and 15 of each cycle, the maximum duration of treatment is 12 months. For Copa+R-B, one cycle is 28 days. For Copa+R-CHOP, from C1 to C6, one cycle is 21 days, from C7 onward, one cycle is 28 days.

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

Dosage and administration details:

90 mg/m^2 body surface on D1 and D2 of each cycle, from C1 to C6, one cycle is 28 days

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

Dosage and administration details:

100 mg daily orally (PO) from D2 to D6, from C1 to C6, one cycle is 21 days

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

Dosage and administration details:

50 mg/m^2 body surface on D2, from C1 to C6, one cycle is 21 days

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

Dosage and administration details:

1.4 mg/m^2 body surface (maximum dose 2.0 mg) on D2, from C1 to C6, one cycle is 21 days

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

Dosage and administration details:

For Copa+R-B, 375 mg/m^2 body surface on D1, from C1 to C6, one cycle is 28 days. For Copa+R-CHOP, 375 mg/m2 body surface on D2, one cycle is 21 days.

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

Dosage and administration details:

750 mg/m^2 body surface on D2, from C1 to C6, one cycle is 21 days

Arm title	Phase 3: Pbo+R-B/R-CHOP

Arm description:

In Phase 3 part, subjects who never received R-B as a previous line of therapy were randomized to placebo + R-B. Subjects who received R-B as a previous line of therapy were randomized to placebo + R-CHOP or, if progression-free interval after the last R-B treatment was ≥ 24 months, to placebo + R-B.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

Dosage and administration details:

Copanlisib matching placebo on Days 1, 8 and 15 of each cycle, the maximum duration of treatment is 12 months. For Pbo+R-B, one cycle is 28 days. For Pbo+R-CHOP, from C1 to C6, one cycle is 21 days, from C7 onward, one cycle is 28 days.

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

Dosage and administration details:

For Pbo+R-B, 375 mg/m^2 body surface on D1, from C1 to C6, one cycle is 28 days. For Pbo+R-CHOP, 375 mg/m2 body surface on D2, one cycle is 21 days.

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

Dosage and administration details:

90 mg/m^2 body surface on D1 and D2 of each cycle, from C1 to C6, one cycle is 28 days

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

Dosage and administration details:

100 mg daily orally (PO) from D2 to D6, from C1 to C6, one cycle is 21 days

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

Dosage and administration details:

50 mg/m^2 body surface on D2, from C1 to C6, one cycle is 21 days

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

Dosage and administration details:

1.4 mg/m^2 body surface (maximum dose 2.0 mg) on D2, from C1 to C6, one cycle is 21 days

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

Dosage and administration details:

750 mg/m^2 body surface on D2, from C1 to C6, one cycle is 21 days

Number of subjects in period 1[1]	SRI: Copa+R-B 45 mg	SRI: Copa+R-B 60 mg (excluding subjects from Japan)	SRI: Copa+R-CHOP 45 mg
Started	3	7	5
Completed	0	2	3
Not completed	3	5	2
Progressive disease – radiological progression	-	-	-
Physician decision	-	2	2
Logistical reason: COVID-19 pandemic related	-	-	-
Physician decision: COVID-19 pandemic related	-	-	-
Study intervention never administered	-	-	-
AE not related to clinical disease progression	1	1	-
Progressive disease – clinical progression	-	-	-
Consent withdrawn by subject	1	-	-
Patient decision	-	1	-
Other	1	1	-
AE related to clinical disease progression	-	-	-
Lost to follow-up	-	-	-
Patient decision: COVID-19 pandemic related	-	-	-
Protocol deviation	-	-	-

Number of subjects in period 1[1]	SRI: Copa+R-CHOP 60 mg	SRI: Japan Copa+R-B 60 mg	Phase 3: Copa+R-B/R-CHOP
Started	6	6	262
Completed	2	3	108
Not completed	4	3	154
Progressive disease – radiological progression	-	-	11
Physician decision	2	1	10
Logistical reason: COVID-19 pandemic related	-	-	1
Physician decision: COVID-19 pandemic related	-	-	-
Study intervention never administered	-	-	1

AE not related to clinical disease progression	2	1	65
Progressive disease – clinical progression	-	-	1
Consent withdrawn by subject	-	-	10
Patient decision	-	1	36
Other	-	-	17
AE related to clinical disease progression	-	-	1
Lost to follow-up	-	-	1
Patient decision: COVID-19 pandemic related	-	-	-
Protocol deviation	-	-	-

Number of subjects in period 1[1]	Phase 3: Pbo+R-B/R-CHOP
Started	262
Completed	153
Not completed	109
Progressive disease – radiological progression	22
Physician decision	3
Logistical reason: COVID-19 pandemic related	1
Physician decision: COVID-19 pandemic related	2
Study intervention never administered	3
AE not related to clinical disease progression	21
Progressive disease – clinical progression	2
Consent withdrawn by subject	6
Patient decision	22
Other	23
AE related to clinical disease progression	2
Lost to follow-up	-
Patient decision: COVID-19 pandemic related	1
Protocol deviation	1

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: SRI: 42 subjects were screened, 15 subjects discontinued screening, 27 subjects were assigned to treatment and administered. Phase 3: 672 subjects were screened, 148 discontinued screening. 4 subjects were randomized to treatment but never administered, 520 subjects randomized treatment.

Baseline characteristics

Reporting groups	
Reporting group title	SRI: Copa+R-B 45 mg
Reporting group description:	
In SRI part, subjects received copanlisib at dose level of 45 mg in combination with R-B.	
Reporting group title	SRI: Copa+R-B 60 mg (excluding subjects from Japan)
Reporting group description:	
In SRI part, subjects received copanlisib at dose level of 60 mg in combination with R-B.	
Reporting group title	SRI: Copa+R-CHOP 45 mg
Reporting group description:	
In SRI part, subjects received copanlisib at dose level of 45 mg in combination with R-CHOP.	
Reporting group title	SRI: Copa+R-CHOP 60 mg
Reporting group description:	
In SRI part, subjects received copanlisib at dose level of 60 mg in combination with R-CHOP.	
Reporting group title	SRI: Japan Copa+R-B 60 mg
Reporting group description:	
In SRI part, subjects from Japan received copanlisib at dose level of 60 mg in combination with R-B.	
Reporting group title	Phase 3: Copa+R-B/R-CHOP
Reporting group description:	
In Phase 3 part, subjects who never received R-B as a previous line of therapy were randomized to copanlisib + R-B. Subjects who received R-B as a previous line of therapy were randomized to copanlisib + R-CHOP or, if progression-free interval after the last R-B treatment was ≥ 24 months, to copanlisib + R-B.	
Reporting group title	Phase 3: Pbo+R-B/R-CHOP
Reporting group description:	
In Phase 3 part, subjects who never received R-B as a previous line of therapy were randomized to placebo + R-B. Subjects who received R-B as a previous line of therapy were randomized to placebo + R-CHOP or, if progression-free interval after the last R-B treatment was ≥ 24 months, to placebo + R-B.	

Reporting group values	SRI: Copa+R-B 45 mg	SRI: Copa+R-B 60 mg (excluding subjects from Japan)	SRI: Copa+R-CHOP 45 mg
Number of subjects	3	7	5
Age Categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
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)	2	4	4
From 65-84 years	1	3	1
85 years and over	0	0	0
Age Continuous Units: years			
arithmetic mean	53.3	65.1	61.0
standard deviation	± 12.1	± 13.3	± 6.4

Gender Categorical Units: Subjects			
Female	3	5	4
Male	0	2	1
Race Units: Subjects			
White	2	5	3
Black or African American	0	0	1
Asian	1	2	0
American Indian or Alaska Native	0	0	0
Multiple	0	0	0
Not reported	0	0	1
Ethnicity Units: Subjects			
Hispanic or Latino	0	0	0
Not Hispanic or Latino	3	7	5
Not reported	0	0	0

Reporting group values	SRI: Copa+R-CHOP 60 mg	SRI: Japan Copa+R-B 60 mg	Phase 3: Copa+R-B/R-CHOP
Number of subjects	6	6	262
Age Categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
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)	2	6	160
From 65-84 years	4	0	99
85 years and over	0	0	3
Age Continuous Units: years			
arithmetic mean	65.5	49.5	59.6
standard deviation	± 13.0	± 5.2	± 12.8
Gender Categorical Units: Subjects			
Female	1	2	103
Male	5	4	159
Race Units: Subjects			
White	6	0	144
Black or African American	0	0	4
Asian	0	6	98
American Indian or Alaska Native	0	0	0
Multiple	0	0	1
Not reported	0	0	15
Ethnicity Units: Subjects			

Hispanic or Latino	0	0	24
Not Hispanic or Latino	5	6	223
Not reported	1	0	15

Reporting group values	Phase 3: Pbo+R-B/R-CHOP	Total	
Number of subjects	262	551	
Age Categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	162	340	
From 65-84 years	98	206	
85 years and over	2	5	
Age Continuous Units: years			
arithmetic mean	60.2		
standard deviation	± 11.4	-	
Gender Categorical Units: Subjects			
Female	128	246	
Male	134	305	
Race Units: Subjects			
White	168	328	
Black or African American	1	6	
Asian	82	189	
American Indian or Alaska Native	1	1	
Multiple	0	1	
Not reported	10	26	
Ethnicity Units: Subjects			
Hispanic or Latino	32	56	
Not Hispanic or Latino	215	464	
Not reported	15	31	

End points

End points reporting groups

Reporting group title	SRI: Copa+R-B 45 mg
Reporting group description:	
In SRI part, subjects received copanlisib at dose level of 45 mg in combination with R-B.	
Reporting group title	SRI: Copa+R-B 60 mg (excluding subjects from Japan)
Reporting group description:	
In SRI part, subjects received copanlisib at dose level of 60 mg in combination with R-B.	
Reporting group title	SRI: Copa+R-CHOP 45 mg
Reporting group description:	
In SRI part, subjects received copanlisib at dose level of 45 mg in combination with R-CHOP.	
Reporting group title	SRI: Copa+R-CHOP 60 mg
Reporting group description:	
In SRI part, subjects received copanlisib at dose level of 60 mg in combination with R-CHOP.	
Reporting group title	SRI: Japan Copa+R-B 60 mg
Reporting group description:	
In SRI part, subjects from Japan received copanlisib at dose level of 60 mg in combination with R-B.	
Reporting group title	Phase 3: Copa+R-B/R-CHOP
Reporting group description:	
In Phase 3 part, subjects who never received R-B as a previous line of therapy were randomized to copanlisib + R-B. Subjects who received R-B as a previous line of therapy were randomized to copanlisib + R-CHOP or, if progression-free interval after the last R-B treatment was ≥ 24 months, to copanlisib + R-B.	
Reporting group title	Phase 3: Pbo+R-B/R-CHOP
Reporting group description:	
In Phase 3 part, subjects who never received R-B as a previous line of therapy were randomized to placebo + R-B. Subjects who received R-B as a previous line of therapy were randomized to placebo + R-CHOP or, if progression-free interval after the last R-B treatment was ≥ 24 months, to placebo + R-B.	
Subject analysis set title	SRI: Full analysis set (FAS)
Subject analysis set type	Full analysis
Subject analysis set description:	
All subjects in the SRI part who received at least 1 dose of study intervention.	
Subject analysis set title	SRI: Safety analysis set (SAF)
Subject analysis set type	Safety analysis
Subject analysis set description:	
All subjects in the SRI part who received at least 1 dose of study intervention	
Subject analysis set title	Phase 3: Full analysis set (FAS)
Subject analysis set type	Full analysis
Subject analysis set description:	
All randomized subjects in Phase 3.	
Subject analysis set title	Phase 3: Safety analysis set (SAF)
Subject analysis set type	Safety analysis
Subject analysis set description:	
All randomized subjects in Phase 3 who received at least 1 dose of study intervention (either copanlisib/placebo, R-B, or R-CHOP).	

Primary: SRI: Occurrence of dose-limiting toxicities (DLT)

End point title	SRI: Occurrence of dose-limiting toxicities (DLT)[1][2]
End point description:	
Dose-limiting toxicity is defined as any of the following occurring during Cycle 1 at a given dose level and regarded by the investigator and/or the sponsor to be possibly, probably, or definitely related to copanlisib given in combination with R-B or R-CHOP. General: any grade 5 hematologic or non-	

hematologic toxicity or any delay of >2 weeks of Cycle 2 due to study treatment-related toxicity; Non-hematologic DLT: any non-hematologic toxicity grade ≥ 3; Hematologic DLT: grade 4 absolute neutrophil count decrease lasting >7 days, or grade 4 febrile neutropenia, or grade 4 platelet count decreased or grade 3 platelet count decreased with serious bleeding, or signs of serious bleeding and/or international normalized ratio (INR) increased or partial thromboplastin time (PTT) prolonged of grade 3.

End point type	Primary

End point timeframe:

At Cycle 1: 28 days for Copa+R-B or 21 days for Copa+R-CHOP

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Descriptive statistics were done, no inferential statistical analyses were performed.

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint analysis is only for SRI part arms.

End point values	SRI: Copa+R-B 45 mg	SRI: Copa+R-B 60 mg (excluding subjects from Japan)	SRI: Copa+R-CHOP 45 mg	SRI: Copa+R-CHOP 60 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3[3]	7[4]	5[5]	6[6]
Units: Percentage				
number (not applicable)	0	0	0	0

Notes:

[3] - SAF

[4] - SAF

[5] - SAF

[6] - SAF

End point values	SRI: Japan Copa+R-B 60 mg			
Subject group type	Reporting group			
Number of subjects analysed	6[7]			
Units: Percentage				
number (not applicable)	16.7			

Notes:

[7] - SAF

Statistical analyses

No statistical analyses for this end point

Primary: Phase 3: Progression-free survival (PFS) by independent central review

End point title	Phase 3: Progression-free survival (PFS) by independent central review[8]

End point description:

PFS is defined as the time from randomization to progressive disease (PD) or death from any cause (if no progression is documented).

End point type	Primary

End point timeframe:

Approximately to 6 years 4 months

Notes:

[8] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint analysis is only for phase 3 part arms.

End point values	Phase 3: Copa+R-B/R-CHOP	Phase 3: Pbo+R-B/R-CHOP		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	262[9]	262[10]		
Units: Months				
median (confidence interval 95%)	32.9 (24.4 to 38.6)	33.3 (27.8 to 42.8)		

Notes:

[9] - FAS

[10] - FAS

Statistical analyses

Statistical analysis title	Comparison of PFS

Statistical analysis description:

PFS was evaluated with the unstratified log-rank test. HR and 95% CI are based on the unstratified Cox regression model.

Comparison groups	Phase 3: Copa+R-B/R-CHOP v Phase 3: Pbo+R-B/R-CHOP
Number of subjects included in analysis	524
Analysis specification	Pre-specified
Analysis type	superiority[11]
P-value	= 0.827974 [12]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.125
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.881
upper limit	1.437

Notes:

[11] - Stratification is by baseline randomization factors

[12] - Significance level is 0.025. P-values are descriptive (nominal) due to multiplicity testing. Stratification is by baseline randomization factors

Secondary: SRI: Best overall response

End point title	SRI: Best overall response[13]

End point description:

Best overall response is defined as the best response achieved during the treatment and active follow-up periods; prior to end of study or start of new anti-tumor treatment, whichever occurs first.

End point type	Secondary

End point timeframe:

Approximately 7 years 8 months.

Notes:

[13] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint analysis is only for SRI part arms.

End point values	SRI: Copa+R-B 45 mg	SRI: Copa+R-B 60 mg (excluding subjects from Japan)	SRI: Copa+R-CHOP 45 mg	SRI: Copa+R-CHOP 60 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3[14]	7[15]	5[16]	6[17]
Units: Percentage				
number (confidence interval 95%)				
Best response (BR) -Complete response (CR)	33.3 (0.8 to 90.6)	71.4 (29.0 to 96.3)	60.0 (14.7 to 94.7)	16.7 (0.4 to 64.1)
BR - Very good partial response (VGPR)	0 (0 to 0)	0 (0 to 0)	0 (0 to 0)	0 (0 to 0)
BR - Partial response (PR)	66.7 (9.4 to 99.2)	28.6 (3.7 to 71.0)	20.0 (0.5 to 71.6)	83.3 (35.9 to 99.6)
BR - Minor response (MR)	0 (0 to 0)	0 (0 to 0)	0 (0 to 0)	0 (0 to 0)
BR - Stable disease	0 (0 to 0)	0 (0 to 0)	20.0 (0.5 to 71.6)	0 (0 to 0)
BR - Progressive disease (PD)	0 (0 to 0)	0 (0 to 0)	0 (0 to 0)	0 (0 to 0)
BR - Unconfirmed early stable disease (uSD)	0 (0 to 0)	0 (0 to 0)	0 (0 to 0)	0 (0 to 0)
BR - Not evaluable	0 (0 to 0)	0 (0 to 0)	0 (0 to 0)	0 (0 to 0)
BR - Not available	0 (0 to 0)	0 (0 to 0)	0 (0 to 0)	0 (0 to 0)
Response rate - Objective response rate (ORR)	100.0 (29.2 to 100.0)	100.0 (59.0 to 100.0)	80.0 (28.4 to 99.5)	100.0 (54.1 to 100.0)
Response rate - Disease control rate (DCR)	100.0 (29.2 to 100.0)	100.0 (59.0 to 100.0)	100.0 (47.8 to 100.0)	100.0 (54.1 to 100.0)
Response rate - Complete response rate (CRR)	33.3 (0.8 to 90.6)	71.4 (29.0 to 96.3)	60.0 (14.7 to 94.7)	16.7 (0.4 to 64.1)

Notes:

[14] - FAS

[15] - FAS

[16] - FAS

[17] - FAS

End point values	SRI: Japan Copa+R-B 60 mg			
Subject group type	Reporting group			
Number of subjects analysed	6[18]			
Units: Percentage				
number (confidence interval 95%)				
Best response (BR) -Complete response (CR)	50.0 (11.8 to 88.2)			
BR - Very good partial response (VGPR)	0 (0 to 0)			
BR - Partial response (PR)	33.3 (4.3 to 77.7)			
BR - Minor response (MR)	0 (0 to 0)			
BR - Stable disease	0 (0 to 0)			
BR - Progressive disease (PD)	0 (0 to 0)			
BR - Unconfirmed early stable disease (uSD)	0 (0 to 0)			
BR - Not evaluable	16.7 (0.4 to 64.1)			
BR - Not available	0 (0 to 0)			
Response rate - Objective response rate (ORR)	83.3 (35.9 to 99.6)			
Response rate - Disease control rate (DCR)	83.3 (35.9 to 99.6)			

Response rate - Complete response rate (CRR)	50.0 (11.8 to 88.2)			

Notes:

[18] - FAS

Statistical analyses

No statistical analyses for this end point

Secondary: SRI: Number of subjects with treatment-emergent adverse event (TEAE)

End point title	SRI: Number of subjects with treatment-emergent adverse event (TEAE)[19]

End point description:

A treatment-emergent AE is defined as any event arising or worsening after start of study drug administration until 30 days after the last study drug intake.

End point type	Secondary

End point timeframe:

Approximately 4 years 10 months

Notes:

[19] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint analysis is only for SRI part arms.

End point values	SRI: Copa+R-B 45 mg	SRI: Copa+R-B 60 mg (excluding subjects from Japan)	SRI: Copa+R-CHOP 45 mg	SRI: Copa+R-CHOP 60 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3[20]	7[21]	5[22]	6[23]
Units: Subjects				
Any TEAE	3	7	5	6
TESAEs	2	3	3	6

Notes:

[20] - SAF

[21] - SAF

[22] - SAF

[23] - SAF

End point values	SRI: Japan Copa+R-B 60 mg			
Subject group type	Reporting group			
Number of subjects analysed	6[24]			
Units: Subjects				
Any TEAE	6			
TESAEs	3			

Notes:

[24] - SAF

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 3: Objective tumor response rate (ORR) - Independent central review

End point title	Phase 3: Objective tumor response rate (ORR) - Independent central review[25]

End point description:

ORR, as assessed by independent central review, is defined as the percentage of participants who had a best response rating of CR or PR according to the Lugano classification and for subjects with LPL/WM, a response rating of CR, VGPR, PR, or MR according to the Owen criteria, over the whole duration of the study (i.e., until time of analysis of PFS).

End point type	Secondary

End point timeframe:

Approximately 6 years 4 months

Notes:

[25] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint analysis is only for phase 3 part arms.

End point values	Phase 3: Copa+R-B/R-CHOP	Phase 3: Pbo+R-B/R-CHOP		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	262[26]	262[27]		
Units: Percentage				
number (confidence interval 95%)	85.5 (80.6 to 89.5)	86.6 (81.9 to 90.5)		

Notes:

[26] - FAS

[27] - FAS

Statistical analyses

Statistical analysis title	Difference in ORR

Statistical analysis description:

ORR of Copa+R-B/R-CHOP minus ORR of Pbo+R-B/R-CHOP was evaluated using a one-sided stratified Cochran-Mantel-Haenszel (CMH) test. Point estimate and 95% CI are based on Mantel-Haenszel weighted treatment difference.

Comparison groups	Phase 3: Copa+R-B/R-CHOP v Phase 3: Pbo+R-B/R-CHOP
Number of subjects included in analysis	524
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.658652 [28]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference
Point estimate	-1.25
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.25
upper limit	4.75

Notes:

[28] - Significance level is 0.025. P-values are descriptive (nominal) due to multiplicity testing. Stratification is by baseline randomization factors.

Secondary: Phase 3: ORR-Investigator assessment

End point title	Phase 3: ORR-Investigator assessment[29]

End point description:

ORR, as assessed by investigator, is defined as the percentage of participants who had a best response rating of CR or PR according to the Lugano classification and for subjects with LPL/WM, a response rating of CR, VGPR, PR, or MR according to the Owen criteria, over the whole duration of the study (i.e., until time of analysis of PFS).

End point type	Secondary

End point timeframe:

Up to 6 years 4 months

Notes:

[29] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint analysis is only for phase 3 part arms.

End point values	Phase 3: Copa+R-B/R-CHOP	Phase 3: Pbo+R-B/R-CHOP		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	262[30]	262[31]		
Units: Percentage				
number (confidence interval 95%)	85.5 (80.6 to 89.5)	86.6 (81.9 to 90.5)		

Notes:

[30] - FAS

[31] - FAS

Statistical analyses

Statistical analysis title	Difference in ORR

Statistical analysis description:

ORR of Copa+R-B/R-CHOP minus ORR of Pbo+R-B/R-CHOP was evaluated using a one-sided stratified Cochran-Mantel-Haenszel (CMH) test. Point estimate and 95% CI are based on Mantel-Haenszel weighted treatment difference.

Comparison groups	Phase 3: Copa+R-B/R-CHOP v Phase 3: Pbo+R-B/R-CHOP
Number of subjects included in analysis	524
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.605183 [32]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference
Point estimate	-0.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.64
upper limit	5.05

Notes:

[32] - Significance level is 0.025. P-values are descriptive (nominal) due to multiplicity testing. Stratification is by baseline randomization factors

Secondary: Phase 3: Duration of tumor response (DOR) -Independent central review

End point title	Phase 3: Duration of tumor response (DOR) -Independent central review[33]

End point description:

DOR, as assessed by independent central review, is defined as the time (in days) from first observed tumor response (CR, VGPR, PR, or MR) until progression or death from any cause, whichever occurred earlier. The DOR was only defined for patients with at least 1 CR, VGPR, PR, or MR.

End point type	Secondary

End point timeframe:

Approximately 6 years 4 months

Notes:

[33] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint analysis is only for phase 3 part arms.

End point values	Phase 3: Copa+R-B/R-CHOP	Phase 3: Pbo+R-B/R-CHOP	Phase 3: Full analysis set (FAS)	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	224[34]	227[35]	451[36]	
Units: Months				
median (confidence interval 95%)	32.2 (22.8 to 38.8)	32.4 (27.7 to 42.0)	32.4 (28.1 to 38.4)	

Notes:

[34] - FAS

[35] - FAS

[36] - Best overall response (BOR) of CR or PR

Statistical analyses

Statistical analysis title	Comparison of DOR

Statistical analysis description:

DOR was evaluated with the stratified log-rank test. HR and its 95% CI were based on the Cox regression model

Comparison groups	Phase 3: Copa+R-B/R-CHOP v Phase 3: Pbo+R-B/R-CHOP v Phase 3: Full analysis set (FAS)
Number of subjects included in analysis	902
Analysis specification	Pre-specified
Analysis type	superiority[37]
P-value	= 0.846204 [38]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.145
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.883
upper limit	1.484

Notes:

[37] - The total number of subjects analyzed was 451. Below "Subjects in this analysis: 902" was erroneously calculated by database due to database constraints.
[38] - Significance level is 0.025. P-values are descriptive (nominal) due to multiplicity testing. Stratification is by baseline randomization factors.

Secondary: Phase 3: DOR-Investigator assessment

End point title	Phase 3: DOR-Investigator assessment[39]

End point description:

DOR, as assessed by investigator, is defined as the time (in days) from first observed tumor response

(CR, VGPR, PR, or MR) until progression or death from any cause, whichever occurred earlier. The DOR was only defined for patients with at least 1 CR, VGPR, PR, or MR.

End point type	Secondary

End point timeframe:

Approximately 6 years 4 months

Notes:

[39] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint analysis is only for phase 3 part arms.

End point values	Phase 3: Copa+R-B/R-CHOP	Phase 3: Pbo+R-B/R-CHOP	Phase 3: Full analysis set (FAS)	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	227[40]	229[41]	456[42]	
Units: Months				
median (confidence interval 95%)	32.4 (24.3 to 38.8)	30.9 (24.8 to 42.0)	32.4 (27.6 to 38.5)	

Notes:

[40] - FAS

[41] - FAS

[42] - BOR of CR or PR

Statistical analyses

Statistical analysis title	Comparison of DOR

Statistical analysis description:

DOR was evaluated with a one-side stratified log-rank test. HR and its 95% CI were based on the stratified Cox regression model

Comparison groups	Phase 3: Copa+R-B/R-CHOP v Phase 3: Pbo+R-B/R-CHOP v Phase 3: Full analysis set (FAS)
Number of subjects included in analysis	912
Analysis specification	Pre-specified
Analysis type	superiority[43]
P-value	= 0.801735 [44]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.117
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.865
upper limit	1.443

Notes:

[43] - The total number of subjects analyzed was 456. Below "Subjects in this analysis: 912" was erroneously calculated by database due to database constraints.
[44] - Significance level is 0.025. P-values are descriptive (nominal) due to multiplicity testing. Stratification is by baseline randomization factors.

Secondary: Phase 3: Complete tumor response rate (CRR) -Independent central review

End point title	Phase 3: Complete tumor response rate (CRR) -Independent central review[45]

End point description:

CRR, as assessed by independent central review, is defined as the proportion of patients who had a best

response rating of CR according to the Lugano classification, and for patients with LPL/WM, a response rating of CR according to the Owen criteria, over the whole duration of the study (i.e., until the time of analysis of PFS).

End point type	Secondary

End point timeframe:

Approximately 6 years 4 months

Notes:

[45] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint analysis is only for phase 3 part arms.

End point values	Phase 3: Copa+R-B/R-CHOP	Phase 3: Pbo+R-B/R-CHOP		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	262[46]	262[47]		
Units: Percentage				
number (confidence interval 95%)	38.5 (32.6 to 44.7)	41.2 (35.2 to 47.4)		

Notes:

[46] - FAS

[47] - FAS

Statistical analyses

Statistical analysis title	Difference in CRR

Statistical analysis description:

CRR of Copa+R-B/R-CHOP minus CRR of Pbo+R-B/R-CHOP was evaluated using a one-side stratified Cochran-Mantel-Haenszel (CMH) test. Point estimate and 95% CI are based on Mantel-Haenszel weighted treatment difference.

Comparison groups	Phase 3: Copa+R-B/R-CHOP v Phase 3: Pbo+R-B/R-CHOP
Number of subjects included in analysis	524
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.741153 [48]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference
Point estimate	-2.74
Confidence interval	
level	95 %
sides	2-sided
lower limit	-11.06
upper limit	5.57

Notes:

[48] - Significance level is 0.025. P-value is descriptive (nominal) due to multiplicity testing. Stratification is by baseline randomization factors.

Secondary: Phase 3: CRR-Investigator assessment

End point title	Phase 3: CRR-Investigator assessment[49]

End point description:

CRR, as assessed by investigator, is defined as the proportion of patients who had a best response rating of CR according to the Lugano classification, and for patients with LPL/WM, a response rating of CR according to the Owen criteria, over the whole duration of the study (i.e., until the time of analysis of PFS).

End point type	Secondary

End point timeframe:

Approximately 6 years 4 months

Notes:

[49] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint analysis is only for phase 3 part arms.

End point values	Phase 3: Copa+R-B/R-CHOP	Phase 3: Pbo+R-B/R-CHOP		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	262[50]	262[51]		
Units: Percentage				
number (confidence interval 95%)	39.7 (33.7 to 45.9)	42.0 (35.9 to 48.2)		

Notes:

[50] - FAS

[51] - FAS

Statistical analyses

Statistical analysis title	Difference in CRR

Statistical analysis description:

CRR of Copa+R-B/R-CHOP minus CRR of Pbo+R-B/R-CHOP was evaluated using a one-side stratified Cochran-Mantel-Haenszel (CMH) test. Point estimate and 95% CI are based on Mantel-Haenszel weighted treatment difference.

Comparison groups	Phase 3: Copa+R-B/R-CHOP v Phase 3: Pbo+R-B/R-CHOP
Number of subjects included in analysis	524
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.696482 [52]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference
Point estimate	-2.21
Confidence interval	
level	95 %
sides	2-sided
lower limit	-10.62
upper limit	6.2

Notes:

[52] - Significance level is 0.025. P-value is descriptive (nominal) due to multiplicity testing. Stratification is by baseline randomization factors.

Secondary: Phase 3: Disease control rate (DCR) - Independent central review

End point title	Phase 3: Disease control rate (DCR) - Independent central review[53]

End point description:

DCR, as assessed by independent central review, is defined as the proportion of patients who had a best response rating of CR, VGPR, PR, MR, or stable disease (excluding unconfirmed early stable disease).

End point type	Secondary

End point timeframe:

Approximately 6 years 4 months

Notes:

[53] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint analysis is only for phase 3 part arms.

End point values	Phase 3: Copa+R-B/R-CHOP	Phase 3: Pbo+R-B/R-CHOP		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	262[54]	262[55]		
Units: Percentage				
number (confidence interval 95%)	88.5 (84.1 to 92.1)	92.4 (88.5 to 95.3)		

Notes:

[54] - FAS

[55] - FAS

Statistical analyses

Statistical analysis title	Difference in DCR

Statistical analysis description:

DCR of Copa+R-B/R-CHOP minus DCR of Pbo+R-B/R-CHOP was evaluated using a one-sided stratified Cochran-Mantel-Haenszel (CMH) test. Point estimate and 95% CI are based on Mantel-Haenszel weighted treatment difference.

Comparison groups	Phase 3: Copa+R-B/R-CHOP v Phase 3: Pbo+R-B/R-CHOP
Number of subjects included in analysis	524
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.936009 [56]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference
Point estimate	-3.95
Confidence interval	
level	95 %
sides	2-sided
lower limit	-9.04
upper limit	1.14

Notes:

[56] - Significance level is 0.025. P-value is descriptive (nominal) due to multiplicity testing. Stratification is by baseline randomization factors.

Secondary: Phase 3: DCR-Investigator assessment

End point title	Phase 3: DCR-Investigator assessment[57]

End point description:

DCR, as assessed by investigator, is defined as the proportion of patients who had a best response rating of CR, VGPR, PR, MR, or stable disease (excluding unconfirmed early stable disease).

End point type	Secondary

End point timeframe:

Approximately 6 years 4 months

Notes:

[57] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint analysis is only for phase 3 part arms.

End point values	Phase 3: Copa+R-B/R-CHOP	Phase 3: Pbo+R-B/R-CHOP		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	262[58]	262[59]		
Units: Percentage				
number (confidence interval 95%)	88.5 (84.1 to 92.1)	92.4 (88.5 to 95.3)		

Notes:

[58] - FAS

[59] - FAS

Statistical analyses

Statistical analysis title	Difference in DCR

Statistical analysis description:

DCR of Copa+R-B/R-CHOP minus DCR of Pbo+R-B/R-CHOP was evaluated using a one-sided stratified Cochran-Mantel-Haenszel (CMH) test. Point estimate and 95% CI are based on Mantel-Haenszel weighted treatment difference.

Comparison groups	Phase 3: Copa+R-B/R-CHOP v Phase 3: Pbo+R-B/R-CHOP
Number of subjects included in analysis	524
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.944242 [60]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference
Point estimate	-3.89
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.68
upper limit	0.9

Notes:

[60] - Significance level is 0.025. P-value is descriptive (nominal) due to multiplicity testing. Stratification is by baseline randomization factors.

Secondary: Phase 3: Time to tumor progression (TTP) - Independent central review

End point title	Phase 3: Time to tumor progression (TTP) - Independent central review[61]

End point description:

TTP, as assessed by independent central review, is defined as the time from randomization to progression or death related to progression, whichever occurred earlier. Death related to progression was any death except for: death due to an AE unrelated to progression; or death with a specification of "other" as reason (which excludes PD).

End point type	Secondary

End point timeframe:

Approximately 6 years 4 months

Notes:

[61] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint analysis is only for phase 3 part arms.

End point values	Phase 3: Copa+R-B/R-CHOP	Phase 3: Pbo+R-B/R-CHOP		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	262[62]	262[63]		
Units: Months				
median (confidence interval 95%)	36.1 (30.3 to 44.0)	35.0 (30.4 to 44.8)		

Notes:

[62] - FAS

[63] - FAS

Statistical analyses

Statistical analysis title	Comparison of TTP

Statistical analysis description:

TTP was evaluated with a one-sided stratified log- rank test. HR and its 95% CI are based on the stratified Cox regression model.

Comparison groups	Phase 3: Copa+R-B/R-CHOP v Phase 3: Pbo+R-B/R-CHOP
Number of subjects included in analysis	524
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.517849 [64]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.006
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.777
upper limit	1.303

Notes:

[64] - Significance level is 0.025. P-value is descriptive (nominal) due to multiplicity testing. Stratification is by baseline randomization factors.

Secondary: Phase 3: TTP-Investigator assessment

End point title	Phase 3: TTP-Investigator assessment[65]

End point description:

TTP, as assessed by investigator, is defined as the time from randomization to progression or death related to progression, whichever occurred earlier. Death related to progression was any death except for: death due to an AE unrelated to progression; or death with a specification of "other" as reason (which excludes PD).

End point type	Secondary

End point timeframe:

Approximately 6 years 4 months

Notes:

[65] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint analysis is only for phase 3 part arms.

End point values	Phase 3: Copa+R-B/R-CHOP	Phase 3: Pbo+R-B/R-CHOP		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	262[66]	262[67]		
Units: Months				
median (confidence interval 95%)	36.1 (30.3 to 44.0)	35.0 (30.4 to 44.8)		

Notes:

[66] - FAS

[67] - FAS

Statistical analyses

Statistical analysis title	Comparison of TTP

Statistical analysis description:

TTP was evaluated with a one-sided stratified log- rank test. HR and its 95% CI are based on the stratified Cox regression model.

Comparison groups	Phase 3: Copa+R-B/R-CHOP v Phase 3: Pbo+R-B/R-CHOP
Number of subjects included in analysis	524
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.411398 [68]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.971
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.75
upper limit	1.257

Notes:

[68] - Significance level is 0.025. P-value is descriptive (nominal) due to multiplicity testing. Stratification is by baseline randomization factors

Secondary: Phase 3: Time to next anti-lymphoma treatment (TTNT)

End point title	Phase 3: Time to next anti-lymphoma treatment (TTNT)[69]

End point description:

A new anti-lymphoma therapy is any new systemic anticancer treatment or radiotherapy for lymphoma, with a consolidation intent. TTNT was defined as the time from the date of randomization to the start of new anti-lymphoma therapy, where the date of randomization was considered Day 1. '99999' denotes value could not be estimated due to censored data

End point type	Secondary

End point timeframe:

Approximately 6 years 4 months

Notes:

[69] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint analysis is only for phase 3 part arms.

End point values	Phase 3: Copa+R-B/R-CHOP	Phase 3: Pbo+R-B/R-CHOP		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	262[70]	262[71]		
Units: Months				
median (confidence interval 95%)	99999 (50.1 to 99999)	99999 (99999 to 99999)		

Notes:

[70] - FAS

[71] - FAS

Statistical analyses

Statistical analysis title	Comparison of TTNT

Statistical analysis description:

TTNT was evaluated with a one-sided stratified log-rank test. HR and its 95% CI are based on the stratified Cox regression model.

Comparison groups	Phase 3: Copa+R-B/R-CHOP v Phase 3: Pbo+R-B/R-CHOP
Number of subjects included in analysis	524
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.955865 [72]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.289
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.962
upper limit	1.728

Notes:

[72] - Significance level IS 0.025. P-values are descriptive (nominal) due to multiplicity testing. Stratification is by baseline randomization factors.

Secondary: Phase 3: Overall survival (OS)

End point title	Phase 3: Overall survival (OS)[73]

End point description:

Overall survival is defined as the time from randomization until death from any cause. The OS for patients alive at the time of the database cut-off date was censored to the last date they were known to be alive. Deaths that occurred after the database cut-off date, reported during data cleaning, were considered for establishing the last known alive date at data cut-off. '99999' denotes value could not be estimated due to censored data.

End point type	Secondary

End point timeframe:

Approximately 6 years 4 months

Notes:

[73] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint analysis is only for phase 3 part arms.

End point values	Phase 3: Copa+R-B/R-CHOP	Phase 3: Pbo+R-B/R-CHOP		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	262[74]	262[75]		
Units: Months				
median (confidence interval 95%)	99999 (99999 to 99999)	99999 (99999 to 99999)		

Notes:

[74] - FAS

[75] - FAS

Statistical analyses

Statistical analysis title	Comparison of OS

Statistical analysis description:

OS was evaluated with a one-sided stratified log-rank test. HR and 95% CI are based on the unstratified Cox regression model.

Comparison groups	Phase 3: Copa+R-B/R-CHOP v Phase 3: Pbo+R-B/R-CHOP
Number of subjects included in analysis	524
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.758563 [76]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.132
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.8
upper limit	1.603

Notes:

[76] - Significance level is 0.025. P-values are descriptive (nominal) due to multiplicity testing. Stratification is by baseline randomization factors.

Secondary: Phase 3: time to deterioration in disease-related symptoms-physical (DRS-P) of at least 3 points of lymphoma

End point title	Phase 3: time to deterioration in disease-related symptoms-physical (DRS-P) of at least 3 points of lymphoma[77]

End point description:

Time to deterioration in DRS-P of at least 3 points, as measured by the FLymSI-18 questionnaire, was evaluated in all patients. It is defined as the time from randomization to DRS-P decline, progression, or death from any reason, whichever occurred earlier.

End point type	Secondary

End point timeframe:

Approximately 6 years 4 months

Notes:

[77] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint analysis is only for phase 3 part arms.

End point values	Phase 3: Copa+R-B/R-CHOP	Phase 3: Pbo+R-B/R-CHOP		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	262[78]	262[79]		
Units: Months				
median (confidence interval 95%)	2.7 (1.9 to 3.3)	6.3 (4.6 to 8.3)		

Notes:

[78] - FAS

[79] - FAS

Statistical analyses

Statistical analysis title	Comparison of time to deterioration in DRS-P

Statistical analysis description:

Time to deterioration in DRS-P was evaluated with a one-sided stratified log-rank test.HR and its 95% CI are based on the stratified Cox regression model.

Comparison groups	Phase 3: Copa+R-B/R-CHOP v Phase 3: Pbo+R-B/R-CHOP
Number of subjects included in analysis	524
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.999695 [80]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.394
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.149
upper limit	1.691

Notes:

[80] - Significance level IS 0.025. P-values are descriptive (nominal) due to multiplicity testing. Stratification is by baseline randomization factors.

Secondary: Phase 3: time to improvement in disease-related symptoms-physical (DRS-P) of at least 3 points of lymphoma

End point title	Phase 3: time to improvement in disease-related symptoms-physical (DRS-P) of at least 3 points of lymphoma[81]

End point description:

Time to improvement in DRS-P of at least 3 points, as measured by the FLymSI-18 questionnaire, was evaluated for all patients. It is defined as the time from randomization to DRS-P improvement of at least 3 points.

End point type	Secondary

End point timeframe:

Approximately 6 years 4 months

Notes:

[81] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint analysis is only for phase 3 part arms.

End point values	Phase 3: Copa+R-B/R-CHOP	Phase 3: Pbo+R-B/R-CHOP		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	262[82]	262[83]		
Units: Months				
median (confidence interval 95%)	12.8 (6.7 to 36.1)	5.1 (2.8 to 8.3)		

Notes:

[82] - FAS

[83] - FAS

Statistical analyses

Statistical analysis title	Comparison of time to improvement in DRS-P

Statistical analysis description:

Time to improvement in DRS-P was evaluated with a one-sided stratified log-rank test. HR and its 95% CI are based on the stratified Cox regression model.

Comparison groups	Phase 3: Copa+R-B/R-CHOP v Phase 3: Pbo+R-B/R-CHOP
Number of subjects included in analysis	524
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.965639 [84]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.81
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.642
upper limit	1.02

Notes:

[84] - Significance level is 0.025. P-value is descriptive (nominal) due to multiplicity testing. Analysis is stratified by baseline randomization factors.

Secondary: Phase 3: Number of subjects with treatment-emergent adverse event (TEAE)

End point title	Phase 3: Number of subjects with treatment-emergent adverse event (TEAE)[85]

End point description:

A treatment-emergent AE is defined as any event arising or worsening after start of study drug administration until 30 days after the last study drug intake.

End point type	Secondary

End point timeframe:

Approximately 4 years

Notes:

[85] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint analysis is only for phase 3 part arms.

End point values	Phase 3: Copa+R-B/R-CHOP	Phase 3: Pbo+R-B/R-CHOP		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	262[86]	257[87]		
Units: Subjects				
Any TEAE	263	250		
TESAEs	161	54		
Any copanlisib or placebo related TEAE	250	214		
Any copanlisib or placebo related TESAEs	118	26		
Any R-B/R-CHOP related TEAE	245	224		
Any R-B/R-CHOP related TESAEs	109	26		

Notes:

[86] - Actual number is 263. One subject was not valid. Two Pbo+R-B/R-CHOP were analyzed as they took Copa.

[87] - Three subjects were not valid. Two subjects were analyzed under Copa+R-B/R-CHOP as they took Copa.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

After the first study intervention up to 30 days after the end of study intervention. For SRI, this is over a period of approximately 4 years 10 months and for phase 3, over a period of approximately 4 years.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	26.0

Reporting groups

Reporting group title	SRI: Copa+R-CHOP 45 mg

Reporting group description:

In SRI part, subjects received 45 mg of copanlisib in combination with R-CHOP.

Reporting group title	SRI: Copa+R-B 60 mg (excluding subjects from Japan)

Reporting group description:

In SRI part, subjects received 60 mg of copanlisib in combination with R-B.

Reporting group title	SRI: Copa+R-B 45 mg

Reporting group description:

In SRI part, subjects received 45 mg of copanlisib in combination with R-B.

Reporting group title	Phase 3: Copa+R-B/R-CHOP

Reporting group description:

In Phase 3 part, subjects who never received R-B as a previous line of therapy were randomized to copanlisib + R-B. Subjects who received R-B as a previous line of therapy were randomized to copanlisib + R-CHOP or, if progression-free interval after the last R-B treatment was >= 24 months, to copanlisib + R-B.

Reporting group title	SRI: Japan Copa+R-B 60 mg

Reporting group description:

In SRI part, Subjects from Japan only received 60 mg of copanlisib in combination with R-B.

Reporting group title	Phase 3: Pbo+R-B/R-CHOP

Reporting group description:

In Phase 3 part, subjects who never received R-B as a previous line of therapy were randomized to placebo + R-B. Subjects who received R-B as a previous line of therapy were randomized to placebo + R-CHOP or, if progression-free interval after the last R-B treatment was >= 24 months, to placebo + R-B.

Reporting group title	SRI: Copa+R-CHOP 60 mg

Reporting group description:

In SRI part, subjects received 60 mg of copanlisib in combination with R-CHOP.

Serious adverse events	SRI: Copa+R-CHOP 45 mg	SRI: Copa+R-B 60 mg (excluding subjects from Japan)	SRI: Copa+R-B 45 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 5 (60.00%)	3 / 7 (42.86%)	2 / 3 (66.67%)
number of deaths (all causes)	0	0	1
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			

Colon cancer			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 3 (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
Kaposi's sarcoma			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 3 (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
Squamous cell carcinoma			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 3 (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
Squamous cell carcinoma of skin			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 3 (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
Prostate cancer			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 3 (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
Lung neoplasm malignant			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 3 (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
Vascular disorders			
Haematoma			
subjects affected / exposed	1 / 5 (20.00%)	0 / 7 (0.00%)	0 / 3 (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
Hypertension			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 3 (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
Hypertensive crisis			

subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 3 (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	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 3 (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			
Chest pain			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 3 (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
Chills			
subjects affected / exposed	0 / 5 (0.00%)	1 / 7 (14.29%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oedema peripheral			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 3 (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
Malaise			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 3 (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
Hyperthermia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 3 (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
Pyrexia			
subjects affected / exposed	1 / 5 (20.00%)	2 / 7 (28.57%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	2 / 2	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General physical health deterioration			

subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 3 (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
Inflammation			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 3 (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
Device related thrombosis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 3 (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
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 3 (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
Hypersensitivity			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 3 (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
Infusion related hypersensitivity reaction			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 3 (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
Reproductive system and breast disorders			
Benign prostatic hyperplasia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 3 (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, thoracic and mediastinal disorders			
Acute respiratory distress syndrome			

subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 3 (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
Bronchospasm			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 3 (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	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 3 (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
Hypoxia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 3 (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
Interstitial lung disease			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 3 (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
Pneumonitis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 3 (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	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 3 (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	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 3 (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 / 5 (0.00%)	0 / 7 (0.00%)	0 / 3 (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
Investigations			
Blood creatine phosphokinase increased			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 3 (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
Amylase increased			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 3 (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
Alanine aminotransferase increased			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 3 (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 creatinine increased			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 3 (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
Lymphocyte count decreased			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 3 (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
Neutrophil count decreased			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 3 (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
Platelet count decreased			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 3 (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
White blood cell count decreased			

subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 3 (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
Cytomegalovirus test positive			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 3 (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
Norovirus test positive			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 3 (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			
Overdose			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 3 (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
Femoral neck fracture			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 3 (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
Limb injury			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 3 (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 disorders			
Atrial fibrillation			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 3 (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
Bradycardia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 3 (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

Myocardial ischaemia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 3 (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	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 3 (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 dysfunction			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 3 (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
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 3 (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
Coma			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 3 (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
Post herpetic neuralgia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 3 (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 / 5 (0.00%)	0 / 7 (0.00%)	0 / 3 (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
Toxic encephalopathy			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 3 (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			

Febrile neutropenia			
subjects affected / exposed	1 / 5 (20.00%)	0 / 7 (0.00%)	0 / 3 (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
Eosinophilia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	1 / 3 (33.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anaemia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 3 (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
Haemolysis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 3 (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
Leukocytosis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 3 (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
Leukopenia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 3 (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
Myelosuppression			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 3 (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
Bone marrow failure			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 3 (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
Thrombocytopenia			

subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 3 (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	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 3 (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
Eye disorders			
Uveitis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 3 (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 disorders			
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 3 (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
Diarrhoea			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 3 (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
Stomatitis			
subjects affected / exposed	0 / 5 (0.00%)	1 / 7 (14.29%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholangitis acute			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 3 (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
Liver disorder			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 3 (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

Gallbladder disorder			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 3 (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
Skin and subcutaneous tissue disorders			
Dermatitis allergic			
subjects affected / exposed	0 / 5 (0.00%)	1 / 7 (14.29%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dermatitis exfoliative generalised			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 3 (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
Eczema			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 3 (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
Drug eruption			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 3 (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
Erythema multiforme			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 3 (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
Rash			
subjects affected / exposed	0 / 5 (0.00%)	1 / 7 (14.29%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rash pruritic			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 3 (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
Rash maculo-papular			

subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 3 (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
Stevens-Johnson syndrome			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 3 (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
Toxic skin eruption			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 3 (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
Skin toxicity			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 3 (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
Renal and urinary disorders			
Hydronephrosis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 3 (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
Urinary retention			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 3 (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
Renal impairment			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 3 (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 kidney injury			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 3 (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
Endocrine disorders			

Inappropriate antidiuretic hormone secretion			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 3 (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
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 3 (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
Infections and infestations			
Bacteraemia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 3 (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
Bronchitis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 3 (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
Cytomegalovirus infection			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 3 (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 colitis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 3 (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
Diarrhoea infectious			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 3 (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
Disseminated cryptococcosis			

subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 3 (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
Diverticulitis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 3 (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
Epididymitis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 3 (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
Erysipelas			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 3 (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
Gastroenteritis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 3 (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
Genital herpes			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 3 (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
Herpes zoster			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 3 (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
Influenza			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 3 (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
Infection			

subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 3 (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
Meningitis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 3 (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
Lower respiratory tract infection			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 3 (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
Laryngitis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 3 (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
Meningitis cryptococcal			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 3 (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			
subjects affected / exposed	0 / 5 (0.00%)	1 / 7 (14.29%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia cytomegaloviral			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 3 (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 viral			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 3 (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	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 3 (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
Rash pustular			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 3 (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
Pyelonephritis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 3 (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
Skin infection			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 3 (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
Upper respiratory tract infection			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 3 (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
Urinary tract infection			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 3 (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
Varicella			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 3 (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
Ludwig angina			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 3 (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	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 3 (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
Cytomegalovirus colitis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 3 (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
Pneumococcal sepsis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	1 / 3 (33.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Febrile infection			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 3 (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 infection			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 3 (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
Infective thrombosis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 3 (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
Cytomegalovirus infection reactivation			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 3 (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
Enterocolitis infectious			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 3 (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
Enteritis infectious			

subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 3 (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
Cytomegalovirus viraemia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 3 (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
Viraemia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 3 (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 syncytial virus infection			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 3 (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 bacterial			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 3 (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 tract infection fungal			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 3 (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
Anorectal infection			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 3 (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 tract infection			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 3 (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
Device related infection			

subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 3 (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
Herpes zoster disseminated			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 3 (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
Pneumocystis jirovecii pneumonia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 3 (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
Large intestine infection			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 3 (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
Vascular device infection			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 3 (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
Urinary tract candidiasis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 3 (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
COVID-19			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 3 (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
COVID-19 pneumonia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 3 (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			
Dehydration			

subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 3 (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
Diabetes mellitus inadequate control			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 3 (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
Hyperglycaemia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 3 (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 / 5 (0.00%)	0 / 7 (0.00%)	0 / 3 (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
Type 2 diabetes mellitus			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 3 (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	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 3 (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

Serious adverse events	Phase 3: Copa+R-B/R-CHOP	SRI: Japan Copa+R-B 60 mg	Phase 3: Pbo+R-B/R-CHOP
Total subjects affected by serious adverse events			
subjects affected / exposed	161 / 263 (61.22%)	3 / 6 (50.00%)	54 / 257 (21.01%)
number of deaths (all causes)	68	0	62
number of deaths resulting from adverse events	8	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Colon cancer			
subjects affected / exposed	0 / 263 (0.00%)	0 / 6 (0.00%)	1 / 257 (0.39%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Kaposi's sarcoma			
subjects affected / exposed	1 / 263 (0.38%)	0 / 6 (0.00%)	0 / 257 (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
Squamous cell carcinoma			
subjects affected / exposed	1 / 263 (0.38%)	0 / 6 (0.00%)	0 / 257 (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
Squamous cell carcinoma of skin			
subjects affected / exposed	0 / 263 (0.00%)	0 / 6 (0.00%)	1 / 257 (0.39%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Prostate cancer			
subjects affected / exposed	1 / 263 (0.38%)	0 / 6 (0.00%)	0 / 257 (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 neoplasm malignant			
subjects affected / exposed	0 / 263 (0.00%)	0 / 6 (0.00%)	1 / 257 (0.39%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Haematoma			
subjects affected / exposed	0 / 263 (0.00%)	0 / 6 (0.00%)	0 / 257 (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
Hypertension			
subjects affected / exposed	3 / 263 (1.14%)	0 / 6 (0.00%)	0 / 257 (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
Hypertensive crisis			
subjects affected / exposed	1 / 263 (0.38%)	0 / 6 (0.00%)	1 / 257 (0.39%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypotension			

subjects affected / exposed	2 / 263 (0.76%)	0 / 6 (0.00%)	0 / 257 (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
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	0 / 263 (0.00%)	0 / 6 (0.00%)	1 / 257 (0.39%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chills			
subjects affected / exposed	0 / 263 (0.00%)	0 / 6 (0.00%)	0 / 257 (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
Oedema peripheral			
subjects affected / exposed	0 / 263 (0.00%)	0 / 6 (0.00%)	1 / 257 (0.39%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Malaise			
subjects affected / exposed	1 / 263 (0.38%)	0 / 6 (0.00%)	0 / 257 (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
Hyperthermia			
subjects affected / exposed	1 / 263 (0.38%)	0 / 6 (0.00%)	0 / 257 (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
Pyrexia			
subjects affected / exposed	22 / 263 (8.37%)	1 / 6 (16.67%)	4 / 257 (1.56%)
occurrences causally related to treatment / all	13 / 26	1 / 1	3 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General physical health deterioration			
subjects affected / exposed	3 / 263 (1.14%)	0 / 6 (0.00%)	0 / 257 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 2	0 / 0	0 / 0
Inflammation			

subjects affected / exposed	1 / 263 (0.38%)	0 / 6 (0.00%)	0 / 257 (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
Device related thrombosis			
subjects affected / exposed	1 / 263 (0.38%)	0 / 6 (0.00%)	0 / 257 (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
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	1 / 263 (0.38%)	0 / 6 (0.00%)	1 / 257 (0.39%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypersensitivity			
subjects affected / exposed	0 / 263 (0.00%)	0 / 6 (0.00%)	0 / 257 (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
Infusion related hypersensitivity reaction			
subjects affected / exposed	1 / 263 (0.38%)	0 / 6 (0.00%)	0 / 257 (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
Reproductive system and breast disorders			
Benign prostatic hyperplasia			
subjects affected / exposed	1 / 263 (0.38%)	0 / 6 (0.00%)	0 / 257 (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, thoracic and mediastinal disorders			
Acute respiratory distress syndrome			
subjects affected / exposed	2 / 263 (0.76%)	0 / 6 (0.00%)	0 / 257 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 2	0 / 0	0 / 0
Bronchospasm			

subjects affected / exposed	1 / 263 (0.38%)	0 / 6 (0.00%)	0 / 257 (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
Dyspnoea			
subjects affected / exposed	1 / 263 (0.38%)	0 / 6 (0.00%)	0 / 257 (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
Hypoxia			
subjects affected / exposed	1 / 263 (0.38%)	0 / 6 (0.00%)	0 / 257 (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
Interstitial lung disease			
subjects affected / exposed	7 / 263 (2.66%)	0 / 6 (0.00%)	0 / 257 (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
Pneumonitis			
subjects affected / exposed	4 / 263 (1.52%)	0 / 6 (0.00%)	2 / 257 (0.78%)
occurrences causally related to treatment / all	4 / 4	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			
subjects affected / exposed	3 / 263 (1.14%)	0 / 6 (0.00%)	0 / 257 (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
Respiratory distress			
subjects affected / exposed	1 / 263 (0.38%)	0 / 6 (0.00%)	0 / 257 (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 oedema			
subjects affected / exposed	1 / 263 (0.38%)	0 / 6 (0.00%)	0 / 257 (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
Investigations			
Blood creatine phosphokinase increased			

subjects affected / exposed	0 / 263 (0.00%)	0 / 6 (0.00%)	1 / 257 (0.39%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Amylase increased			
subjects affected / exposed	1 / 263 (0.38%)	0 / 6 (0.00%)	0 / 257 (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
Alanine aminotransferase increased			
subjects affected / exposed	0 / 263 (0.00%)	0 / 6 (0.00%)	1 / 257 (0.39%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood creatinine increased			
subjects affected / exposed	0 / 263 (0.00%)	0 / 6 (0.00%)	1 / 257 (0.39%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lymphocyte count decreased			
subjects affected / exposed	2 / 263 (0.76%)	0 / 6 (0.00%)	0 / 257 (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
Neutrophil count decreased			
subjects affected / exposed	7 / 263 (2.66%)	0 / 6 (0.00%)	3 / 257 (1.17%)
occurrences causally related to treatment / all	6 / 8	0 / 0	1 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Platelet count decreased			
subjects affected / exposed	3 / 263 (1.14%)	0 / 6 (0.00%)	1 / 257 (0.39%)
occurrences causally related to treatment / all	3 / 4	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
White blood cell count decreased			
subjects affected / exposed	2 / 263 (0.76%)	0 / 6 (0.00%)	1 / 257 (0.39%)
occurrences causally related to treatment / all	1 / 3	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cytomegalovirus test positive			

subjects affected / exposed	2 / 263 (0.76%)	0 / 6 (0.00%)	0 / 257 (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
Norovirus test positive			
subjects affected / exposed	0 / 263 (0.00%)	0 / 6 (0.00%)	0 / 257 (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			
Overdose			
subjects affected / exposed	1 / 263 (0.38%)	0 / 6 (0.00%)	0 / 257 (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
Femoral neck fracture			
subjects affected / exposed	1 / 263 (0.38%)	0 / 6 (0.00%)	0 / 257 (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
Limb injury			
subjects affected / exposed	1 / 263 (0.38%)	0 / 6 (0.00%)	0 / 257 (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 disorders			
Atrial fibrillation			
subjects affected / exposed	1 / 263 (0.38%)	0 / 6 (0.00%)	0 / 257 (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
Bradycardia			
subjects affected / exposed	0 / 263 (0.00%)	0 / 6 (0.00%)	1 / 257 (0.39%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial ischaemia			
subjects affected / exposed	1 / 263 (0.38%)	0 / 6 (0.00%)	0 / 257 (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

Tachycardia			
subjects affected / exposed	0 / 263 (0.00%)	0 / 6 (0.00%)	1 / 257 (0.39%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Left ventricular dysfunction			
subjects affected / exposed	1 / 263 (0.38%)	0 / 6 (0.00%)	0 / 257 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	1 / 263 (0.38%)	0 / 6 (0.00%)	0 / 257 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Coma			
subjects affected / exposed	1 / 263 (0.38%)	0 / 6 (0.00%)	0 / 257 (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
Post herpetic neuralgia			
subjects affected / exposed	0 / 263 (0.00%)	0 / 6 (0.00%)	1 / 257 (0.39%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			
subjects affected / exposed	0 / 263 (0.00%)	0 / 6 (0.00%)	1 / 257 (0.39%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Toxic encephalopathy			
subjects affected / exposed	1 / 263 (0.38%)	0 / 6 (0.00%)	0 / 257 (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
Blood and lymphatic system disorders			
Febrile neutropenia			
subjects affected / exposed	18 / 263 (6.84%)	0 / 6 (0.00%)	8 / 257 (3.11%)
occurrences causally related to treatment / all	14 / 18	0 / 0	6 / 8
deaths causally related to treatment / all	1 / 2	0 / 0	0 / 0

Eosinophilia			
subjects affected / exposed	0 / 263 (0.00%)	0 / 6 (0.00%)	0 / 257 (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
Anaemia			
subjects affected / exposed	3 / 263 (1.14%)	0 / 6 (0.00%)	2 / 257 (0.78%)
occurrences causally related to treatment / all	1 / 3	0 / 0	4 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemolysis			
subjects affected / exposed	1 / 263 (0.38%)	0 / 6 (0.00%)	0 / 257 (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
Leukocytosis			
subjects affected / exposed	0 / 263 (0.00%)	0 / 6 (0.00%)	1 / 257 (0.39%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Leukopenia			
subjects affected / exposed	1 / 263 (0.38%)	0 / 6 (0.00%)	0 / 257 (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
Myelosuppression			
subjects affected / exposed	3 / 263 (1.14%)	0 / 6 (0.00%)	0 / 257 (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
Bone marrow failure			
subjects affected / exposed	1 / 263 (0.38%)	0 / 6 (0.00%)	0 / 257 (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
Thrombocytopenia			
subjects affected / exposed	0 / 263 (0.00%)	0 / 6 (0.00%)	1 / 257 (0.39%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutropenia			

subjects affected / exposed	3 / 263 (1.14%)	0 / 6 (0.00%)	5 / 257 (1.95%)
occurrences causally related to treatment / all	5 / 5	0 / 0	4 / 6
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Uveitis			
subjects affected / exposed	0 / 263 (0.00%)	1 / 6 (16.67%)	0 / 257 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Gastrointestinal haemorrhage			
subjects affected / exposed	1 / 263 (0.38%)	0 / 6 (0.00%)	0 / 257 (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
Diarrhoea			
subjects affected / exposed	6 / 263 (2.28%)	0 / 6 (0.00%)	0 / 257 (0.00%)
occurrences causally related to treatment / all	3 / 6	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Stomatitis			
subjects affected / exposed	0 / 263 (0.00%)	0 / 6 (0.00%)	0 / 257 (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
Hepatobiliary disorders			
Cholangitis acute			
subjects affected / exposed	0 / 263 (0.00%)	0 / 6 (0.00%)	1 / 257 (0.39%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Liver disorder			
subjects affected / exposed	1 / 263 (0.38%)	0 / 6 (0.00%)	0 / 257 (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
Gallbladder disorder			
subjects affected / exposed	0 / 263 (0.00%)	0 / 6 (0.00%)	1 / 257 (0.39%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Skin and subcutaneous tissue disorders			
Dermatitis allergic			
subjects affected / exposed	0 / 263 (0.00%)	0 / 6 (0.00%)	0 / 257 (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
Dermatitis exfoliative generalised			
subjects affected / exposed	2 / 263 (0.76%)	0 / 6 (0.00%)	0 / 257 (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
Eczema			
subjects affected / exposed	1 / 263 (0.38%)	0 / 6 (0.00%)	0 / 257 (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
Drug eruption			
subjects affected / exposed	0 / 263 (0.00%)	1 / 6 (16.67%)	0 / 257 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Erythema multiforme			
subjects affected / exposed	1 / 263 (0.38%)	1 / 6 (16.67%)	0 / 257 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rash			
subjects affected / exposed	2 / 263 (0.76%)	0 / 6 (0.00%)	0 / 257 (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
Rash pruritic			
subjects affected / exposed	1 / 263 (0.38%)	0 / 6 (0.00%)	0 / 257 (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
Rash maculo-papular			
subjects affected / exposed	5 / 263 (1.90%)	0 / 6 (0.00%)	0 / 257 (0.00%)
occurrences causally related to treatment / all	6 / 6	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Stevens-Johnson syndrome			

subjects affected / exposed	1 / 263 (0.38%)	0 / 6 (0.00%)	0 / 257 (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
Toxic skin eruption			
subjects affected / exposed	2 / 263 (0.76%)	0 / 6 (0.00%)	0 / 257 (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
Skin toxicity			
subjects affected / exposed	1 / 263 (0.38%)	0 / 6 (0.00%)	0 / 257 (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			
Hydronephrosis			
subjects affected / exposed	1 / 263 (0.38%)	0 / 6 (0.00%)	0 / 257 (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
Urinary retention			
subjects affected / exposed	1 / 263 (0.38%)	0 / 6 (0.00%)	0 / 257 (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
Renal impairment			
subjects affected / exposed	0 / 263 (0.00%)	0 / 6 (0.00%)	1 / 257 (0.39%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute kidney injury			
subjects affected / exposed	3 / 263 (1.14%)	0 / 6 (0.00%)	1 / 257 (0.39%)
occurrences causally related to treatment / all	1 / 3	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocrine disorders			
Inappropriate antidiuretic hormone secretion			
subjects affected / exposed	1 / 263 (0.38%)	0 / 6 (0.00%)	0 / 257 (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			
Back pain			
subjects affected / exposed	0 / 263 (0.00%)	0 / 6 (0.00%)	2 / 257 (0.78%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Bacteraemia			
subjects affected / exposed	2 / 263 (0.76%)	0 / 6 (0.00%)	0 / 257 (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
Bronchitis			
subjects affected / exposed	2 / 263 (0.76%)	0 / 6 (0.00%)	0 / 257 (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
Cytomegalovirus infection			
subjects affected / exposed	12 / 263 (4.56%)	0 / 6 (0.00%)	2 / 257 (0.78%)
occurrences causally related to treatment / all	15 / 16	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Clostridium difficile colitis			
subjects affected / exposed	0 / 263 (0.00%)	0 / 6 (0.00%)	1 / 257 (0.39%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea infectious			
subjects affected / exposed	1 / 263 (0.38%)	0 / 6 (0.00%)	0 / 257 (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
Disseminated cryptococcosis			
subjects affected / exposed	1 / 263 (0.38%)	0 / 6 (0.00%)	0 / 257 (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
Diverticulitis			
subjects affected / exposed	0 / 263 (0.00%)	0 / 6 (0.00%)	1 / 257 (0.39%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Epididymitis			
subjects affected / exposed	1 / 263 (0.38%)	0 / 6 (0.00%)	0 / 257 (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
Erysipelas			
subjects affected / exposed	0 / 263 (0.00%)	0 / 6 (0.00%)	1 / 257 (0.39%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis			
subjects affected / exposed	1 / 263 (0.38%)	0 / 6 (0.00%)	0 / 257 (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
Genital herpes			
subjects affected / exposed	1 / 263 (0.38%)	0 / 6 (0.00%)	0 / 257 (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
Herpes zoster			
subjects affected / exposed	2 / 263 (0.76%)	0 / 6 (0.00%)	1 / 257 (0.39%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Influenza			
subjects affected / exposed	3 / 263 (1.14%)	0 / 6 (0.00%)	1 / 257 (0.39%)
occurrences causally related to treatment / all	3 / 3	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infection			
subjects affected / exposed	2 / 263 (0.76%)	0 / 6 (0.00%)	0 / 257 (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
Meningitis			
subjects affected / exposed	1 / 263 (0.38%)	0 / 6 (0.00%)	0 / 257 (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
Lower respiratory tract infection			

subjects affected / exposed	3 / 263 (1.14%)	0 / 6 (0.00%)	1 / 257 (0.39%)
occurrences causally related to treatment / all	2 / 3	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Laryngitis			
subjects affected / exposed	1 / 263 (0.38%)	0 / 6 (0.00%)	0 / 257 (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
Meningitis cryptococcal			
subjects affected / exposed	1 / 263 (0.38%)	0 / 6 (0.00%)	0 / 257 (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
Pneumonia			
subjects affected / exposed	34 / 263 (12.93%)	0 / 6 (0.00%)	3 / 257 (1.17%)
occurrences causally related to treatment / all	28 / 38	0 / 0	1 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia cytomegaloviral			
subjects affected / exposed	2 / 263 (0.76%)	0 / 6 (0.00%)	0 / 257 (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
Pneumonia viral			
subjects affected / exposed	1 / 263 (0.38%)	0 / 6 (0.00%)	0 / 257 (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
Sepsis			
subjects affected / exposed	4 / 263 (1.52%)	1 / 6 (16.67%)	1 / 257 (0.39%)
occurrences causally related to treatment / all	3 / 4	0 / 1	1 / 1
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Rash pustular			
subjects affected / exposed	1 / 263 (0.38%)	0 / 6 (0.00%)	0 / 257 (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
Pyelonephritis			

subjects affected / exposed	3 / 263 (1.14%)	0 / 6 (0.00%)	0 / 257 (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
Skin infection			
subjects affected / exposed	1 / 263 (0.38%)	0 / 6 (0.00%)	0 / 257 (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
Upper respiratory tract infection			
subjects affected / exposed	5 / 263 (1.90%)	0 / 6 (0.00%)	2 / 257 (0.78%)
occurrences causally related to treatment / all	4 / 5	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	4 / 263 (1.52%)	0 / 6 (0.00%)	2 / 257 (0.78%)
occurrences causally related to treatment / all	2 / 5	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Varicella			
subjects affected / exposed	1 / 263 (0.38%)	0 / 6 (0.00%)	0 / 257 (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
Ludwig angina			
subjects affected / exposed	0 / 263 (0.00%)	0 / 6 (0.00%)	1 / 257 (0.39%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anal abscess			
subjects affected / exposed	1 / 263 (0.38%)	0 / 6 (0.00%)	0 / 257 (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
Cytomegalovirus colitis			
subjects affected / exposed	1 / 263 (0.38%)	0 / 6 (0.00%)	0 / 257 (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
Pneumococcal sepsis			

subjects affected / exposed	0 / 263 (0.00%)	0 / 6 (0.00%)	0 / 257 (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
Febrile infection			
subjects affected / exposed	2 / 263 (0.76%)	0 / 6 (0.00%)	0 / 257 (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
Hepatic infection			
subjects affected / exposed	1 / 263 (0.38%)	0 / 6 (0.00%)	0 / 257 (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
Infective thrombosis			
subjects affected / exposed	1 / 263 (0.38%)	0 / 6 (0.00%)	0 / 257 (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
Cytomegalovirus infection reactivation			
subjects affected / exposed	3 / 263 (1.14%)	0 / 6 (0.00%)	0 / 257 (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
Enterocolitis infectious			
subjects affected / exposed	2 / 263 (0.76%)	0 / 6 (0.00%)	0 / 257 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Enteritis infectious			
subjects affected / exposed	1 / 263 (0.38%)	0 / 6 (0.00%)	0 / 257 (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
Cytomegalovirus viraemia			
subjects affected / exposed	1 / 263 (0.38%)	0 / 6 (0.00%)	0 / 257 (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
Viraemia			

subjects affected / exposed	1 / 263 (0.38%)	0 / 6 (0.00%)	0 / 257 (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
Respiratory syncytial virus infection			
subjects affected / exposed	1 / 263 (0.38%)	0 / 6 (0.00%)	0 / 257 (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 bacterial			
subjects affected / exposed	1 / 263 (0.38%)	0 / 6 (0.00%)	0 / 257 (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
Respiratory tract infection fungal			
subjects affected / exposed	1 / 263 (0.38%)	0 / 6 (0.00%)	0 / 257 (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
Anorectal infection			
subjects affected / exposed	1 / 263 (0.38%)	0 / 6 (0.00%)	0 / 257 (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
Respiratory tract infection			
subjects affected / exposed	1 / 263 (0.38%)	0 / 6 (0.00%)	2 / 257 (0.78%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Device related infection			
subjects affected / exposed	1 / 263 (0.38%)	0 / 6 (0.00%)	0 / 257 (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
Herpes zoster disseminated			
subjects affected / exposed	0 / 263 (0.00%)	0 / 6 (0.00%)	1 / 257 (0.39%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumocystis jirovecii pneumonia			

subjects affected / exposed	1 / 263 (0.38%)	0 / 6 (0.00%)	0 / 257 (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
Large intestine infection			
subjects affected / exposed	0 / 263 (0.00%)	0 / 6 (0.00%)	1 / 257 (0.39%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular device infection			
subjects affected / exposed	0 / 263 (0.00%)	0 / 6 (0.00%)	1 / 257 (0.39%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract candidiasis			
subjects affected / exposed	1 / 263 (0.38%)	0 / 6 (0.00%)	0 / 257 (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
COVID-19			
subjects affected / exposed	2 / 263 (0.76%)	0 / 6 (0.00%)	0 / 257 (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
COVID-19 pneumonia			
subjects affected / exposed	2 / 263 (0.76%)	0 / 6 (0.00%)	2 / 257 (0.78%)
occurrences causally related to treatment / all	1 / 3	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	1 / 263 (0.38%)	0 / 6 (0.00%)	0 / 257 (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 inadequate control			
subjects affected / exposed	0 / 263 (0.00%)	0 / 6 (0.00%)	0 / 257 (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
Hyperglycaemia			

subjects affected / exposed	10 / 263 (3.80%)	0 / 6 (0.00%)	1 / 257 (0.39%)
occurrences causally related to treatment / all	11 / 11	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypokalaemia			
subjects affected / exposed	2 / 263 (0.76%)	0 / 6 (0.00%)	1 / 257 (0.39%)
occurrences causally related to treatment / all	5 / 5	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Type 2 diabetes mellitus			
subjects affected / exposed	1 / 263 (0.38%)	0 / 6 (0.00%)	0 / 257 (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
Tumour lysis syndrome			
subjects affected / exposed	1 / 263 (0.38%)	0 / 6 (0.00%)	0 / 257 (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

Serious adverse events	SRI: Copa+R-CHOP 60 mg		
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 6 (100.00%)		
number of deaths (all causes)	1		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Colon cancer			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Kaposi's sarcoma			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Squamous cell carcinoma			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Squamous cell carcinoma of skin				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Prostate cancer				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Lung neoplasm malignant				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Vascular disorders				
Haematoma				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hypertension				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hypertensive crisis				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hypotension				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
General disorders and administration site conditions				
Chest pain				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			

Chills				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Oedema peripheral				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Malaise				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hyperthermia				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pyrexia				
subjects affected / exposed	1 / 6 (16.67%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
General physical health deterioration				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Inflammation				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Device related thrombosis				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Immune system disorders				

Drug hypersensitivity			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hypersensitivity			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infusion related hypersensitivity reaction			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Reproductive system and breast disorders			
Benign prostatic hyperplasia			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Acute respiratory distress syndrome			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Bronchospasm			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Dyspnoea			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hypoxia			

subjects affected / exposed	0 / 6 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Interstitial lung disease				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pneumonitis				
subjects affected / exposed	1 / 6 (16.67%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Pulmonary embolism				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Respiratory distress				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pulmonary oedema				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Investigations				
Blood creatine phosphokinase increased				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Amylase increased				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Alanine aminotransferase increased				

subjects affected / exposed	0 / 6 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Blood creatinine increased				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Lymphocyte count decreased				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Neutrophil count decreased				
subjects affected / exposed	1 / 6 (16.67%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Platelet count decreased				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
White blood cell count decreased				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cytomegalovirus test positive				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Norovirus test positive				
subjects affected / exposed	1 / 6 (16.67%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Injury, poisoning and procedural complications				
Overdose				

subjects affected / exposed	0 / 6 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Femoral neck fracture				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Limb injury				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cardiac disorders				
Atrial fibrillation				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Bradycardia				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Myocardial ischaemia				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Tachycardia				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Left ventricular dysfunction				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Nervous system disorders				

Cerebrovascular accident				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Coma				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Post herpetic neuralgia				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Syncope				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Toxic encephalopathy				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Blood and lymphatic system disorders				
Febrile neutropenia				
subjects affected / exposed	2 / 6 (33.33%)			
occurrences causally related to treatment / all	1 / 4			
deaths causally related to treatment / all	0 / 0			
Eosinophilia				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Anaemia				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Haemolysis				

subjects affected / exposed	0 / 6 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Leukocytosis				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Leukopenia				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Myelosuppression				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Bone marrow failure				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Thrombocytopenia				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Neutropenia				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Eye disorders				
Uveitis				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal disorders				

Gastrointestinal haemorrhage				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Diarrhoea				
subjects affected / exposed	1 / 6 (16.67%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Stomatitis				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hepatobiliary disorders				
Cholangitis acute				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Liver disorder				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gallbladder disorder				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Skin and subcutaneous tissue disorders				
Dermatitis allergic				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Dermatitis exfoliative generalised				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			

Eczema				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Drug eruption				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Erythema multiforme				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Rash				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Rash pruritic				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Rash maculo-papular				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Stevens-Johnson syndrome				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Toxic skin eruption				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Skin toxicity				

subjects affected / exposed	0 / 6 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Hydronephrosis			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Urinary retention			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Renal impairment			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Acute kidney injury			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Endocrine disorders			
Inappropriate antidiuretic hormone secretion			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Bacteraemia			

subjects affected / exposed	0 / 6 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Bronchitis				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cytomegalovirus infection				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Clostridium difficile colitis				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Diarrhoea infectious				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Disseminated cryptococcosis				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Diverticulitis				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Epididymitis				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Erysipelas				

subjects affected / exposed	0 / 6 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastroenteritis				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Genital herpes				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Herpes zoster				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Influenza				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Infection				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Meningitis				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Lower respiratory tract infection				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Laryngitis				

subjects affected / exposed	0 / 6 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Meningitis cryptococcal				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pneumonia				
subjects affected / exposed	2 / 6 (33.33%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Pneumonia cytomegaloviral				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pneumonia viral				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Sepsis				
subjects affected / exposed	1 / 6 (16.67%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Rash pustular				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pyelonephritis				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Skin infection				

subjects affected / exposed	0 / 6 (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	0 / 6 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Urinary tract infection				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Varicella				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Ludwig angina				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Anal abscess				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cytomegalovirus colitis				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pneumococcal sepsis				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Febrile infection				

subjects affected / exposed	0 / 6 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hepatic infection				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Infective thrombosis				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cytomegalovirus infection reactivation				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Enterocolitis infectious				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Enteritis infectious				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cytomegalovirus viraemia				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Viraemia				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Respiratory syncytial virus infection				

subjects affected / exposed	0 / 6 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pneumonia bacterial				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Respiratory tract infection fungal				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Anorectal infection				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Respiratory tract infection				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Device related infection				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Herpes zoster disseminated				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pneumocystis jirovecii pneumonia				
subjects affected / exposed	1 / 6 (16.67%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Large intestine infection				

subjects affected / exposed	0 / 6 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Vascular device infection				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Urinary tract candidiasis				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
COVID-19				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
COVID-19 pneumonia				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Metabolism and nutrition disorders				
Dehydration				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Diabetes mellitus inadequate control				
subjects affected / exposed	1 / 6 (16.67%)			
occurrences causally related to treatment / all	6 / 6			
deaths causally related to treatment / all	0 / 0			
Hyperglycaemia				
subjects affected / exposed	1 / 6 (16.67%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Hypokalaemia				

subjects affected / exposed	0 / 6 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Type 2 diabetes mellitus			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Tumour lysis syndrome			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	SRI: Copa+R-CHOP 45 mg	SRI: Copa+R-B 60 mg (excluding subjects from Japan)	SRI: Copa+R-B 45 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	5 / 5 (100.00%)	7 / 7 (100.00%)	3 / 3 (100.00%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Seborrhoeic keratosis			
subjects affected / exposed	1 / 5 (20.00%)	0 / 7 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Vascular disorders			
Secondary hypertension			
subjects affected / exposed	1 / 5 (20.00%)	0 / 7 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Phlebitis			
subjects affected / exposed	1 / 5 (20.00%)	0 / 7 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Hypotension			
subjects affected / exposed	1 / 5 (20.00%)	1 / 7 (14.29%)	0 / 3 (0.00%)
occurrences (all)	1	1	0
Hypertension			
subjects affected / exposed	4 / 5 (80.00%)	2 / 7 (28.57%)	1 / 3 (33.33%)
occurrences (all)	6	10	1

Vasculitis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Surgical and medical procedures			
Ureteral stent insertion			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
General disorders and administration site conditions			
Chills			
subjects affected / exposed	0 / 5 (0.00%)	1 / 7 (14.29%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Asthenia			
subjects affected / exposed	1 / 5 (20.00%)	2 / 7 (28.57%)	0 / 3 (0.00%)
occurrences (all)	1	6	0
Face oedema			
subjects affected / exposed	0 / 5 (0.00%)	1 / 7 (14.29%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Injection site reaction			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Fatigue			
subjects affected / exposed	1 / 5 (20.00%)	1 / 7 (14.29%)	2 / 3 (66.67%)
occurrences (all)	1	1	3
Malaise			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Mucosal inflammation			
subjects affected / exposed	0 / 5 (0.00%)	1 / 7 (14.29%)	1 / 3 (33.33%)
occurrences (all)	0	6	1
Pyrexia			
subjects affected / exposed	2 / 5 (40.00%)	4 / 7 (57.14%)	1 / 3 (33.33%)
occurrences (all)	2	6	1
Oedema			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Swelling face			

subjects affected / exposed	0 / 5 (0.00%)	1 / 7 (14.29%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Immune system disorders			
Contrast media allergy			
subjects affected / exposed	0 / 5 (0.00%)	1 / 7 (14.29%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Drug hypersensitivity			
subjects affected / exposed	0 / 5 (0.00%)	2 / 7 (28.57%)	0 / 3 (0.00%)
occurrences (all)	0	2	0
Reproductive system and breast disorders			
Vulvovaginal inflammation			
subjects affected / exposed	0 / 5 (0.00%)	1 / 7 (14.29%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	2 / 5 (40.00%)	1 / 7 (14.29%)	0 / 3 (0.00%)
occurrences (all)	2	1	0
Nasal congestion			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Hypoxia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Hiccups			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Dyspnoea			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Upper-airway cough syndrome			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Oropharyngeal pain			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Productive cough			

subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Psychiatric disorders			
Insomnia			
subjects affected / exposed	1 / 5 (20.00%)	1 / 7 (14.29%)	0 / 3 (0.00%)
occurrences (all)	1	1	0
Investigations			
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 5 (0.00%)	3 / 7 (42.86%)	1 / 3 (33.33%)
occurrences (all)	0	3	2
Amylase increased			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Activated partial thromboplastin time prolonged			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Alanine aminotransferase increased			
subjects affected / exposed	0 / 5 (0.00%)	3 / 7 (42.86%)	1 / 3 (33.33%)
occurrences (all)	0	3	1
Blood bilirubin increased			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Blood cholesterol increased			
subjects affected / exposed	1 / 5 (20.00%)	0 / 7 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Blood creatine phosphokinase increased			
subjects affected / exposed	1 / 5 (20.00%)	0 / 7 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Blood creatinine increased			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Blood lactate dehydrogenase increased			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0

C-reactive protein increased			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
CD4 lymphocytes decreased			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Electrocardiogram QT prolonged			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Gamma-glutamyltransferase increased			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Lipase increased			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Lymphocyte count decreased			
subjects affected / exposed	1 / 5 (20.00%)	1 / 7 (14.29%)	0 / 3 (0.00%)
occurrences (all)	1	1	0
Neutrophil count decreased			
subjects affected / exposed	0 / 5 (0.00%)	3 / 7 (42.86%)	1 / 3 (33.33%)
occurrences (all)	0	3	1
Platelet count decreased			
subjects affected / exposed	1 / 5 (20.00%)	1 / 7 (14.29%)	0 / 3 (0.00%)
occurrences (all)	5	1	0
Weight decreased			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
White blood cell count decreased			
subjects affected / exposed	0 / 5 (0.00%)	2 / 7 (28.57%)	0 / 3 (0.00%)
occurrences (all)	0	2	0
Ejection fraction decreased			
subjects affected / exposed	1 / 5 (20.00%)	0 / 7 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Cytomegalovirus test positive			

subjects affected / exposed	0 / 5 (0.00%)	1 / 7 (14.29%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Troponin I increased			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Blood alkaline phosphatase increased			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Norovirus test positive			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Pseudomonas test positive			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Inflammatory marker increased			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Injury, poisoning and procedural complications			
Facial bones fracture			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Patella fracture			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Contusion			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Infusion related reaction			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Wound			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Tooth fracture			

subjects affected / exposed	1 / 5 (20.00%)	0 / 7 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Nervous system disorders			
Dizziness			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Dysaesthesia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Headache			
subjects affected / exposed	1 / 5 (20.00%)	1 / 7 (14.29%)	1 / 3 (33.33%)
occurrences (all)	1	1	2
Dysgeusia			
subjects affected / exposed	0 / 5 (0.00%)	1 / 7 (14.29%)	1 / 3 (33.33%)
occurrences (all)	0	1	1
Neuropathy peripheral			
subjects affected / exposed	1 / 5 (20.00%)	0 / 7 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Sciatica			
subjects affected / exposed	1 / 5 (20.00%)	1 / 7 (14.29%)	0 / 3 (0.00%)
occurrences (all)	1	1	0
Presyncope			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Peripheral sensory neuropathy			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Paraesthesia			
subjects affected / exposed	1 / 5 (20.00%)	0 / 7 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Taste disorder			

subjects affected / exposed	0 / 5 (0.00%)	1 / 7 (14.29%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Vagus nerve disorder			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Tremor			
subjects affected / exposed	0 / 5 (0.00%)	1 / 7 (14.29%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 5 (40.00%)	3 / 7 (42.86%)	2 / 3 (66.67%)
occurrences (all)	3	10	2
Febrile neutropenia			
subjects affected / exposed	1 / 5 (20.00%)	0 / 7 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Leukopenia			
subjects affected / exposed	1 / 5 (20.00%)	1 / 7 (14.29%)	1 / 3 (33.33%)
occurrences (all)	1	8	2
Eosinophilia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Lymphopenia			
subjects affected / exposed	1 / 5 (20.00%)	1 / 7 (14.29%)	1 / 3 (33.33%)
occurrences (all)	1	2	1
Neutropenia			
subjects affected / exposed	4 / 5 (80.00%)	5 / 7 (71.43%)	2 / 3 (66.67%)
occurrences (all)	20	24	5
Thrombocytopenia			
subjects affected / exposed	2 / 5 (40.00%)	3 / 7 (42.86%)	2 / 3 (66.67%)
occurrences (all)	8	7	3
Ear and labyrinth disorders			
Tinnitus			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Eye disorders			

Dry eye			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Uveitis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	0 / 5 (0.00%)	1 / 7 (14.29%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Abdominal pain			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Constipation			
subjects affected / exposed	3 / 5 (60.00%)	2 / 7 (28.57%)	1 / 3 (33.33%)
occurrences (all)	5	4	1
Diarrhoea			
subjects affected / exposed	3 / 5 (60.00%)	3 / 7 (42.86%)	1 / 3 (33.33%)
occurrences (all)	5	5	4
Dry mouth			
subjects affected / exposed	1 / 5 (20.00%)	0 / 7 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Dysphagia			
subjects affected / exposed	1 / 5 (20.00%)	0 / 7 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Dyspepsia			
subjects affected / exposed	1 / 5 (20.00%)	0 / 7 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Enterocolitis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal pain			

subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Gingival pain			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Haemorrhoids			
subjects affected / exposed	0 / 5 (0.00%)	1 / 7 (14.29%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Rectal haemorrhage			
subjects affected / exposed	0 / 5 (0.00%)	1 / 7 (14.29%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Periodontal disease			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Nausea			
subjects affected / exposed	3 / 5 (60.00%)	5 / 7 (71.43%)	3 / 3 (100.00%)
occurrences (all)	3	8	6
Stomatitis			
subjects affected / exposed	0 / 5 (0.00%)	4 / 7 (57.14%)	2 / 3 (66.67%)
occurrences (all)	0	5	2
Mouth ulceration			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Paraesthesia oral			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Vomiting			
subjects affected / exposed	0 / 5 (0.00%)	2 / 7 (28.57%)	0 / 3 (0.00%)
occurrences (all)	0	2	0
Skin and subcutaneous tissue disorders			
Angioedema			
subjects affected / exposed	0 / 5 (0.00%)	1 / 7 (14.29%)	0 / 3 (0.00%)
occurrences (all)	0	2	0
Alopecia			
subjects affected / exposed	1 / 5 (20.00%)	0 / 7 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0

Drug eruption			
subjects affected / exposed	0 / 5 (0.00%)	1 / 7 (14.29%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Nail disorder			
subjects affected / exposed	0 / 5 (0.00%)	1 / 7 (14.29%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Erythema multiforme			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Erythema			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Eczema asteatotic			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Eczema			
subjects affected / exposed	0 / 5 (0.00%)	1 / 7 (14.29%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Nail dystrophy			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Photosensitivity reaction			
subjects affected / exposed	1 / 5 (20.00%)	0 / 7 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Pruritus			
subjects affected / exposed	1 / 5 (20.00%)	1 / 7 (14.29%)	2 / 3 (66.67%)
occurrences (all)	1	1	2
Purpura			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Rash			
subjects affected / exposed	0 / 5 (0.00%)	4 / 7 (57.14%)	1 / 3 (33.33%)
occurrences (all)	0	8	1
Rash maculo-papular			
subjects affected / exposed	1 / 5 (20.00%)	0 / 7 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0

Toxic skin eruption			
subjects affected / exposed	0 / 5 (0.00%)	1 / 7 (14.29%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Nephrolithiasis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Pollakiuria			
subjects affected / exposed	1 / 5 (20.00%)	0 / 7 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Acute kidney injury			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Musculoskeletal and connective tissue disorders			
Muscle spasms			
subjects affected / exposed	1 / 5 (20.00%)	0 / 7 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Back pain			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Arthralgia			
subjects affected / exposed	1 / 5 (20.00%)	1 / 7 (14.29%)	0 / 3 (0.00%)
occurrences (all)	1	1	0
Limb mass			
subjects affected / exposed	1 / 5 (20.00%)	0 / 7 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Pain in extremity			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Myositis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Infections and infestations			

Bronchitis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Bronchopulmonary aspergillosis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Cytomegalovirus infection			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Conjunctivitis			
subjects affected / exposed	1 / 5 (20.00%)	0 / 7 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Gastroenteritis			
subjects affected / exposed	1 / 5 (20.00%)	1 / 7 (14.29%)	0 / 3 (0.00%)
occurrences (all)	1	1	0
Genital herpes			
subjects affected / exposed	0 / 5 (0.00%)	1 / 7 (14.29%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Oral candidiasis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Nasopharyngitis			
subjects affected / exposed	1 / 5 (20.00%)	0 / 7 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Influenza			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Herpes zoster			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Pneumonia			
subjects affected / exposed	0 / 5 (0.00%)	1 / 7 (14.29%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Pharyngitis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0

Sinusitis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Tinea pedis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Upper respiratory tract infection			
subjects affected / exposed	1 / 5 (20.00%)	1 / 7 (14.29%)	0 / 3 (0.00%)
occurrences (all)	1	1	0
Urinary tract infection			
subjects affected / exposed	2 / 5 (40.00%)	1 / 7 (14.29%)	0 / 3 (0.00%)
occurrences (all)	2	1	0
Cytomegalovirus infection reactivation			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Borrelia infection			
subjects affected / exposed	0 / 5 (0.00%)	1 / 7 (14.29%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Parainfluenzae virus infection			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Respiratory tract infection			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Device related sepsis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Erythema migrans			
subjects affected / exposed	0 / 5 (0.00%)	1 / 7 (14.29%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Candida infection			
subjects affected / exposed	0 / 5 (0.00%)	1 / 7 (14.29%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Herpes simplex reactivation			

subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Metabolism and nutrition disorders			
Hyperglycaemia			
subjects affected / exposed	5 / 5 (100.00%)	6 / 7 (85.71%)	1 / 3 (33.33%)
occurrences (all)	8	15	2
Diabetes mellitus			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Hypocalcaemia			
subjects affected / exposed	0 / 5 (0.00%)	1 / 7 (14.29%)	1 / 3 (33.33%)
occurrences (all)	0	2	1
Hypoalbuminaemia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Hyperuricaemia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Hypertriglyceridaemia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Hyperkalaemia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Hypokalaemia			
subjects affected / exposed	2 / 5 (40.00%)	1 / 7 (14.29%)	0 / 3 (0.00%)
occurrences (all)	3	1	0
Hypomagnesaemia			
subjects affected / exposed	0 / 5 (0.00%)	2 / 7 (28.57%)	1 / 3 (33.33%)
occurrences (all)	0	3	1
Decreased appetite			
subjects affected / exposed	0 / 5 (0.00%)	3 / 7 (42.86%)	0 / 3 (0.00%)
occurrences (all)	0	7	0

Non-serious adverse events	Phase 3: Copa+R-B/R-CHOP	SRI: Japan Copa+R-B 60 mg	Phase 3: Pbo+R-B/R-CHOP
Total subjects affected by non-serious adverse events			

subjects affected / exposed	259 / 263 (98.48%)	6 / 6 (100.00%)	250 / 257 (97.28%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Seborrhoeic keratosis			
subjects affected / exposed	0 / 263 (0.00%)	0 / 6 (0.00%)	0 / 257 (0.00%)
occurrences (all)	0	0	0
Vascular disorders			
Secondary hypertension			
subjects affected / exposed	0 / 263 (0.00%)	0 / 6 (0.00%)	0 / 257 (0.00%)
occurrences (all)	0	0	0
Phlebitis			
subjects affected / exposed	11 / 263 (4.18%)	0 / 6 (0.00%)	6 / 257 (2.33%)
occurrences (all)	12	0	6
Hypotension			
subjects affected / exposed	8 / 263 (3.04%)	0 / 6 (0.00%)	7 / 257 (2.72%)
occurrences (all)	18	0	9
Hypertension			
subjects affected / exposed	114 / 263 (43.35%)	3 / 6 (50.00%)	42 / 257 (16.34%)
occurrences (all)	328	3	90
Vasculitis			
subjects affected / exposed	2 / 263 (0.76%)	3 / 6 (50.00%)	2 / 257 (0.78%)
occurrences (all)	2	3	2
Surgical and medical procedures			
Ureteral stent insertion			
subjects affected / exposed	0 / 263 (0.00%)	0 / 6 (0.00%)	0 / 257 (0.00%)
occurrences (all)	0	0	0
General disorders and administration site conditions			
Chills			
subjects affected / exposed	18 / 263 (6.84%)	0 / 6 (0.00%)	6 / 257 (2.33%)
occurrences (all)	24	0	9
Asthenia			
subjects affected / exposed	18 / 263 (6.84%)	0 / 6 (0.00%)	21 / 257 (8.17%)
occurrences (all)	20	0	28
Face oedema			
subjects affected / exposed	4 / 263 (1.52%)	0 / 6 (0.00%)	1 / 257 (0.39%)
occurrences (all)	4	0	1
Injection site reaction			

subjects affected / exposed	0 / 263 (0.00%)	0 / 6 (0.00%)	1 / 257 (0.39%)
occurrences (all)	0	0	1
Fatigue			
subjects affected / exposed	51 / 263 (19.39%)	3 / 6 (50.00%)	49 / 257 (19.07%)
occurrences (all)	65	4	63
Malaise			
subjects affected / exposed	26 / 263 (9.89%)	0 / 6 (0.00%)	15 / 257 (5.84%)
occurrences (all)	47	0	26
Mucosal inflammation			
subjects affected / exposed	9 / 263 (3.42%)	0 / 6 (0.00%)	1 / 257 (0.39%)
occurrences (all)	14	0	1
Pyrexia			
subjects affected / exposed	87 / 263 (33.08%)	2 / 6 (33.33%)	34 / 257 (13.23%)
occurrences (all)	130	4	51
Oedema			
subjects affected / exposed	4 / 263 (1.52%)	1 / 6 (16.67%)	3 / 257 (1.17%)
occurrences (all)	4	1	3
Swelling face			
subjects affected / exposed	0 / 263 (0.00%)	0 / 6 (0.00%)	1 / 257 (0.39%)
occurrences (all)	0	0	1
Immune system disorders			
Contrast media allergy			
subjects affected / exposed	1 / 263 (0.38%)	0 / 6 (0.00%)	0 / 257 (0.00%)
occurrences (all)	2	0	0
Drug hypersensitivity			
subjects affected / exposed	1 / 263 (0.38%)	0 / 6 (0.00%)	3 / 257 (1.17%)
occurrences (all)	1	0	3
Reproductive system and breast disorders			
Vulvovaginal inflammation			
subjects affected / exposed	1 / 263 (0.38%)	0 / 6 (0.00%)	0 / 257 (0.00%)
occurrences (all)	1	0	0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	41 / 263 (15.59%)	0 / 6 (0.00%)	37 / 257 (14.40%)
occurrences (all)	59	0	47
Nasal congestion			

subjects affected / exposed	5 / 263 (1.90%)	0 / 6 (0.00%)	3 / 257 (1.17%)
occurrences (all)	5	0	3
Hypoxia			
subjects affected / exposed	6 / 263 (2.28%)	0 / 6 (0.00%)	0 / 257 (0.00%)
occurrences (all)	6	0	0
Hiccups			
subjects affected / exposed	4 / 263 (1.52%)	1 / 6 (16.67%)	1 / 257 (0.39%)
occurrences (all)	4	1	2
Dyspnoea			
subjects affected / exposed	14 / 263 (5.32%)	0 / 6 (0.00%)	11 / 257 (4.28%)
occurrences (all)	15	0	12
Upper-airway cough syndrome			
subjects affected / exposed	0 / 263 (0.00%)	0 / 6 (0.00%)	0 / 257 (0.00%)
occurrences (all)	0	0	0
Oropharyngeal pain			
subjects affected / exposed	11 / 263 (4.18%)	0 / 6 (0.00%)	10 / 257 (3.89%)
occurrences (all)	12	0	10
Productive cough			
subjects affected / exposed	9 / 263 (3.42%)	0 / 6 (0.00%)	7 / 257 (2.72%)
occurrences (all)	10	0	10
Psychiatric disorders			
Insomnia			
subjects affected / exposed	23 / 263 (8.75%)	1 / 6 (16.67%)	13 / 257 (5.06%)
occurrences (all)	29	1	13
Investigations			
Aspartate aminotransferase increased			
subjects affected / exposed	34 / 263 (12.93%)	3 / 6 (50.00%)	18 / 257 (7.00%)
occurrences (all)	51	4	27
Amylase increased			
subjects affected / exposed	13 / 263 (4.94%)	1 / 6 (16.67%)	10 / 257 (3.89%)
occurrences (all)	15	1	17
Activated partial thromboplastin time prolonged			
subjects affected / exposed	2 / 263 (0.76%)	0 / 6 (0.00%)	0 / 257 (0.00%)
occurrences (all)	2	0	0
Alanine aminotransferase increased			

subjects affected / exposed	38 / 263 (14.45%)	3 / 6 (50.00%)	22 / 257 (8.56%)
occurrences (all)	62	3	38
Blood bilirubin increased			
subjects affected / exposed	19 / 263 (7.22%)	1 / 6 (16.67%)	13 / 257 (5.06%)
occurrences (all)	33	1	27
Blood cholesterol increased			
subjects affected / exposed	12 / 263 (4.56%)	0 / 6 (0.00%)	7 / 257 (2.72%)
occurrences (all)	23	0	8
Blood creatine phosphokinase increased			
subjects affected / exposed	9 / 263 (3.42%)	0 / 6 (0.00%)	2 / 257 (0.78%)
occurrences (all)	11	0	2
Blood creatinine increased			
subjects affected / exposed	9 / 263 (3.42%)	1 / 6 (16.67%)	14 / 257 (5.45%)
occurrences (all)	11	2	17
Blood lactate dehydrogenase increased			
subjects affected / exposed	27 / 263 (10.27%)	0 / 6 (0.00%)	11 / 257 (4.28%)
occurrences (all)	53	0	14
C-reactive protein increased			
subjects affected / exposed	8 / 263 (3.04%)	0 / 6 (0.00%)	3 / 257 (1.17%)
occurrences (all)	13	0	3
CD4 lymphocytes decreased			
subjects affected / exposed	16 / 263 (6.08%)	1 / 6 (16.67%)	2 / 257 (0.78%)
occurrences (all)	16	1	2
Electrocardiogram QT prolonged			
subjects affected / exposed	5 / 263 (1.90%)	1 / 6 (16.67%)	6 / 257 (2.33%)
occurrences (all)	6	1	7
Gamma-glutamyltransferase increased			
subjects affected / exposed	15 / 263 (5.70%)	0 / 6 (0.00%)	7 / 257 (2.72%)
occurrences (all)	16	0	9
Lipase increased			
subjects affected / exposed	18 / 263 (6.84%)	1 / 6 (16.67%)	13 / 257 (5.06%)
occurrences (all)	21	1	18
Lymphocyte count decreased			

subjects affected / exposed	72 / 263 (27.38%)	4 / 6 (66.67%)	50 / 257 (19.46%)
occurrences (all)	232	6	145
Neutrophil count decreased			
subjects affected / exposed	109 / 263 (41.44%)	3 / 6 (50.00%)	82 / 257 (31.91%)
occurrences (all)	489	5	301
Platelet count decreased			
subjects affected / exposed	72 / 263 (27.38%)	1 / 6 (16.67%)	52 / 257 (20.23%)
occurrences (all)	209	1	126
Weight decreased			
subjects affected / exposed	64 / 263 (24.33%)	1 / 6 (16.67%)	21 / 257 (8.17%)
occurrences (all)	74	1	29
White blood cell count decreased			
subjects affected / exposed	78 / 263 (29.66%)	3 / 6 (50.00%)	65 / 257 (25.29%)
occurrences (all)	386	6	272
Ejection fraction decreased			
subjects affected / exposed	2 / 263 (0.76%)	0 / 6 (0.00%)	3 / 257 (1.17%)
occurrences (all)	2	0	3
Cytomegalovirus test positive			
subjects affected / exposed	20 / 263 (7.60%)	3 / 6 (50.00%)	13 / 257 (5.06%)
occurrences (all)	28	3	22
Troponin I increased			
subjects affected / exposed	0 / 263 (0.00%)	0 / 6 (0.00%)	0 / 257 (0.00%)
occurrences (all)	0	0	0
Blood alkaline phosphatase increased			
subjects affected / exposed	20 / 263 (7.60%)	1 / 6 (16.67%)	7 / 257 (2.72%)
occurrences (all)	28	2	11
Norovirus test positive			
subjects affected / exposed	0 / 263 (0.00%)	0 / 6 (0.00%)	0 / 257 (0.00%)
occurrences (all)	0	0	0
Pseudomonas test positive			
subjects affected / exposed	0 / 263 (0.00%)	0 / 6 (0.00%)	0 / 257 (0.00%)
occurrences (all)	0	0	0
Inflammatory marker increased			
subjects affected / exposed	0 / 263 (0.00%)	0 / 6 (0.00%)	0 / 257 (0.00%)
occurrences (all)	0	0	0
Injury, poisoning and procedural			

complications			
Facial bones fracture			
subjects affected / exposed	0 / 263 (0.00%)	0 / 6 (0.00%)	0 / 257 (0.00%)
occurrences (all)	0	0	0
Patella fracture			
subjects affected / exposed	0 / 263 (0.00%)	0 / 6 (0.00%)	0 / 257 (0.00%)
occurrences (all)	0	0	0
Contusion			
subjects affected / exposed	3 / 263 (1.14%)	0 / 6 (0.00%)	2 / 257 (0.78%)
occurrences (all)	3	0	3
Infusion related reaction			
subjects affected / exposed	9 / 263 (3.42%)	2 / 6 (33.33%)	15 / 257 (5.84%)
occurrences (all)	13	3	17
Wound			
subjects affected / exposed	0 / 263 (0.00%)	1 / 6 (16.67%)	1 / 257 (0.39%)
occurrences (all)	0	1	1
Tooth fracture			
subjects affected / exposed	0 / 263 (0.00%)	0 / 6 (0.00%)	0 / 257 (0.00%)
occurrences (all)	0	0	0
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	3 / 263 (1.14%)	0 / 6 (0.00%)	0 / 257 (0.00%)
occurrences (all)	5	0	0
Nervous system disorders			
Dizziness			
subjects affected / exposed	18 / 263 (6.84%)	0 / 6 (0.00%)	12 / 257 (4.67%)
occurrences (all)	22	0	17
Dysaesthesia			
subjects affected / exposed	1 / 263 (0.38%)	1 / 6 (16.67%)	0 / 257 (0.00%)
occurrences (all)	1	1	0
Headache			
subjects affected / exposed	35 / 263 (13.31%)	2 / 6 (33.33%)	29 / 257 (11.28%)
occurrences (all)	44	2	42
Dysgeusia			
subjects affected / exposed	9 / 263 (3.42%)	2 / 6 (33.33%)	10 / 257 (3.89%)
occurrences (all)	21	2	11
Neuropathy peripheral			

subjects affected / exposed	5 / 263 (1.90%)	0 / 6 (0.00%)	4 / 257 (1.56%)
occurrences (all)	6	0	5
Sciatica			
subjects affected / exposed	0 / 263 (0.00%)	0 / 6 (0.00%)	4 / 257 (1.56%)
occurrences (all)	0	0	4
Presyncope			
subjects affected / exposed	3 / 263 (1.14%)	0 / 6 (0.00%)	1 / 257 (0.39%)
occurrences (all)	3	0	1
Peripheral sensory neuropathy			
subjects affected / exposed	2 / 263 (0.76%)	0 / 6 (0.00%)	3 / 257 (1.17%)
occurrences (all)	2	0	3
Paraesthesia			
subjects affected / exposed	5 / 263 (1.90%)	0 / 6 (0.00%)	2 / 257 (0.78%)
occurrences (all)	5	0	2
Taste disorder			
subjects affected / exposed	4 / 263 (1.52%)	0 / 6 (0.00%)	1 / 257 (0.39%)
occurrences (all)	4	0	1
Vagus nerve disorder			
subjects affected / exposed	0 / 263 (0.00%)	1 / 6 (16.67%)	0 / 257 (0.00%)
occurrences (all)	0	1	0
Tremor			
subjects affected / exposed	3 / 263 (1.14%)	0 / 6 (0.00%)	1 / 257 (0.39%)
occurrences (all)	3	0	1
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	85 / 263 (32.32%)	0 / 6 (0.00%)	64 / 257 (24.90%)
occurrences (all)	166	0	147
Febrile neutropenia			
subjects affected / exposed	8 / 263 (3.04%)	1 / 6 (16.67%)	2 / 257 (0.78%)
occurrences (all)	11	1	2
Leukopenia			
subjects affected / exposed	13 / 263 (4.94%)	0 / 6 (0.00%)	21 / 257 (8.17%)
occurrences (all)	18	0	39
Eosinophilia			
subjects affected / exposed	5 / 263 (1.90%)	0 / 6 (0.00%)	3 / 257 (1.17%)
occurrences (all)	9	0	5

Lymphopenia			
subjects affected / exposed	15 / 263 (5.70%)	0 / 6 (0.00%)	22 / 257 (8.56%)
occurrences (all)	29	0	42
Neutropenia			
subjects affected / exposed	86 / 263 (32.70%)	1 / 6 (16.67%)	88 / 257 (34.24%)
occurrences (all)	213	1	232
Thrombocytopenia			
subjects affected / exposed	44 / 263 (16.73%)	0 / 6 (0.00%)	28 / 257 (10.89%)
occurrences (all)	68	0	57
Ear and labyrinth disorders			
Tinnitus			
subjects affected / exposed	1 / 263 (0.38%)	0 / 6 (0.00%)	0 / 257 (0.00%)
occurrences (all)	1	0	0
Eye disorders			
Dry eye			
subjects affected / exposed	1 / 263 (0.38%)	0 / 6 (0.00%)	0 / 257 (0.00%)
occurrences (all)	1	0	0
Uveitis			
subjects affected / exposed	0 / 263 (0.00%)	1 / 6 (16.67%)	2 / 257 (0.78%)
occurrences (all)	0	1	2
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	12 / 263 (4.56%)	1 / 6 (16.67%)	13 / 257 (5.06%)
occurrences (all)	13	1	14
Abdominal pain			
subjects affected / exposed	14 / 263 (5.32%)	0 / 6 (0.00%)	14 / 257 (5.45%)
occurrences (all)	17	0	17
Constipation			
subjects affected / exposed	36 / 263 (13.69%)	0 / 6 (0.00%)	49 / 257 (19.07%)
occurrences (all)	43	0	57
Diarrhoea			
subjects affected / exposed	88 / 263 (33.46%)	2 / 6 (33.33%)	38 / 257 (14.79%)
occurrences (all)	137	4	45
Dry mouth			
subjects affected / exposed	8 / 263 (3.04%)	0 / 6 (0.00%)	5 / 257 (1.95%)
occurrences (all)	11	0	5
Dysphagia			

subjects affected / exposed	2 / 263 (0.76%)	0 / 6 (0.00%)	4 / 257 (1.56%)
occurrences (all)	2	0	4
Dyspepsia			
subjects affected / exposed	8 / 263 (3.04%)	0 / 6 (0.00%)	8 / 257 (3.11%)
occurrences (all)	10	0	13
Enterocolitis			
subjects affected / exposed	0 / 263 (0.00%)	1 / 6 (16.67%)	0 / 257 (0.00%)
occurrences (all)	0	1	0
Gastrooesophageal reflux disease			
subjects affected / exposed	8 / 263 (3.04%)	0 / 6 (0.00%)	7 / 257 (2.72%)
occurrences (all)	8	0	7
Gastrointestinal pain			
subjects affected / exposed	0 / 263 (0.00%)	1 / 6 (16.67%)	2 / 257 (0.78%)
occurrences (all)	0	1	2
Gingival pain			
subjects affected / exposed	0 / 263 (0.00%)	0 / 6 (0.00%)	0 / 257 (0.00%)
occurrences (all)	0	0	0
Haemorrhoids			
subjects affected / exposed	6 / 263 (2.28%)	0 / 6 (0.00%)	1 / 257 (0.39%)
occurrences (all)	6	0	1
Rectal haemorrhage			
subjects affected / exposed	1 / 263 (0.38%)	0 / 6 (0.00%)	1 / 257 (0.39%)
occurrences (all)	1	0	1
Periodontal disease			
subjects affected / exposed	0 / 263 (0.00%)	1 / 6 (16.67%)	0 / 257 (0.00%)
occurrences (all)	0	1	0
Nausea			
subjects affected / exposed	112 / 263 (42.59%)	4 / 6 (66.67%)	92 / 257 (35.80%)
occurrences (all)	208	4	156
Stomatitis			
subjects affected / exposed	25 / 263 (9.51%)	1 / 6 (16.67%)	10 / 257 (3.89%)
occurrences (all)	31	4	10
Mouth ulceration			
subjects affected / exposed	16 / 263 (6.08%)	0 / 6 (0.00%)	4 / 257 (1.56%)
occurrences (all)	21	0	5
Paraesthesia oral			

subjects affected / exposed	0 / 263 (0.00%)	0 / 6 (0.00%)	0 / 257 (0.00%)
occurrences (all)	0	0	0
Vomiting			
subjects affected / exposed	59 / 263 (22.43%)	2 / 6 (33.33%)	31 / 257 (12.06%)
occurrences (all)	123	3	44
Skin and subcutaneous tissue disorders			
Angioedema			
subjects affected / exposed	0 / 263 (0.00%)	0 / 6 (0.00%)	0 / 257 (0.00%)
occurrences (all)	0	0	0
Alopecia			
subjects affected / exposed	1 / 263 (0.38%)	0 / 6 (0.00%)	3 / 257 (1.17%)
occurrences (all)	1	0	3
Drug eruption			
subjects affected / exposed	0 / 263 (0.00%)	0 / 6 (0.00%)	0 / 257 (0.00%)
occurrences (all)	0	0	0
Nail disorder			
subjects affected / exposed	0 / 263 (0.00%)	0 / 6 (0.00%)	0 / 257 (0.00%)
occurrences (all)	0	0	0
Erythema multiforme			
subjects affected / exposed	3 / 263 (1.14%)	1 / 6 (16.67%)	0 / 257 (0.00%)
occurrences (all)	5	1	0
Erythema			
subjects affected / exposed	6 / 263 (2.28%)	1 / 6 (16.67%)	6 / 257 (2.33%)
occurrences (all)	7	1	6
Eczema asteatotic			
subjects affected / exposed	0 / 263 (0.00%)	0 / 6 (0.00%)	1 / 257 (0.39%)
occurrences (all)	0	0	2
Eczema			
subjects affected / exposed	6 / 263 (2.28%)	1 / 6 (16.67%)	3 / 257 (1.17%)
occurrences (all)	14	1	3
Nail dystrophy			
subjects affected / exposed	0 / 263 (0.00%)	0 / 6 (0.00%)	0 / 257 (0.00%)
occurrences (all)	0	0	0
Photosensitivity reaction			
subjects affected / exposed	1 / 263 (0.38%)	0 / 6 (0.00%)	0 / 257 (0.00%)
occurrences (all)	1	0	0

Pruritus			
subjects affected / exposed	30 / 263 (11.41%)	0 / 6 (0.00%)	24 / 257 (9.34%)
occurrences (all)	39	0	29
Purpura			
subjects affected / exposed	0 / 263 (0.00%)	1 / 6 (16.67%)	0 / 257 (0.00%)
occurrences (all)	0	1	0
Rash			
subjects affected / exposed	59 / 263 (22.43%)	1 / 6 (16.67%)	26 / 257 (10.12%)
occurrences (all)	75	1	33
Rash maculo-papular			
subjects affected / exposed	25 / 263 (9.51%)	3 / 6 (50.00%)	14 / 257 (5.45%)
occurrences (all)	38	3	16
Toxic skin eruption			
subjects affected / exposed	4 / 263 (1.52%)	0 / 6 (0.00%)	2 / 257 (0.78%)
occurrences (all)	5	0	3
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	2 / 263 (0.76%)	0 / 6 (0.00%)	5 / 257 (1.95%)
occurrences (all)	2	0	5
Nephrolithiasis			
subjects affected / exposed	1 / 263 (0.38%)	0 / 6 (0.00%)	0 / 257 (0.00%)
occurrences (all)	2	0	0
Pollakiuria			
subjects affected / exposed	4 / 263 (1.52%)	0 / 6 (0.00%)	1 / 257 (0.39%)
occurrences (all)	4	0	1
Acute kidney injury			
subjects affected / exposed	7 / 263 (2.66%)	0 / 6 (0.00%)	3 / 257 (1.17%)
occurrences (all)	8	0	3
Musculoskeletal and connective tissue disorders			
Muscle spasms			
subjects affected / exposed	6 / 263 (2.28%)	1 / 6 (16.67%)	3 / 257 (1.17%)
occurrences (all)	6	1	3
Back pain			
subjects affected / exposed	11 / 263 (4.18%)	1 / 6 (16.67%)	23 / 257 (8.95%)
occurrences (all)	12	1	31
Arthralgia			

subjects affected / exposed	8 / 263 (3.04%)	0 / 6 (0.00%)	15 / 257 (5.84%)
occurrences (all)	11	0	20
Limb mass			
subjects affected / exposed	0 / 263 (0.00%)	0 / 6 (0.00%)	0 / 257 (0.00%)
occurrences (all)	0	0	0
Pain in extremity			
subjects affected / exposed	8 / 263 (3.04%)	0 / 6 (0.00%)	7 / 257 (2.72%)
occurrences (all)	8	0	7
Myositis			
subjects affected / exposed	0 / 263 (0.00%)	0 / 6 (0.00%)	0 / 257 (0.00%)
occurrences (all)	0	0	0
Infections and infestations			
Bronchitis			
subjects affected / exposed	14 / 263 (5.32%)	0 / 6 (0.00%)	7 / 257 (2.72%)
occurrences (all)	16	0	10
Bronchopulmonary aspergillosis			
subjects affected / exposed	0 / 263 (0.00%)	0 / 6 (0.00%)	1 / 257 (0.39%)
occurrences (all)	0	0	1
Cytomegalovirus infection			
subjects affected / exposed	47 / 263 (17.87%)	1 / 6 (16.67%)	14 / 257 (5.45%)
occurrences (all)	70	2	14
Conjunctivitis			
subjects affected / exposed	4 / 263 (1.52%)	1 / 6 (16.67%)	5 / 257 (1.95%)
occurrences (all)	4	1	5
Gastroenteritis			
subjects affected / exposed	3 / 263 (1.14%)	0 / 6 (0.00%)	2 / 257 (0.78%)
occurrences (all)	3	0	2
Genital herpes			
subjects affected / exposed	1 / 263 (0.38%)	0 / 6 (0.00%)	0 / 257 (0.00%)
occurrences (all)	1	0	0
Oral candidiasis			
subjects affected / exposed	9 / 263 (3.42%)	1 / 6 (16.67%)	1 / 257 (0.39%)
occurrences (all)	9	2	1
Nasopharyngitis			
subjects affected / exposed	14 / 263 (5.32%)	0 / 6 (0.00%)	11 / 257 (4.28%)
occurrences (all)	16	0	15

Influenza			
subjects affected / exposed	5 / 263 (1.90%)	1 / 6 (16.67%)	5 / 257 (1.95%)
occurrences (all)	10	1	7
Herpes zoster			
subjects affected / exposed	13 / 263 (4.94%)	0 / 6 (0.00%)	15 / 257 (5.84%)
occurrences (all)	14	0	16
Pneumonia			
subjects affected / exposed	31 / 263 (11.79%)	0 / 6 (0.00%)	4 / 257 (1.56%)
occurrences (all)	34	0	4
Pharyngitis			
subjects affected / exposed	10 / 263 (3.80%)	1 / 6 (16.67%)	7 / 257 (2.72%)
occurrences (all)	12	2	7
Sinusitis			
subjects affected / exposed	5 / 263 (1.90%)	1 / 6 (16.67%)	9 / 257 (3.50%)
occurrences (all)	5	1	10
Tinea pedis			
subjects affected / exposed	0 / 263 (0.00%)	0 / 6 (0.00%)	0 / 257 (0.00%)
occurrences (all)	0	0	0
Upper respiratory tract infection			
subjects affected / exposed	44 / 263 (16.73%)	3 / 6 (50.00%)	37 / 257 (14.40%)
occurrences (all)	63	4	51
Urinary tract infection			
subjects affected / exposed	19 / 263 (7.22%)	0 / 6 (0.00%)	17 / 257 (6.61%)
occurrences (all)	32	0	22
Cytomegalovirus infection reactivation			
subjects affected / exposed	14 / 263 (5.32%)	0 / 6 (0.00%)	4 / 257 (1.56%)
occurrences (all)	29	0	6
Borrelia infection			
subjects affected / exposed	0 / 263 (0.00%)	0 / 6 (0.00%)	0 / 257 (0.00%)
occurrences (all)	0	0	0
Parainfluenzae virus infection			
subjects affected / exposed	0 / 263 (0.00%)	0 / 6 (0.00%)	0 / 257 (0.00%)
occurrences (all)	0	0	0
Respiratory tract infection			

subjects affected / exposed	8 / 263 (3.04%)	0 / 6 (0.00%)	4 / 257 (1.56%)
occurrences (all)	10	0	7
Device related sepsis			
subjects affected / exposed	0 / 263 (0.00%)	0 / 6 (0.00%)	0 / 257 (0.00%)
occurrences (all)	0	0	0
Erythema migrans			
subjects affected / exposed	0 / 263 (0.00%)	0 / 6 (0.00%)	0 / 257 (0.00%)
occurrences (all)	0	0	0
Candida infection			
subjects affected / exposed	1 / 263 (0.38%)	0 / 6 (0.00%)	0 / 257 (0.00%)
occurrences (all)	1	0	0
Herpes simplex reactivation			
subjects affected / exposed	0 / 263 (0.00%)	0 / 6 (0.00%)	0 / 257 (0.00%)
occurrences (all)	0	0	0
Metabolism and nutrition disorders			
Hyperglycaemia			
subjects affected / exposed	150 / 263 (57.03%)	4 / 6 (66.67%)	53 / 257 (20.62%)
occurrences (all)	318	4	145
Diabetes mellitus			
subjects affected / exposed	5 / 263 (1.90%)	0 / 6 (0.00%)	1 / 257 (0.39%)
occurrences (all)	5	0	1
Hypocalcaemia			
subjects affected / exposed	11 / 263 (4.18%)	0 / 6 (0.00%)	3 / 257 (1.17%)
occurrences (all)	16	0	3
Hypoalbuminaemia			
subjects affected / exposed	13 / 263 (4.94%)	1 / 6 (16.67%)	2 / 257 (0.78%)
occurrences (all)	16	1	3
Hyperuricaemia			
subjects affected / exposed	4 / 263 (1.52%)	1 / 6 (16.67%)	21 / 257 (8.17%)
occurrences (all)	6	1	34
Hypertriglyceridaemia			
subjects affected / exposed	26 / 263 (9.89%)	1 / 6 (16.67%)	17 / 257 (6.61%)
occurrences (all)	40	1	24
Hyperkalaemia			
subjects affected / exposed	1 / 263 (0.38%)	1 / 6 (16.67%)	5 / 257 (1.95%)
occurrences (all)	1	1	5

Hypokalaemia			
subjects affected / exposed	44 / 263 (16.73%)	0 / 6 (0.00%)	9 / 257 (3.50%)
occurrences (all)	62	0	13
Hypomagnesaemia			
subjects affected / exposed	24 / 263 (9.13%)	0 / 6 (0.00%)	8 / 257 (3.11%)
occurrences (all)	29	0	10
Decreased appetite			
subjects affected / exposed	43 / 263 (16.35%)	1 / 6 (16.67%)	32 / 257 (12.45%)
occurrences (all)	54	2	40

Non-serious adverse events	SRI: Copa+R-CHOP 60 mg		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	6 / 6 (100.00%)		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Seborrhoeic keratosis			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Vascular disorders			
Secondary hypertension			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Phlebitis			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Hypotension			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Hypertension			
subjects affected / exposed	3 / 6 (50.00%)		
occurrences (all)	3		
Vasculitis			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Surgical and medical procedures			
Ureteral stent insertion			

subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
General disorders and administration site conditions			
Chills			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Asthenia			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Face oedema			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Injection site reaction			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Fatigue			
subjects affected / exposed	2 / 6 (33.33%)		
occurrences (all)	2		
Malaise			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Mucosal inflammation			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Pyrexia			
subjects affected / exposed	2 / 6 (33.33%)		
occurrences (all)	2		
Oedema			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Swelling face			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Immune system disorders			

Contrast media allergy subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0		
Drug hypersensitivity subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0		
Reproductive system and breast disorders Vulvovaginal inflammation subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0		
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all)	3 / 6 (50.00%) 3		
Nasal congestion subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 1		
Hypoxia subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 1		
Hiccups subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0		
Dyspnoea subjects affected / exposed occurrences (all)	2 / 6 (33.33%) 2		
Upper-airway cough syndrome subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 1		
Oropharyngeal pain subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0		
Productive cough subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 1		
Psychiatric disorders			

Insomnia			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Investigations			
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Amylase increased			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Activated partial thromboplastin time prolonged			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Alanine aminotransferase increased			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Blood bilirubin increased			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Blood cholesterol increased			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Blood creatine phosphokinase increased			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Blood creatinine increased			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Blood lactate dehydrogenase increased			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
C-reactive protein increased			
subjects affected / exposed	2 / 6 (33.33%)		
occurrences (all)	2		

CD4 lymphocytes decreased				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences (all)	0			
Electrocardiogram QT prolonged				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences (all)	0			
Gamma-glutamyltransferase increased				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences (all)	0			
Lipase increased				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences (all)	0			
Lymphocyte count decreased				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences (all)	0			
Neutrophil count decreased				
subjects affected / exposed	2 / 6 (33.33%)			
occurrences (all)	6			
Platelet count decreased				
subjects affected / exposed	3 / 6 (50.00%)			
occurrences (all)	3			
Weight decreased				
subjects affected / exposed	2 / 6 (33.33%)			
occurrences (all)	2			
White blood cell count decreased				
subjects affected / exposed	1 / 6 (16.67%)			
occurrences (all)	1			
Ejection fraction decreased				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences (all)	0			
Cytomegalovirus test positive				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences (all)	0			
Troponin I increased				

subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Blood alkaline phosphatase increased			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Norovirus test positive			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Pseudomonas test positive			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	2		
Inflammatory marker increased			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Injury, poisoning and procedural complications			
Facial bones fracture			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Patella fracture			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Contusion			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Infusion related reaction			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Wound			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Tooth fracture			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Cardiac disorders			

Atrial fibrillation			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Nervous system disorders			
Dizziness			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Dysaesthesia			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Headache			
subjects affected / exposed	2 / 6 (33.33%)		
occurrences (all)	3		
Dysgeusia			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Neuropathy peripheral			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Sciatica			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Presyncope			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Peripheral sensory neuropathy			
subjects affected / exposed	3 / 6 (50.00%)		
occurrences (all)	4		
Paraesthesia			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Taste disorder			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Vagus nerve disorder			

subjects affected / exposed occurrences (all) Tremor subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0 0 / 6 (0.00%) 0		
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all) Febrile neutropenia subjects affected / exposed occurrences (all) Leukopenia subjects affected / exposed occurrences (all) Eosinophilia subjects affected / exposed occurrences (all) Lymphopenia subjects affected / exposed occurrences (all) Neutropenia subjects affected / exposed occurrences (all) Thrombocytopenia subjects affected / exposed occurrences (all)	 3 / 6 (50.00%) 5 0 / 6 (0.00%) 0 0 / 6 (0.00%) 0 0 / 6 (0.00%) 0 1 / 6 (16.67%) 1 1 / 6 (16.67%) 1 1 / 6 (16.67%) 3		
Ear and labyrinth disorders Tinnitus subjects affected / exposed occurrences (all)	 1 / 6 (16.67%) 1		
Eye disorders Dry eye subjects affected / exposed occurrences (all) Uveitis	 1 / 6 (16.67%) 1		

subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	2 / 6 (33.33%)		
occurrences (all)	2		
Abdominal pain			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Constipation			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Diarrhoea			
subjects affected / exposed	4 / 6 (66.67%)		
occurrences (all)	4		
Dry mouth			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Dysphagia			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Dyspepsia			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Enterocolitis			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Gastrointestinal pain			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Gingival pain			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		

Haemorrhoids subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0		
Rectal haemorrhage subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0		
Periodontal disease subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0		
Nausea subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 1		
Stomatitis subjects affected / exposed occurrences (all)	2 / 6 (33.33%) 2		
Mouth ulceration subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0		
Paraesthesia oral subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 1		
Vomiting subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0		
Skin and subcutaneous tissue disorders			
Angioedema subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0		
Alopecia subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 1		
Drug eruption subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0		
Nail disorder			

subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Erythema multiforme			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Erythema			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Eczema asteatotic			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Eczema			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Nail dystrophy			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Photosensitivity reaction			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Pruritus			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Purpura			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Rash			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Rash maculo-papular			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Toxic skin eruption			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Renal and urinary disorders			

Dysuria			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Nephrolithiasis			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Pollakiuria			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Acute kidney injury			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Musculoskeletal and connective tissue disorders			
Muscle spasms			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Back pain			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Arthralgia			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Limb mass			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Pain in extremity			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Myositis			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Infections and infestations			
Bronchitis			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Bronchopulmonary aspergillosis			

subjects affected / exposed	0 / 6 (0.00%)			
occurrences (all)	0			
Cytomegalovirus infection				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences (all)	0			
Conjunctivitis				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences (all)	0			
Gastroenteritis				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences (all)	0			
Genital herpes				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences (all)	0			
Oral candidiasis				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences (all)	0			
Nasopharyngitis				
subjects affected / exposed	1 / 6 (16.67%)			
occurrences (all)	2			
Influenza				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences (all)	0			
Herpes zoster				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences (all)	0			
Pneumonia				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences (all)	0			
Pharyngitis				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences (all)	0			
Sinusitis				
subjects affected / exposed	2 / 6 (33.33%)			
occurrences (all)	2			
Tinea pedis				

subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Upper respiratory tract infection			
subjects affected / exposed	2 / 6 (33.33%)		
occurrences (all)	4		
Urinary tract infection			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Cytomegalovirus infection reactivation			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Borrelia infection			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Parainfluenzae virus infection			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Respiratory tract infection			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	2		
Device related sepsis			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Erythema migrans			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Candida infection			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Herpes simplex reactivation			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Metabolism and nutrition disorders			
Hyperglycaemia			

subjects affected / exposed	3 / 6 (50.00%)		
occurrences (all)	3		
Diabetes mellitus			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Hypocalcaemia			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Hypoalbuminaemia			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Hyperuricaemia			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Hypertriglyceridaemia			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Hyperkalaemia			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Hypokalaemia			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Hypomagnesaemia			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Decreased appetite			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
01 September 2015	Clarification of exclusion criteria for patients who had received bendamustine-based therapy. Clarification of timing of blood count collection for dosing criteria. Addition of an additional plasma collection for non-genetic biomarker analysis for patients in the R-CHOP treatment arm.
18 July 2016	The allowed prior immunochemotherapy regimens and treatment assignment were clarified. Text describing the rules for randomization based on prior immunochemotherapy and exclusion criterion 29 regarding the prior treatment with bendamustine was modified in accordance with the standard treatment for iNHL. Updated inclusion criteria to remove requirement for the absolute lymphocyte count at diagnosis, clarified screening requirements for WM patients who do not have a radiologically measurable lesion, updated text referring to platelet count in patients with confirmed lymphomatous bone marrow infiltration, and updated criterion for the use of effective contraception. Modified exclusion criterion related to arterial hypertension to eliminate the conservative requirement for blood pressure levels during eligibility evaluation. Exclusion of patients based on plasma glucose levels was removed to eliminate the eligibility evaluation requirement for plasma glucose testing and to ensure enrollment of patients with diabetes mellitus in a compensation state confirmed by HbA1c testing at Screening. Clarification added that the HbA1c >8.5% level concerns all patients, not only patients with diabetes mellitus. Allowed for inclusion of patients with a chronic HCV or HBV infection; prophylaxis for HBV and monitoring of HBV and HCV were added as patients with HBV and HCV are at risk of recurrence while receiving rituximab. Exclusion criterion related to proteinuria was modified to allow proteinuria assessment using a method other than UPCR. Clarification was added for how the tests should be performed and reported. Clarification added for corticosteroid therapy use prior to and during the study. Added prior treatment with copanlisib to the list of prohibited previous therapies and medications. An updated guidance for the management of transient glucose increases was provided to ensure patient safety. Table continued.
30 March 2017	Study eligibility criteria and treatment allocation language were modified to include patients who have received prior treatment with rituximab-based immunochemotherapy and alkylating agents. Study design was modified to allow patients who have received R-B as a previous line of therapy to be randomized to study intervention plus R-B arm when there is ≥24 months progression-free interval after the last R-B treatment; exclusion criteria modified to reflect this change. Total sample size was reduced from 676 patients to 520 patients, with primary efficacy analysis to be performed in the FAS instead of both FAS and FL subgroups. Clarification was added that patients recruited into the SRI part were not to be evaluated as part of the Phase 3 part of the study. RP3D for copanlisib in combination with R-B was determined in accordance with the DMC, and clarification was added to allow starting the Phase 3 part of the study. A new exclusion criterion was added to exclude patients who had received live vaccination within 6 months before the start of study treatment. Language was modified to allow patients beyond progression to continue treatment with copanlisib if, in the investigator's opinion, treatment is providing clinical benefit. Clarifications were made to the bone marrow assessments relating to confirmation of WM diagnosis and biomarker analysis in patients with WM, local assessment of bone marrow biopsies prior to central pathology review, and modified text for platelet count values in patients with lymphomatous bone marrow infiltration to consider values at study entry. Clarifications were made for the radiological tumor assessments regarding timing and calculation of time points for tumor assessments, the use of PET-CT imaging and modification of withdrawal criteria to clarify the assessment of disease progression leading to the discontinuation of study treatment. Guidance regarding drug–drug interactions was updated based on new data.

14 August 2017	Language was modified to not allow patients to continue treatment in CHRONOS-4 beyond disease progression
25 September 2018	Updated guidance for the management of glucose increases regarding dose reduction guidance and withdrawal criterion, fasting requirements, glucose monitoring, the timing of post-infusion glucose measurements, and the schedule for HbA1c measurements. Guidance related to blood pressure measurements on infusion days was clarified to be aligned with copanlisib and rituximab labeling information. Updated guidance for dermatologic to align with copanlisib labeling information, and hematological toxicity was modified to clarify the use of G-CSF. Inclusion criteria were modified for the use of prior line of rituximab-based immunochemotherapy and alkylating agents and for assessment requirements for nodal and extranodal involvement in patients with splenic MZL. Exclusion criteria were modified to remove study participation restrictions, including the exclusion of patients with a history of current autoimmune disease, and to clarify the definition of rituximab resistance. Clarification of the administration of study treatment regarding permanent discontinuation and drug administration delay of any of the study treatment and prohibition of the use of rituximab biosimilars during the study. Eligibility criteria modifications for laboratory assessments included criterion for total bilirubin, testing criterion for CMV and HBV/HCV, and criterion to perform blood cultures. Clarification of tumor assessments regarding bone marrow biopsy requirements, PET functional imaging preference, and timing and requirements for CT/MRI scans. Clarification was added that patients would be stratified by the duration of progression-free interval from the last rituximab-containing regimen (previously duration of treatment-free interval). Change to prohibited concomitant therapy prohibiting use of biotin at least 72 hours prior to immunoassay test collection.
14 August 2019	The eligibility criterion was modified to allow prior anticancer therapies with rituximab biosimilars, and/or anti-CD20 MAb. Change from use of electronic PRO to paper PRO and updated version. Other changes included corrections of the descriptive text for excluding blood count test at Cycle(x), Day 8 and removal of BP measurement at Day 2 (Cycles 1–6).
21 March 2023	Changed the number of PFS events for primary completion from approximately 256 events to approximately 280 events, and detailed that confirmatory statistical testing strategies will be provided in SAP. Changed the end of the active follow-up period to extend up to 2 years after study primary completion. Changed the time for collecting survival follow-up data from 5 to 10 years after the last patient started study treatment. Added disease control rate as a secondary objective and defined the respective analyses. Revised information for FLymSI questionnaire to change the version of the form being used from version 4 to version 2 and the timing of the form to be completed for up to at least 1 year after study primary completion or until sponsor’s decision to terminate form completion. Provided guidance to specify the tumor assessments beyond Year 5 study period. Removed text that required submission of a tumor sample from a biopsy or excision occurring during the study based on medical need. Added text to clarify that central pathology would be analyzed only as an exploratory analysis. Changed the post-baseline bone marrow biopsy assessment central review to local assessment to confirm the first CR. Added text regarding disclosure of study results. Added text for participant visits, assessments, and monitoring in the event of study continuity issues. Aligned text throughout to state that disease progression is assessed by blinded independent central review.

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.

NA

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/34389273