Clinical trial results:
A Randomized, Open-label, Safety and Efficacy Study of Ibrutinib in Pediatric and Young Adult Patients With Relapsed or Refractory Mature B-cell non-Hodgkin Lymphoma

Summary

EudraCT number	2016-000259-28
Trial protocol	GB IT BE CZ HU DE NL ES PL BG Outside EU/EEA SE
Global end of trial date	11 June 2021

Results information

Result version number	v1 (current)
This version publication date	22 December 2021
First version publication date	22 December 2021

Trial information

Trial identification

Sponsor protocol code	54179060LYM3003

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02703272
WHO universal trial number (UTN)	-

Notes:

Sponsors

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

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-001397-PIP03-14
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?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	11 June 2021
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	11 June 2021
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The main objectives of this trial was to confirm that the pharmacokinetics (PK) in pediatric subjects was consistent with that in adults (Part 1) and to assess efficacy (event free survival [EFS]) of ibrutinib in combination with RICE (rituximab, ifosfamide, carboplatin, etoposide, and dexamethasone) or RVICI (rituximab, vincristine, ifosfamide, carboplatin, idarubicin, and dexamethasone) background therapy compared to RICE or RVICI background therapy alone (Part 2).

Protection of trial subjects:

This study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with Good Clinical Practices and applicable regulatory requirements. Known instances of nonconformance were documented and are not considered to have had an impact on the overall conclusions of this study. Safety assessments were based upon the occurrence, type, and severity of adverse events (AEs) reported throughout the study, AEs of interest, vital signs, electrocardiogram (ECG), clinical laboratory tests (that is, hematology, serum chemistry, viral serology), and physical examinations.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	14 December 2016
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Belgium: 2
Country: Number of subjects enrolled	Bulgaria: 2
Country: Number of subjects enrolled	Brazil: 4
Country: Number of subjects enrolled	Canada: 1
Country: Number of subjects enrolled	Czechia: 4
Country: Number of subjects enrolled	Germany: 6
Country: Number of subjects enrolled	Spain: 2
Country: Number of subjects enrolled	France: 7
Country: Number of subjects enrolled	United Kingdom: 2
Country: Number of subjects enrolled	Italy: 9
Country: Number of subjects enrolled	Korea, Republic of: 10
Country: Number of subjects enrolled	Netherlands: 2
Country: Number of subjects enrolled	Poland: 3
Country: Number of subjects enrolled	Romania: 1
Country: Number of subjects enrolled	Russian Federation: 2

Country: Number of subjects enrolled	Sweden: 1
Country: Number of subjects enrolled	Turkey: 8
Country: Number of subjects enrolled	Taiwan: 3
Country: Number of subjects enrolled	Ukraine: 1
Country: Number of subjects enrolled	United States: 2
Worldwide total number of subjects	72
EEA total number of subjects	39

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)	25
Adolescents (12-17 years)	41
Adults (18-64 years)	6
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 72 subjects (21 subjects in Part 1 and 51 subjects in Part 2) were enrolled in this study. Total of 72 subjects, 71 subjects received the study treatment. One of the 51 subjects, randomized to chemotherapy (CIT) group, withdrew consent following randomization and did not receive study treatment.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Part 1: Ibrutinib+RICE

Arm description:

Subjects received ibrutinib based on age group and body surface area (BSA) in combination with chemoimmunotherapy (CIT) (investigator choice of RICE [rituximab, ifosfamide, carboplatin, etoposide, and dexamethasone]) for 3 treatment cycles with each cycle 28 or 21 days long. The RICE regimen was composed of rituximab 750 milligrams per meter square (mg/m^2), ifosfamide 9 grams per meter square (g/m^2), carboplatin 635 mg/m^2, etoposide 300 mg/m^2, and dexamethasone 100 mg/m^2. Study treatment continued for 3 cycles, unless the subject experienced unacceptable toxicity or disease progression.

Arm type	Experimental
Investigational medicinal product name	Ibrutinib
Investigational medicinal product code	
Other name	JNJ-54179060
Pharmaceutical forms	Concentrate for oral suspension, Capsule
Routes of administration	Oral use

Dosage and administration details:

Subjects received ibrutinib orally once daily, starting at Cycle 1 Day 1 with a maximum dose of 440 mg/m^2 in Part 1.

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

Dosage and administration details:

Subjects received cumulative dose of 750 milligrams per meter square (mg/m^2) rituximab as part of RICE in Part 1.

Investigational medicinal product name	Ifosfamide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Subjects received cumulative dose of 9 grams per meter square (g/m^2) ifosfamide as part of RICE in Part 1.

Investigational medicinal product name	Carboplatin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Subjects received cumulative dose of 635 mg/m^2 carboplatin as part of RICE in Part 1.

Investigational medicinal product name	Etoposide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Subjects received cumulative dose of 300 mg/m^2 etoposide as part of RICE in Part 1.

Investigational medicinal product name	Dexamethasone
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Subjects received cumulative dose of 100 mg/m^2 dexamethasone as part of RICE in Part 1.

Arm title	Part 1: Ibrutinib+RVICI

Arm description:

Subjects received ibrutinib based on age group and BSA in combination with CIT (investigator choice of RVICI [rituximab, vincristine, ifosfamide, carboplatin, idarubicin, and dexamethasone]) for 3 treatment cycles with each cycle 28 or 21 days long. The RVICI regimen was composed of rituximab 750 mg/m^2, vincristine 1.6 mg/m^2, ifosfamide 10 g/m^2, carboplatin 800 mg/m^2, idarubicin 20 mg/m^2, and dexamethasone 100 mg/m^2. Study treatment continued for 3 cycles, unless the subject experienced unacceptable toxicity or disease progression.

Arm type	Experimental
Investigational medicinal product name	Ibrutinib
Investigational medicinal product code	
Other name	JNJ-54179060
Pharmaceutical forms	Capsule, Concentrate for oral suspension
Routes of administration	Oral use

Dosage and administration details:

Subjects received ibrutinib orally once daily, starting at Cycle 1 Day 1 with a maximum dose of 440 mg/m^2 in Part 1.

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

Dosage and administration details:

Subjects received cumulative dose of 750 mg/m^2 rituximab as part of RVICI in Part 1.

Investigational medicinal product name	Vincristine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Subjects received cumulative dose of 1.6 mg/m^2 vincristine as part of RVICI in Part 1.

Investigational medicinal product name	Idarubicin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Subjects received cumulative dose of 20 mg/m^2 idarubicin as part of RVICI in Part 1.

Investigational medicinal product name	Carboplatin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Subjects received cumulative dose of 800 mg/m^2 carboplatin as part of RVICI in Part 1.

Investigational medicinal product name	Ifosfamide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Subjects received cumulative dose of 10 g/m^2 ifosfamide as part of RVICI in Part 1.

Investigational medicinal product name	Dexamethasone
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Subjects received cumulative dose of 100 mg/m^2 dexamethasone as part of RVICI in Part 1

Arm title	Part 2: Ibrutinib+CIT (RICE or RVICI)

Arm description:

Subjects received ibrutinib based on age group and BSA in combination with CIT (investigator choice of RICE or RVICI) until 3 treatment cycles, transplantation if indicated, or until progressive disease (PD) or unacceptable toxicity.

Arm type	Experimental
Investigational medicinal product name	Chemoimmunotherapy (CIT) (RICE or RVICI)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Subjects received CIT (investigator choice of RICE or RVICI) in Part 2.

Investigational medicinal product name	Ibrutinib
Investigational medicinal product code	
Other name	JNJ-54179060
Pharmaceutical forms	Capsule, Concentrate for oral suspension
Routes of administration	Oral use

Dosage and administration details:

Subjects received ibrutinib orally once daily, starting at Cycle 1 Day 1 with a maximum dose of 440 mg/m^2 in Part 2.

Arm title	Part 2: Chemotherapy (CIT)

Arm description:

Subjects received CIT (investigator choice of RICE or RVICI) alone based on age group and BSA until 3

treatment cycles, transplantation if indicated, or until progressive disease (PD) or unacceptable toxicity.

Arm type	Active comparator
Investigational medicinal product name	CIT (RICE or RVICI)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Subjects received CIT (investigator choice of RICE or RVICI) alone in Part 2.

Number of subjects in period 1	Part 1: Ibrutinib+RICE	Part 1: Ibrutinib+RVICI	Part 2: Ibrutinib+CIT (RICE or RVICI)
Started	11	10	35
Completed	0	0	0
Not completed	11	10	35
Adverse event, serious fatal	4	9	19
Consent withdrawn by subject	-	-	4
Other	1	-	-
Study terminated by sponsor	6	1	12

Number of subjects in period 1	Part 2: Chemotherapy (CIT)
Started	16
Completed	0
Not completed	16
Adverse event, serious fatal	10
Consent withdrawn by subject	2
Other	-
Study terminated by sponsor	4

Baseline characteristics

Reporting groups	
Reporting group title	Part 1: Ibrutinib+RICE
Reporting group description:	
Subjects received ibrutinib based on age group and body surface area (BSA) in combination with chemoimmunotherapy (CIT) (investigator choice of RICE [rituximab, ifosfamide, carboplatin, etoposide, and dexamethasone]) for 3 treatment cycles with each cycle 28 or 21 days long. The RICE regimen was composed of rituximab 750 milligrams per meter square (mg/m^2), ifosfamide 9 grams per meter square (g/m^2), carboplatin 635 mg/m^2, etoposide 300 mg/m^2, and dexamethasone 100 mg/m^2. Study treatment continued for 3 cycles, unless the subject experienced unacceptable toxicity or disease progression.	
Reporting group title	Part 1: Ibrutinib+RVICI
Reporting group description:	
Subjects received ibrutinib based on age group and BSA in combination with CIT (investigator choice of RVICI [rituximab, vincristine, ifosfamide, carboplatin, idarubicin, and dexamethasone]) for 3 treatment cycles with each cycle 28 or 21 days long. The RVICI regimen was composed of rituximab 750 mg/m^2, vincristine 1.6 mg/m^2, ifosfamide 10 g/m^2, carboplatin 800 mg/m^2, idarubicin 20 mg/m^2, and dexamethasone 100 mg/m^2. Study treatment continued for 3 cycles, unless the subject experienced unacceptable toxicity or disease progression.	
Reporting group title	Part 2: Ibrutinib+CIT (RICE or RVICI)
Reporting group description:	
Subjects received ibrutinib based on age group and BSA in combination with CIT (investigator choice of RICE or RVICI) until 3 treatment cycles, transplantation if indicated, or until progressive disease (PD) or unacceptable toxicity.	
Reporting group title	Part 2: Chemotherapy (CIT)
Reporting group description:	
Subjects received CIT (investigator choice of RICE or RVICI) alone based on age group and BSA until 3 treatment cycles, transplantation if indicated, or until progressive disease (PD) or unacceptable toxicity.	

Reporting group values	Part 1: Ibrutinib+RICE	Part 1: Ibrutinib+RVICI	Part 2: Ibrutinib+CIT (RICE or RVICI)
Number of subjects	11	10	35
Title for AgeCategorical Units: subjects			
Children (2-11 years)	6	8	7
Adolescents (12-17 years)	5	2	23
Adults (18-64 years)	0	0	5
From 65 to 84 years	0	0	0
85 years and over	0	0	0
Title for AgeContinuous Units: years			
arithmetic mean	10.5	8.3	13.9
standard deviation	± 4.91	± 3.43	± 3.94
Title for Gender Units: subjects			
Female	3	1	12
Male	8	9	23

Reporting group values	Part 2: Chemotherapy (CIT)	Total	
Number of subjects	16	72	

Title for AgeCategorical Units: subjects			
Children (2-11 years)	4	25	
Adolescents (12-17 years)	11	41	
Adults (18-64 years)	1	6	
From 65 to 84 years	0	0	
85 years and over	0	0	
Title for AgeContinuous Units: years			
arithmetic mean	13.3		
standard deviation	± 4.51	-	
Title for Gender Units: subjects			
Female	3	19	
Male	13	53	

End points

End points reporting groups

Reporting group title	Part 1: Ibrutinib+RICE
Reporting group description:	
Subjects received ibrutinib based on age group and body surface area (BSA) in combination with chemoimmunotherapy (CIT) (investigator choice of RICE [rituximab, ifosfamide, carboplatin, etoposide, and dexamethasone]) for 3 treatment cycles with each cycle 28 or 21 days long. The RICE regimen was composed of rituximab 750 milligrams per meter square (mg/m^2), ifosfamide 9 grams per meter square (g/m^2), carboplatin 635 mg/m^2, etoposide 300 mg/m^2, and dexamethasone 100 mg/m^2. Study treatment continued for 3 cycles, unless the subject experienced unacceptable toxicity or disease progression.	
Reporting group title	Part 1: Ibrutinib+RVICI
Reporting group description:	
Subjects received ibrutinib based on age group and BSA in combination with CIT (investigator choice of RVICI [rituximab, vincristine, ifosfamide, carboplatin, idarubicin, and dexamethasone]) for 3 treatment cycles with each cycle 28 or 21 days long. The RVICI regimen was composed of rituximab 750 mg/m^2, vincristine 1.6 mg/m^2, ifosfamide 10 g/m^2, carboplatin 800 mg/m^2, idarubicin 20 mg/m^2, and dexamethasone 100 mg/m^2. Study treatment continued for 3 cycles, unless the subject experienced unacceptable toxicity or disease progression.	
Reporting group title	Part 2: Ibrutinib+CIT (RICE or RVICI)
Reporting group description:	
Subjects received ibrutinib based on age group and BSA in combination with CIT (investigator choice of RICE or RVICI) until 3 treatment cycles, transplantation if indicated, or until progressive disease (PD) or unacceptable toxicity.	
Reporting group title	Part 2: Chemotherapy (CIT)
Reporting group description:	
Subjects received CIT (investigator choice of RICE or RVICI) alone based on age group and BSA until 3 treatment cycles, transplantation if indicated, or until progressive disease (PD) or unacceptable toxicity.	
Subject analysis set title	Part 1: Ibrutinib+RICE
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Subjects received ibrutinib based on age group and body surface area (BSA) in combination with chemoimmunotherapy (CIT) (investigator choice of RICE [rituximab, ifosfamide, carboplatin, etoposide, and dexamethasone]) in Part 1.	
Subject analysis set title	Part 1: Ibrutinib+RVICI
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Subjects received ibrutinib based on age group and BSA in combination with CIT (investigator choice of RVICI [rituximab, vincristine, ifosfamide, carboplatin, idarubicin, and dexamethasone]) in Part 1.	
Subject analysis set title	Part 2: Ibrutinib+CIT
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Subjects received ibrutinib based on age group and BSA in combination with CIT (investigator choice of RICE or RVICI) in Part 2.	
Subject analysis set title	Part 2: Chemotherapy (CIT)
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Subjects received CIT (investigator choice of RICE or RVICI) alone in Part 2.	
Subject analysis set title	Part 1: Ibrutinub: 240 mg/m^2
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Subjects received 240 mg/m^2 ibrutinib based on age group for 3 treatment cycles with each cycle 28 or 21 days long in part 1.	
Subject analysis set title	Part 1: Ibrutinub; 329 mg/m^2
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Subjects received 329 mg/m^2 ibrutinib based on age group for 3 treatment cycles with each cycle 28 or 21 days long in part 1.

Subject analysis set title	Part 1: Ibrutinub; 440 mg/m^2
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Subjects received 440 mg/m^2 ibrutinib based on age group for 3 treatment cycles with each cycle 28 or 21 days long in part 1.

Subject analysis set title	Part 2: Ibrutinub; 329 mg/m^2
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Subjects received 329 mg/m^2 ibrutinib based on age group for 3 treatment cycles with each cycle 28 or 21 days long in Part 2.

Subject analysis set title	Part 2: Ibrutinub; 440 mg/m^2
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Subjects received 440 mg/m^2 ibrutinib based on age group for 3 treatment cycles with each cycle 28 or 21 days long in part 2.

Subject analysis set title	Part 1 and Part 2: Disease Specific Biomarkers
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Subjects received ibrutinib to assess the disease specific biomarkers (SYK, STAT3, caspase-3, BCL-xL and cIAP1 expression) in both Parts.

Subject analysis set title	Part 1: Ibrutinib
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Subjects received ibrutinib based on age group and BSA in Part 1.

Subject analysis set title	Part 2: Ibrutinib
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Subjects received ibrutinib based on age group and BSA in Part 2.

Primary: Part 1: Area Under the Plasma Concentration-time Curve (AUC) of Ibrutinib

End point title	Part 1: Area Under the Plasma Concentration-time Curve (AUC) of Ibrutinib[1]

End point description:

AUC is defined as area under the plasma concentration-time curve. Pharmacokinetic analysis set included subjects in the ibrutinib group that received ibrutinib doses and had quantifiable plasma concentration of ibrutinib. PK parameters were presented per dose group (240 mg/m2, 329 mg/m2 and 440 mg/m2) and age group (1-5, 6-11, 12-17 and >18 years). Here, "n (number analysed)" is defined as number of subjects analyzed for specified category. Here "99999" denotes upper limit which does not have any value.

End point type	Primary

End point timeframe:

Cycle 1: Day 1, Day 7 or 8 and Day 14; Cycle 2: Day 1; Cycle 3: Day 1 (each cycle of 28 days)

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 was done, no inferential statistical analysis was performed.

End point values	Part 1: Ibrutinub: 240 mg/m^2	Part 1: Ibrutinub; 329 mg/m^2	Part 1: Ibrutinub; 440 mg/m^2	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	21	21	21	
Units: hours*nanogram per milliliter (h*ng/mL)				
median (full range (min-max))				
1-5 year (n=2, n=1, n=3)	143 (116 to 170)	386 (386 to 386)	310 (230 to 543)	
6-11 year (n=3, n=10, n=7)	145 (140 to 233)	349 (238 to 562)	324 (185 to 538)	
12-17 year (n=3, n=8, n=0)	1210 (939 to 1450)	661 (394 to 778)	99999 (99999 to 99999)	
18+ year (n=0)	99999 (99999 to 99999)	99999 (99999 to 99999)	99999 (99999 to 99999)	

Statistical analyses

No statistical analyses for this end point

Primary: Part 1: Apparent (Oral) Plasma Clearance (CL/F) of Ibrutinib

End point title	Part 1: Apparent (Oral) Plasma Clearance (CL/F) of Ibrutinib[2]

End point description:

CL/F is defined as apparent plasma clearance of ibrutinib. Pharmacokinetic analysis set included subjects in the ibrutinib group that received ibrutinib doses and had quantifiable plasma concentration of ibrutinib. PK parameters were presented per dose group (240 mg/m2, 329 mg/m2 and 440 mg/m2) and age group (1-5, 6-11, 12-17 and >18 years). Here, "n (number analysed)" is defined as number of subjects analyzed for specified category. Here "99999" denotes upper limit which does not have any value.

End point type	Primary

End point timeframe:

Cycle 1: Day 1, Day 7 or 8 and Day 14; Cycle 2: Day 1; Cycle 3: Day 1 (each cycle of 28 days)

Notes:

[2] - 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 was done, no inferential statistical analysis was performed.

End point values	Part 1: Ibrutinub: 240 mg/m^2	Part 1: Ibrutinub; 329 mg/m^2	Part 1: Ibrutinub; 440 mg/m^2	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	21	21	21	
Units: mL/h (milliliter per hour)				
median (full range (min-max))				
1-5 year (n=2, n=1, n=3)	1220 (1000 to 1430)	508 (508 to 508)	1200 (838 to 1550)	
6-11 year (n=3, n=10, n=7)	1450 (1080 to 1500)	805 (664 to 1100)	1300 (910 to 2460)	
12-17 year (n=3, n=8), n=0)	348 (340 to 433)	729 (568 to 1330)	99999 (99999 to 99999)	
18+ year (n=0)	99999 (99999 to 99999)	99999 (99999 to 99999)	99999 (99999 to 99999)	

Statistical analyses

No statistical analyses for this end point

Primary: Part 1: Apparent (Oral) Volume of Distribution (Vd/F) of Ibrutinib

End point title	Part 1: Apparent (Oral) Volume of Distribution (Vd/F) of Ibrutinib[3]

End point description:

Vd/F is defined as apparent (oral) volume of distribution of ibrutinib. Pharmacokinetic analysis set included subjects in the ibrutinib group that received ibrutinib doses and had quantifiable plasma concentration of ibrutinib. PK parameters were presented per dose group (240 mg/m2, 329 mg/m2 and 440 mg/m2) and age group (1-5, 6-11, 12-17 and >18 years). Here, "n (number analysed)" is defined as number of subjects analyzed for specified category. Here "99999" denotes upper limit which does not have any value.

End point type	Primary

End point timeframe:

Cycle 1: Day 1, Day 7 or 8 and Day 14; Cycle 2: Day 1; Cycle 3: Day 1 (each cycle of 28 days)

Notes:

[3] - 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 was done, no inferential statistical analysis was performed.

End point values	Part 1: Ibrutinub: 240 mg/m^2	Part 1: Ibrutinub; 329 mg/m^2	Part 1: Ibrutinub; 440 mg/m^2	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	21	21	21	
Units: litre(s)				
median (full range (min-max))				
1-5 year (n=2, n=1, n=3)	11.1 (8.26 to 13.9)	5.18 (5.18 to 5.18)	7.63 (5.34 to 11.1)	
6-11 year (n=3, n=10, n=7)	18 (10.8 to 29.9)	7.55 (2.89 to 15.6)	19 (6.09 to 55.9)	
12-17 year (n=3, n=8, n=0)	3.63 (2.32 to 4.77)	11.3 (6.34 to 18.5)	99999 (99999 to 99999)	
18+ year (n=0)	99999 (99999 to 99999)	99999 (99999 to 99999)	99999 (99999 to 99999)	

Statistical analyses

No statistical analyses for this end point

Primary: Part 1: Maximum Observed Plasma Concentration (Cmax) of Ibrutinib

End point title	Part 1: Maximum Observed Plasma Concentration (Cmax) of Ibrutinib[4]

End point description:

Cmax is defined as maximum plasma concentration of ibrutinib. Pharmacokinetic analysis set included

subjects in the ibrutinib group that received ibrutinib doses and had quantifiable plasma concentration of ibrutinib. PK parameters were presented per dose group (240 mg/m2, 329 mg/m2 and 440 mg/m2) and age group (1-5, 6-11, 12-17 and >18 years). Here, "n (number analysed)" is defined as number of subjects analyzed for specified category. Here "99999" denotes upper limit which does not have any value.

End point type	Primary

End point timeframe:

Cycle 1: Day, Day 7 or 8, Day 14; Cycle 2: Day 1; Cycle 3: Day 1 (each cycle of 28 days)

Notes:

[4] - 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 was done, no inferential statistical analysis was performed.

End point values	Part 1: Ibrutinub: 240 mg/m^2	Part 1: Ibrutinub; 329 mg/m^2	Part 1: Ibrutinub; 440 mg/m^2	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	21	21	21	
Units: ng/mL (nanograms per milliliter)				
median (full range (min-max))				
1-5 year (n=2,n=1, n=3)	3.86 (3.75 to 3.98)	4.48 (4.48 to 4.48)	5.07 (4.5 to 5.14)	
6-11 year (n=3, n=10, n=7)	3.46 (3.12 to 3.6)	3.64 (3.32 to 4.59)	3.88 (3.2 to 4.44)	
12-17 year (n=3, n=8, n=0)	4.88 (4.76 to 5.4)	4.73 (4.07 to 5.07)	99999 (99999 to 99999)	
18+ year (n=0)	99999 (99999 to 99999)	99999 (99999 to 99999)	99999 (99999 to 99999)	

Statistical analyses

No statistical analyses for this end point

Primary: Part 1: Relationship between Pharmacokinetic (PK) Parameters and Age or Body Size

End point title	Part 1: Relationship between Pharmacokinetic (PK) Parameters and Age or Body Size[5]

End point description:

The relationship between ibrutinib metrics of systemic exposure with age or body size was assessed to determine the impact on PK parameters which were presented per dose groups (240 mg/m^2, 329 mg/m^2 and 440 mg/m^2) and age groups (1-5, 6-11, 12-17 and >18 years). Separated PK/pharmacodynamics analysis was not performed due to the small sample size of the study. Pharmacokinetic analysis set included subjects in the ibrutinib group that received ibrutinib doses and had quantifiable plasma concentration of ibrutinib. Here "99999" denotes upper limit which does not have any value.

End point type	Primary

End point timeframe:

Up to Cycle 3 (each cycle of 28 days)

Notes:

[5] - 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 was done, no inferential statistical analysis was performed.

End point values	Part 1: Ibrutinib			
Subject group type	Subject analysis set			
Number of subjects analysed	21			
Units: Years				
median (full range (min-max))				
n=0	99999 (99999 to 99999)			

Statistical analyses

No statistical analyses for this end point

Primary: Part 2: Event Free Survival (EFS) Between the 2 Treatment Groups

End point title	Part 2: Event Free Survival (EFS) Between the 2 Treatment Groups[6]

End point description:

EFS is the time interval from randomization to death, disease progression, or lack of complete response (CR) or partial response (PR) after 3 cycles of treatment, whichever occurs first based on blinded independent event review by the Independent Review Committee (IRC). The intent-to-treat (ITT) population consisted of all randomized subjects; subjects analyzed based on randomization, regardless of study drug received. Here "N" (number of subjects analysed) is the number of subjects evaluable for this endpoint.

End point type	Primary

End point timeframe:

Time from Randomization to death, disease progression, or lack of CR or PR after 3 cycles of treatment (up to 3 years)

Notes:

[6] - 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 was done, no inferential statistical analysis was performed.

End point values	Part 2: Ibrutinib+CIT	Part 2: Chemotherapy (CIT)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	22	12		
Units: Months				
median (confidence interval 90%)	6.05 (2.99 to 8.84)	6.97 (2.60 to 11.07)		

Statistical analyses

No statistical analyses for this end point

Secondary: Part 1 and Part 2: Number of Subjects with Adverse Events as Measure of Safety and Tolerability

End point title	Part 1 and Part 2: Number of Subjects with Adverse Events as Measure of Safety and Tolerability

End point description:

An AE is any untoward medical event that occurs in a subject administered an investigational product,

and it does not necessarily indicate only events with clear causal relationship with the relevant investigational product. Safety population consisted of all subjects who received at least 1 dose of treatment. Here "N" (number of subjects analysed) is the number of subjects evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Up to 4.5 years

End point values	Part 1: Ibrutinib+RICE	Part 1: Ibrutinib+RVICI	Part 2: Ibrutinib+CIT	Part 2: Chemotherapy (CIT)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	11	10	35	15
Units: Subjects	11	10	35	15

Statistical analyses

No statistical analyses for this end point

Secondary: Part 1 and Part 2: Overall Response Rate (ORR)

End point title	Part 1 and Part 2: Overall Response Rate (ORR)

End point description:

ORR is defined as the percentage of subjects achieving a best overall response of either complete response (CR) (including CR biopsy-negative [CRb] and unconfirmed CR [CRu]) or partial response (PR) as evaluated by IRC. The ITT Population consisted of all randomized subjects; subjects analyzed based on randomization, regardless of study drug received. The primary efficacy analysis is based on the ITT population for data collected in the Part 2.

End point type	Secondary

End point timeframe:

Up to 4.5 year

End point values	Part 1: Ibrutinib+RICE	Part 1: Ibrutinib+RVICI	Part 2: Ibrutinib+CIT	Part 2: Chemotherapy (CIT)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	11	10	35	16
Units: Percentage of Subjects				
number (not applicable)	9	5	24	13

Statistical analyses

No statistical analyses for this end point

Secondary: Part 1 and Part 2: Change from baseline with Disease-specific

Biomarkers

End point title	Part 1 and Part 2: Change from baseline with Disease-specific Biomarkers

End point description:

Blood samples were taken to evaluate the levels of biomarkers such as Phospho- Bruton’s tyrosine kinase (BTK), spleen tyrosine kinase (SYK), p-signal transducer, activator of transcription 3 (STAT3), Caspase-3 and B-cell receptor (BCR)/CD79B, CARD11, and myeloid differentiation factor (MYD) mutations. Biomarker analyses were conducted on the ITT population.

End point type	Secondary

End point timeframe:

Cycle 1: Days 1, and 7 or 8, Cycle 2: Day 1, and Cycle 3: Day 1 (each cycle of 28 days) and End of treatment visit [30 days after last dose] (Up to 4.5 year)

End point values	Part 1 and Part 2: Disease Specific Biomarkers			
Subject group type	Subject analysis set			
Number of subjects analysed	27			
Units: Transcripts per million				
arithmetic mean (standard deviation)				
BCL-2L1 (BCL-xl)	62.09 (± 52.570)			
BIRC2 (cIAP1)	44.35 (± 14.742)			
Caspase 3 (CASP3)	49.24 (± 24.760)			
STAT3	524.47 (± 391.214)			
SYK	668.14 (± 441.224)			

Statistical analyses

No statistical analyses for this end point

Secondary: Part 1 and Part 2: Bruton’s Tyrosine Kinase (BTK) Percent Occupancy

End point title	Part 1 and Part 2: Bruton’s Tyrosine Kinase (BTK) Percent Occupancy

End point description:

Blood samples were collected to assess BTK occupancy. Biomarker analyses were conducted on the ITT population. Here "N" (number of subjects analysed) is the number of subjects evaluable for this endpoint.

End point type	Secondary

End point timeframe:

4 hours postdose on Day 1, Day 7 or 8 of Cycle 1, predose on Cycle 2 Day 1 or Cycle 3 Day 1 (each cycle of 28 days), and the End-of-Treatment visit [30 days after last dose] (up to 4.5 years)

End point values	Part 1: Ibrutinib	Part 2: Ibrutinib		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	15	13		
Units: Percentage				
number (not applicable)	90	90		

Statistical analyses

No statistical analyses for this end point

Secondary: Part 1 and Part 2: Visual Analog Scale (VAS) Score for Palatability

End point title	Part 1 and Part 2: Visual Analog Scale (VAS) Score for Palatability

End point description:

Palatability of ibrutinib was measured by using a VAS. The scale is a 5-point visual analog scale incorporating a facial hedonic scale designed to span pediatric ages and levels of participant comprehension with a score range of 1 to 5, where 1 represents best score and 5 is worst palatability. The Safety population consisted of all subjects who received at least 1 dose of treatment. Here "n (number analysed)" is defined as number of subjects analyzed for specified category.

End point type	Secondary

End point timeframe:

Day 1 of Cycle 1 and Cycle 3

End point values	Part 1: Ibrutinib+RICE	Part 1: Ibrutinib+RVICI	Part 2: Ibrutinib+CIT	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	11	10	35	
Units: Units on a scale				
arithmetic mean (standard deviation)				
Cycle 1 Day 1 (n=11, n=10, n=32)	2.6 (± 1.21)	3.2 (± 1.40)	2.4 (± 1.16)	
Cycle 3 Day 1 (n=8, n=3, n=16)	3.3 (± 1.39)	2.3 (± 1.15)	2.6 (± 0.89)	

Statistical analyses

No statistical analyses for this end point

Secondary: Part 2: Tumor Volume Reduction Rate at Day 14

End point title	Part 2: Tumor Volume Reduction Rate at Day 14

End point description:

The tumor volume reduction rate is defined as percent decrease in the sum of the products of the lesion diameters at Day 14. It was measured as the mean change in the sum of the products of the lesion diameters (SPD) at Day 14. The ITT Population consisted of all randomized subjects; subjects was analyzed based on randomization, regardless of study drug received. Here "N" (number of subjects analysed) is the number of subjects evaluable for this endpoint.

End point type	Secondary

End point timeframe:

At Day 14

End point values	Part 2: Ibrutinib+CIT	Part 2: Chemotherapy (CIT)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	30	11		
Units: Percent change				
least squares mean (standard deviation)	-49.7 (± 33.41)	-58.60 (± 34.04)		

Statistical analyses

No statistical analyses for this end point

Secondary: Part 2: Number of Subjects who Proceeded to Stem Cell Transplantation

End point title	Part 2: Number of Subjects who Proceeded to Stem Cell Transplantation

End point description:

Number of subjects who proceeded to stem cell transplantation was reported. The ITT Population consisted of all randomized subjects; subjects was analyzed based on randomization, regardless of study drug received.

End point type	Secondary

End point timeframe:

Up to end of the study (Up to 4.5 years)

End point values	Part 2: Ibrutinib+CIT	Part 2: Chemotherapy (CIT)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	35	16		
Units: Subjects	13	7		

Statistical analyses

No statistical analyses for this end point

Secondary: Part 2: Time to Response

End point title	Part 2: Time to Response

End point description:

Time to response defined as the time interval from the first dose of ibrutinib to the first documented response for those subjects who responded. Time to response was summarized for subjects who achieved either CR (including CRb and CRu) or PR. The ITT Population consisted of all randomized

subjects; subjects was analyzed based on randomization, regardless of study drug received.

End point type	Secondary

End point timeframe:

Up to 4.5 years

End point values	Part 2: Ibrutinib+CIT	Part 2: Chemotherapy (CIT)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	35	16		
Units: Months				
median (confidence interval 90%)	0.89 (0.49 to 1.87)	0.82 (0.46 to 1.94)		

Statistical analyses

No statistical analyses for this end point

Secondary: Part 2: Duration of Response

End point title	Part 2: Duration of Response

End point description:

Duration of response defined as the duration from date of initial documentation of a response (CR or PR) to the date of first documented evidence of progressive disease (PD) or death, whichever occurs first. Duration of response was summarized for subjects who achieved either CR (including CRb and CRu) or PR. The ITT Population consisted of all randomized subjects; subjects was analyzed based on randomization, regardless of study drug received. Here "99999"denotes upper limit which does not have any value.

End point type	Secondary

End point timeframe:

Up to 4.5 year

End point values	Part 2: Ibrutinib+CIT	Part 2: Chemotherapy (CIT)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	35	16		
Units: Months				
median (confidence interval 90%)	6.01 (3.06 to 99999)	6.51 (4.53 to 10.64)		

Statistical analyses

No statistical analyses for this end point

Secondary: Part 2: Number of Subjects with EFS

End point title	Part 2: Number of Subjects with EFS

End point description:

EFS is the time interval from randomization to death, disease progression, or lack of complete response (CR) or partial response (PR) after 3 cycles of treatment, whichever occurs first based on blinded independent event review by the Independent Review Committee (IRC). The ITT Population consisted of all randomized subjects; subjects was analyzed based on randomization, regardless of study drug received.

End point type	Secondary

End point timeframe:

2 years and 3 years

End point values	Part 2: Ibrutinib+CIT	Part 2: Chemotherapy (CIT)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	35	16		
Units: Number of subjects				
number (not applicable)				
2 year	5	2		
3 year	3	2		

Statistical analyses

No statistical analyses for this end point

Secondary: Part 2: Overall Survival

End point title	Part 2: Overall Survival

End point description:

Overall survival is defined as duration from the date of randomization to the date of the subject’s death. The ITT Population consisted of all randomized subjects; subjects was analyzed based on randomization, regardless of study drug received. Here "99999" denotes upper limit which does not have any value.

End point type	Secondary

End point timeframe:

Up to 4.5 years

End point values	Part 2: Ibrutinib+CIT	Part 2: Chemotherapy (CIT)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	35	16		
Units: Months				
median (confidence interval 90%)	14.13 (5.98 to 99999)	11.07 (7.39 to 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Part 2: Area Under the Plasma Concentration-time Curve (AUC) of Ibrutinib

End point title	Part 2: Area Under the Plasma Concentration-time Curve (AUC) of Ibrutinib

End point description:

AUC is defined as area under the plasma concentration-time curve. Pharmacokinetic analysis set included subjects in the ibrutinib group that received ibrutinib doses and had quantifiable plasma concentration of ibrutinib. Data of PK parameters of ibrutinib is reported basis of stratified age groups (1-5, 6-11, 12-17 and >18 years). Here, "n (number analysed)" is defined as number of subjects analyzed for specified category. Here "99999" denotes upper limit which does not have any value.

End point type	Secondary

End point timeframe:

Pre-dose, 1, 2, and 4 hours post-dose on Cycle 1 Day 14 (each cycle of 28 days)

End point values	Part 2: Ibrutinub; 329 mg/m^2	Part 2: Ibrutinub; 440 mg/m^2		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	52	52		
Units: h*ng/mL				
median (full range (min-max))				
1-5 year (n=0,n=0, n=2)	99999 (99999 to 099999)	298 (268 to 327)		
6-11year (n=0, n=0, n=3)	99999 (99999 to 99999)	655 (428 to 879)		
12-17 year (n=1, n=19, n=0)	499 (262 to 887)	99999 (99999 to 99999)		
18+ year (n=0, n=2, n=0)	423 (348 to 498)	99999 (99999 to 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Part 2: Relationship between Pharmacokinetic (PK) Parameters and Age or Body Size

End point title	Part 2: Relationship between Pharmacokinetic (PK) Parameters and Age or Body Size

End point description:

The relationship between ibrutinib metrics of systemic exposure with age or body size was assessed to

determine the impact on PK parameters which were presented per dose groups (240 mg/m^2, 329 mg/m^2 and 440 mg/m^2) and age groups (1-5, 6-11, 12-17 and >18 years). Separated PK/pharmacodynamics analysis was not performed due to the small sample size of the study. Pharmacokinetic analysis set included subjects in the ibrutinib group that received ibrutinib doses and had quantifiable plasma concentration of ibrutinib. Here "99999" denotes upper limit which does not have any value.

End point type	Secondary

End point timeframe:

Up to Cycle 3 (each cycle of 28 days)

End point values	Part 2: Ibrutinib			
Subject group type	Subject analysis set			
Number of subjects analysed	52			
Units: Years				
median (full range (min-max))				
n=0	99999 (99999 to 99999)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to 4.5 years (from first subject signs informed consent form to end of the study)

Adverse event reporting additional description:

The safety population consisted of all subjects who received at least 1 dose of treatment. The population used for all safety analyses and subjects was analyzed based on actual study drug received.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	23.1

Reporting groups

Reporting group title	Part 1: Ibrutinib+RICE

Reporting group description:

Subjects received Ibrutinib based on age group and body weight in combination with chemoimmunotherapy (CIT) (investigator choice of RICE [rituximab, ifosfamide, carboplatin, etoposide, and dexamethasone]) in Part 1.

Reporting group title	Part 1: IBRUTINIB+RVICI

Reporting group description:

Subjects received Ibrutinib based on age group and body weight in combination with CIT (investigator choice of RVICI [rituximab, vincristine, ifosfamide, carboplatin, idarubicin, and dexamethasone]) in Part 1.

Reporting group title	Part 2: IBRUTINIB+CIT

Reporting group description:

Subjects received Ibrutinib based on age group and body weight in combination with CIT (investigator choice of RICE or RVICI) in Part 2.

Reporting group title	Part 2: CIT

Reporting group description:

Subjects received CIT (investigator choice of RICE or RVICI) alone in Part 2.

Serious adverse events	Part 1: Ibrutinib+RICE	Part 1: IBRUTINIB+RVICI	Part 2: IBRUTINIB+CIT
Total subjects affected by serious adverse events			
subjects affected / exposed	10 / 11 (90.91%)	9 / 10 (90.00%)	25 / 35 (71.43%)
number of deaths (all causes)	4	9	19
number of deaths resulting from adverse events			
Vascular disorders			
Capillary Leak Syndrome			
subjects affected / exposed	0 / 11 (0.00%)	0 / 10 (0.00%)	1 / 35 (2.86%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypotension			

subjects affected / exposed	0 / 11 (0.00%)	1 / 10 (10.00%)	1 / 35 (2.86%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Mucosal Inflammation			
subjects affected / exposed	0 / 11 (0.00%)	0 / 10 (0.00%)	0 / 35 (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
Multiple Organ Dysfunction Syndrome			
subjects affected / exposed	1 / 11 (9.09%)	0 / 10 (0.00%)	1 / 35 (2.86%)
occurrences causally related to treatment / all	0 / 2	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	1 / 1
Pyrexia			
subjects affected / exposed	0 / 11 (0.00%)	0 / 10 (0.00%)	1 / 35 (2.86%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Systemic Inflammatory Response Syndrome			
subjects affected / exposed	0 / 11 (0.00%)	0 / 10 (0.00%)	1 / 35 (2.86%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
Anaphylactic Reaction			
subjects affected / exposed	0 / 11 (0.00%)	0 / 10 (0.00%)	1 / 35 (2.86%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infusion Related Hypersensitivity Reaction			
subjects affected / exposed	0 / 11 (0.00%)	0 / 10 (0.00%)	0 / 35 (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			
Menorrhagia			

subjects affected / exposed	0 / 11 (0.00%)	0 / 10 (0.00%)	1 / 35 (2.86%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Pneumomediastinum			
subjects affected / exposed	0 / 11 (0.00%)	0 / 10 (0.00%)	1 / 35 (2.86%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary Haemorrhage			
subjects affected / exposed	0 / 11 (0.00%)	0 / 10 (0.00%)	1 / 35 (2.86%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1
Psychiatric disorders			
Psychotic Disorder			
subjects affected / exposed	0 / 11 (0.00%)	0 / 10 (0.00%)	0 / 35 (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			
Alanine Aminotransferase Increased			
subjects affected / exposed	1 / 11 (9.09%)	0 / 10 (0.00%)	0 / 35 (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
Aspartate Aminotransferase Increased			
subjects affected / exposed	1 / 11 (9.09%)	0 / 10 (0.00%)	0 / 35 (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 Bilirubin Increased			
subjects affected / exposed	0 / 11 (0.00%)	1 / 10 (10.00%)	0 / 35 (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
Coagulation Test Abnormal			

subjects affected / exposed	0 / 11 (0.00%)	0 / 10 (0.00%)	0 / 35 (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	1 / 11 (9.09%)	0 / 10 (0.00%)	1 / 35 (2.86%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Platelet Count Decreased			
subjects affected / exposed	1 / 11 (9.09%)	0 / 10 (0.00%)	3 / 35 (8.57%)
occurrences causally related to treatment / all	0 / 3	0 / 0	1 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
White Blood Cell Count Decreased			
subjects affected / exposed	0 / 11 (0.00%)	0 / 10 (0.00%)	1 / 35 (2.86%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Subdural Haematoma			
subjects affected / exposed	0 / 11 (0.00%)	0 / 10 (0.00%)	1 / 35 (2.86%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subdural Haemorrhage			
subjects affected / exposed	0 / 11 (0.00%)	0 / 10 (0.00%)	1 / 35 (2.86%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Sinus Tachycardia			
subjects affected / exposed	0 / 11 (0.00%)	1 / 10 (10.00%)	0 / 35 (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
Nervous system disorders			
Altered State of Consciousness			
subjects affected / exposed	0 / 11 (0.00%)	0 / 10 (0.00%)	1 / 35 (2.86%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Encephalopathy			
subjects affected / exposed	0 / 11 (0.00%)	0 / 10 (0.00%)	1 / 35 (2.86%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhage Intracranial			
subjects affected / exposed	0 / 11 (0.00%)	1 / 10 (10.00%)	0 / 35 (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
Hepatic Encephalopathy			
subjects affected / exposed	0 / 11 (0.00%)	0 / 10 (0.00%)	1 / 35 (2.86%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Paraplegia			
subjects affected / exposed	0 / 11 (0.00%)	1 / 10 (10.00%)	0 / 35 (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
Seizure			
subjects affected / exposed	0 / 11 (0.00%)	0 / 10 (0.00%)	1 / 35 (2.86%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal Cord Haematoma			
subjects affected / exposed	0 / 11 (0.00%)	1 / 10 (10.00%)	0 / 35 (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
Subarachnoid Haemorrhage			
subjects affected / exposed	0 / 11 (0.00%)	1 / 10 (10.00%)	0 / 35 (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
Tonic Convulsion			
subjects affected / exposed	0 / 11 (0.00%)	0 / 10 (0.00%)	1 / 35 (2.86%)
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	0 / 11 (0.00%)	1 / 10 (10.00%)	1 / 35 (2.86%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 11 (0.00%)	0 / 10 (0.00%)	2 / 35 (5.71%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Febrile Bone Marrow Aplasia			
subjects affected / exposed	0 / 11 (0.00%)	0 / 10 (0.00%)	0 / 35 (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 Neutropenia			
subjects affected / exposed	4 / 11 (36.36%)	3 / 10 (30.00%)	21 / 35 (60.00%)
occurrences causally related to treatment / all	3 / 7	0 / 7	19 / 35
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Leukopenia			
subjects affected / exposed	0 / 11 (0.00%)	0 / 10 (0.00%)	0 / 35 (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	2 / 11 (18.18%)	1 / 10 (10.00%)	2 / 35 (5.71%)
occurrences causally related to treatment / all	1 / 2	1 / 1	4 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombocytopenia			
subjects affected / exposed	0 / 11 (0.00%)	0 / 10 (0.00%)	3 / 35 (8.57%)
occurrences causally related to treatment / all	0 / 0	0 / 0	4 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Optic Atrophy			
subjects affected / exposed	0 / 11 (0.00%)	0 / 10 (0.00%)	0 / 35 (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			

Abdominal Pain			
subjects affected / exposed	0 / 11 (0.00%)	0 / 10 (0.00%)	1 / 35 (2.86%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colitis			
subjects affected / exposed	0 / 11 (0.00%)	1 / 10 (10.00%)	1 / 35 (2.86%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	0 / 11 (0.00%)	1 / 10 (10.00%)	0 / 35 (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
Gastric Ulcer			
subjects affected / exposed	0 / 11 (0.00%)	0 / 10 (0.00%)	1 / 35 (2.86%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal Inflammation			
subjects affected / exposed	0 / 11 (0.00%)	0 / 10 (0.00%)	1 / 35 (2.86%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower Gastrointestinal Haemorrhage			
subjects affected / exposed	0 / 11 (0.00%)	0 / 10 (0.00%)	1 / 35 (2.86%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			
subjects affected / exposed	0 / 11 (0.00%)	0 / 10 (0.00%)	1 / 35 (2.86%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Stomatitis			
subjects affected / exposed	0 / 11 (0.00%)	0 / 10 (0.00%)	1 / 35 (2.86%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper Gastrointestinal Haemorrhage			

subjects affected / exposed	0 / 11 (0.00%)	0 / 10 (0.00%)	1 / 35 (2.86%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Hepatic Failure			
subjects affected / exposed	0 / 11 (0.00%)	0 / 10 (0.00%)	1 / 35 (2.86%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute Kidney Injury			
subjects affected / exposed	0 / 11 (0.00%)	0 / 10 (0.00%)	1 / 35 (2.86%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cystitis Haemorrhagic			
subjects affected / exposed	1 / 11 (9.09%)	0 / 10 (0.00%)	0 / 35 (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
Haematuria			
subjects affected / exposed	0 / 11 (0.00%)	0 / 10 (0.00%)	1 / 35 (2.86%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal Failure			
subjects affected / exposed	0 / 11 (0.00%)	1 / 10 (10.00%)	1 / 35 (2.86%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Anorectal Infection			
subjects affected / exposed	0 / 11 (0.00%)	1 / 10 (10.00%)	0 / 35 (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
Bronchitis			
subjects affected / exposed	0 / 11 (0.00%)	0 / 10 (0.00%)	1 / 35 (2.86%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Capnocytophaga Infection			
subjects affected / exposed	0 / 11 (0.00%)	0 / 10 (0.00%)	0 / 35 (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
Corynebacterium Infection			
subjects affected / exposed	1 / 11 (9.09%)	0 / 10 (0.00%)	0 / 35 (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
Cryptosporidiosis Infection			
subjects affected / exposed	0 / 11 (0.00%)	0 / 10 (0.00%)	1 / 35 (2.86%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Device Related Infection			
subjects affected / exposed	0 / 11 (0.00%)	1 / 10 (10.00%)	1 / 35 (2.86%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Escherichia Sepsis			
subjects affected / exposed	0 / 11 (0.00%)	0 / 10 (0.00%)	1 / 35 (2.86%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Herpes Zoster			
subjects affected / exposed	0 / 11 (0.00%)	1 / 10 (10.00%)	0 / 35 (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
Klebsiella Sepsis			
subjects affected / exposed	0 / 11 (0.00%)	1 / 10 (10.00%)	1 / 35 (2.86%)
occurrences causally related to treatment / all	0 / 0	0 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Meningitis			
subjects affected / exposed	0 / 11 (0.00%)	1 / 10 (10.00%)	0 / 35 (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
Neutropenic Sepsis			

subjects affected / exposed	0 / 11 (0.00%)	1 / 10 (10.00%)	1 / 35 (2.86%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Pneumonia			
subjects affected / exposed	0 / 11 (0.00%)	1 / 10 (10.00%)	3 / 35 (8.57%)
occurrences causally related to treatment / all	0 / 0	0 / 2	2 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1
Pulmonary Mycosis			
subjects affected / exposed	0 / 11 (0.00%)	0 / 10 (0.00%)	1 / 35 (2.86%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	1 / 11 (9.09%)	4 / 10 (40.00%)	5 / 35 (14.29%)
occurrences causally related to treatment / all	3 / 3	1 / 5	3 / 6
deaths causally related to treatment / all	0 / 0	0 / 2	0 / 0
Septic Shock			
subjects affected / exposed	1 / 11 (9.09%)	0 / 10 (0.00%)	3 / 35 (8.57%)
occurrences causally related to treatment / all	0 / 1	0 / 0	2 / 4
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Staphylococcal Infection			
subjects affected / exposed	1 / 11 (9.09%)	0 / 10 (0.00%)	0 / 35 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular Device Infection			
subjects affected / exposed	0 / 11 (0.00%)	0 / 10 (0.00%)	1 / 35 (2.86%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Hypernatraemia			
subjects affected / exposed	0 / 11 (0.00%)	0 / 10 (0.00%)	1 / 35 (2.86%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypokalaemia			

subjects affected / exposed	0 / 11 (0.00%)	0 / 10 (0.00%)	0 / 35 (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
Hypophosphataemia			
subjects affected / exposed	0 / 11 (0.00%)	0 / 10 (0.00%)	0 / 35 (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	Part 2: CIT		
Total subjects affected by serious adverse events			
subjects affected / exposed	11 / 15 (73.33%)		
number of deaths (all causes)	10		
number of deaths resulting from adverse events			
Vascular disorders			
Capillary Leak Syndrome			
subjects affected / exposed	0 / 15 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hypotension			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Mucosal Inflammation			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Multiple Organ Dysfunction Syndrome			
subjects affected / exposed	0 / 15 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pyrexia			

subjects affected / exposed	1 / 15 (6.67%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Systemic Inflammatory Response Syndrome				
subjects affected / exposed	0 / 15 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Immune system disorders				
Anaphylactic Reaction				
subjects affected / exposed	0 / 15 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Infusion Related Hypersensitivity Reaction				
subjects affected / exposed	1 / 15 (6.67%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Reproductive system and breast disorders				
Menorrhagia				
subjects affected / exposed	0 / 15 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Respiratory, thoracic and mediastinal disorders				
Pneumomediastinum				
subjects affected / exposed	0 / 15 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pulmonary Haemorrhage				
subjects affected / exposed	0 / 15 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Psychiatric disorders				
Psychotic Disorder				

subjects affected / exposed	1 / 15 (6.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Investigations			
Alanine Aminotransferase Increased			
subjects affected / exposed	0 / 15 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Aspartate Aminotransferase Increased			
subjects affected / exposed	0 / 15 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Blood Bilirubin Increased			
subjects affected / exposed	0 / 15 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Coagulation Test Abnormal			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Neutrophil Count Decreased			
subjects affected / exposed	0 / 15 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Platelet Count Decreased			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
White Blood Cell Count Decreased			
subjects affected / exposed	0 / 15 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			

Subdural Haematoma				
subjects affected / exposed	0 / 15 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Subdural Haemorrhage				
subjects affected / exposed	0 / 15 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cardiac disorders				
Sinus Tachycardia				
subjects affected / exposed	0 / 15 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Nervous system disorders				
Altered State of Consciousness				
subjects affected / exposed	0 / 15 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Encephalopathy				
subjects affected / exposed	0 / 15 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Haemorrhage Intracranial				
subjects affected / exposed	0 / 15 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hepatic Encephalopathy				
subjects affected / exposed	0 / 15 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Paraplegia				
subjects affected / exposed	0 / 15 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			

Seizure				
subjects affected / exposed	0 / 15 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Spinal Cord Haematoma				
subjects affected / exposed	0 / 15 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Subarachnoid Haemorrhage				
subjects affected / exposed	0 / 15 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Tonic Convulsion				
subjects affected / exposed	0 / 15 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Toxic Encephalopathy				
subjects affected / exposed	0 / 15 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Blood and lymphatic system disorders				
Anaemia				
subjects affected / exposed	3 / 15 (20.00%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Febrile Bone Marrow Aplasia				
subjects affected / exposed	1 / 15 (6.67%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Febrile Neutropenia				
subjects affected / exposed	6 / 15 (40.00%)			
occurrences causally related to treatment / all	0 / 10			
deaths causally related to treatment / all	0 / 0			
Leukopenia				

subjects affected / exposed	3 / 15 (20.00%)			
occurrences causally related to treatment / all	0 / 5			
deaths causally related to treatment / all	0 / 0			
Neutropenia				
subjects affected / exposed	3 / 15 (20.00%)			
occurrences causally related to treatment / all	0 / 5			
deaths causally related to treatment / all	0 / 0			
Thrombocytopenia				
subjects affected / exposed	4 / 15 (26.67%)			
occurrences causally related to treatment / all	0 / 5			
deaths causally related to treatment / all	0 / 0			
Eye disorders				
Optic Atrophy				
subjects affected / exposed	1 / 15 (6.67%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal disorders				
Abdominal Pain				
subjects affected / exposed	0 / 15 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Colitis				
subjects affected / exposed	1 / 15 (6.67%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Diarrhoea				
subjects affected / exposed	0 / 15 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastric Ulcer				
subjects affected / exposed	0 / 15 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal Inflammation				

subjects affected / exposed	0 / 15 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Lower Gastrointestinal Haemorrhage				
subjects affected / exposed	1 / 15 (6.67%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Nausea				
subjects affected / exposed	0 / 15 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Stomatitis				
subjects affected / exposed	0 / 15 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Upper Gastrointestinal Haemorrhage				
subjects affected / exposed	0 / 15 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hepatobiliary disorders				
Hepatic Failure				
subjects affected / exposed	0 / 15 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Renal and urinary disorders				
Acute Kidney Injury				
subjects affected / exposed	0 / 15 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cystitis Haemorrhagic				
subjects affected / exposed	0 / 15 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Haematuria				

subjects affected / exposed	0 / 15 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Renal Failure				
subjects affected / exposed	0 / 15 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Infections and infestations				
Anorectal Infection				
subjects affected / exposed	0 / 15 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Bronchitis				
subjects affected / exposed	0 / 15 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Capnocytophaga Infection				
subjects affected / exposed	1 / 15 (6.67%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Corynebacterium Infection				
subjects affected / exposed	0 / 15 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cryptosporidiosis Infection				
subjects affected / exposed	0 / 15 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Device Related Infection				
subjects affected / exposed	1 / 15 (6.67%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 1			
Escherichia Sepsis				

subjects affected / exposed	2 / 15 (13.33%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Herpes Zoster				
subjects affected / exposed	0 / 15 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Klebsiella Sepsis				
subjects affected / exposed	0 / 15 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Meningitis				
subjects affected / exposed	0 / 15 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Neutropenic Sepsis				
subjects affected / exposed	0 / 15 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pneumonia				
subjects affected / exposed	0 / 15 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pulmonary Mycosis				
subjects affected / exposed	0 / 15 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Sepsis				
subjects affected / exposed	3 / 15 (20.00%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 1			
Septic Shock				

subjects affected / exposed	0 / 15 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Staphylococcal Infection			
subjects affected / exposed	0 / 15 (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 / 15 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Hypernatraemia			
subjects affected / exposed	0 / 15 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hypokalaemia			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Hypophosphataemia			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Part 1: Ibrutinib+RICE	Part 1: IBRUTINIB+RVICI	Part 2: IBRUTINIB+CIT
Total subjects affected by non-serious adverse events			
subjects affected / exposed	11 / 11 (100.00%)	10 / 10 (100.00%)	35 / 35 (100.00%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Skin Papilloma			
subjects affected / exposed	1 / 11 (9.09%)	0 / 10 (0.00%)	0 / 35 (0.00%)
occurrences (all)	1	0	0

Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 11 (9.09%)	4 / 10 (40.00%)	2 / 35 (5.71%)
occurrences (all)	1	5	2
Hypotension			
subjects affected / exposed	0 / 11 (0.00%)	2 / 10 (20.00%)	5 / 35 (14.29%)
occurrences (all)	0	2	6
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 11 (9.09%)	0 / 10 (0.00%)	2 / 35 (5.71%)
occurrences (all)	2	0	2
Catheter Site Granuloma			
subjects affected / exposed	1 / 11 (9.09%)	0 / 10 (0.00%)	0 / 35 (0.00%)
occurrences (all)	1	0	0
Catheter Site Pain			
subjects affected / exposed	0 / 11 (0.00%)	0 / 10 (0.00%)	2 / 35 (5.71%)
occurrences (all)	0	0	3
Chest Pain			
subjects affected / exposed	0 / 11 (0.00%)	0 / 10 (0.00%)	3 / 35 (8.57%)
occurrences (all)	0	0	4
Chills			
subjects affected / exposed	0 / 11 (0.00%)	1 / 10 (10.00%)	0 / 35 (0.00%)
occurrences (all)	0	1	0
Device Related Thrombosis			
subjects affected / exposed	0 / 11 (0.00%)	0 / 10 (0.00%)	0 / 35 (0.00%)
occurrences (all)	0	0	0
Face Oedema			
subjects affected / exposed	0 / 11 (0.00%)	1 / 10 (10.00%)	0 / 35 (0.00%)
occurrences (all)	0	1	0
Fatigue			
subjects affected / exposed	1 / 11 (9.09%)	1 / 10 (10.00%)	5 / 35 (14.29%)
occurrences (all)	2	1	5
Generalised Oedema			
subjects affected / exposed	1 / 11 (9.09%)	0 / 10 (0.00%)	2 / 35 (5.71%)
occurrences (all)	1	0	2
Hypothermia			

subjects affected / exposed	0 / 11 (0.00%)	0 / 10 (0.00%)	0 / 35 (0.00%)
occurrences (all)	0	0	0
Mucosal Inflammation			
subjects affected / exposed	2 / 11 (18.18%)	4 / 10 (40.00%)	9 / 35 (25.71%)
occurrences (all)	2	5	10
Mucosal Ulceration			
subjects affected / exposed	0 / 11 (0.00%)	1 / 10 (10.00%)	0 / 35 (0.00%)
occurrences (all)	0	1	0
Pain			
subjects affected / exposed	0 / 11 (0.00%)	0 / 10 (0.00%)	0 / 35 (0.00%)
occurrences (all)	0	0	0
Pyrexia			
subjects affected / exposed	3 / 11 (27.27%)	3 / 10 (30.00%)	14 / 35 (40.00%)
occurrences (all)	4	10	35
Swelling			
subjects affected / exposed	0 / 11 (0.00%)	0 / 10 (0.00%)	0 / 35 (0.00%)
occurrences (all)	0	0	0
Swelling Face			
subjects affected / exposed	1 / 11 (9.09%)	0 / 10 (0.00%)	0 / 35 (0.00%)
occurrences (all)	1	0	0
Immune system disorders			
Drug Hypersensitivity			
subjects affected / exposed	0 / 11 (0.00%)	0 / 10 (0.00%)	2 / 35 (5.71%)
occurrences (all)	0	0	2
Hypersensitivity			
subjects affected / exposed	0 / 11 (0.00%)	1 / 10 (10.00%)	0 / 35 (0.00%)
occurrences (all)	0	1	0
Hypogammaglobulinaemia			
subjects affected / exposed	1 / 11 (9.09%)	1 / 10 (10.00%)	0 / 35 (0.00%)
occurrences (all)	2	1	0
Reproductive system and breast disorders			
Penile Swelling			
subjects affected / exposed	0 / 11 (0.00%)	1 / 10 (10.00%)	0 / 35 (0.00%)
occurrences (all)	0	1	0
Respiratory, thoracic and mediastinal disorders			

Cough			
subjects affected / exposed	1 / 11 (9.09%)	1 / 10 (10.00%)	2 / 35 (5.71%)
occurrences (all)	2	2	4
Dyspnoea			
subjects affected / exposed	1 / 11 (9.09%)	1 / 10 (10.00%)	2 / 35 (5.71%)
occurrences (all)	1	2	2
Epistaxis			
subjects affected / exposed	2 / 11 (18.18%)	1 / 10 (10.00%)	8 / 35 (22.86%)
occurrences (all)	2	1	11
Hypoxia			
subjects affected / exposed	0 / 11 (0.00%)	1 / 10 (10.00%)	2 / 35 (5.71%)
occurrences (all)	0	1	2
Laryngospasm			
subjects affected / exposed	0 / 11 (0.00%)	1 / 10 (10.00%)	0 / 35 (0.00%)
occurrences (all)	0	1	0
Nasal Congestion			
subjects affected / exposed	1 / 11 (9.09%)	0 / 10 (0.00%)	1 / 35 (2.86%)
occurrences (all)	1	0	1
Oropharyngeal Pain			
subjects affected / exposed	0 / 11 (0.00%)	0 / 10 (0.00%)	2 / 35 (5.71%)
occurrences (all)	0	0	2
Respiratory Alkalosis			
subjects affected / exposed	0 / 11 (0.00%)	0 / 10 (0.00%)	2 / 35 (5.71%)
occurrences (all)	0	0	4
Rhinorrhoea			
subjects affected / exposed	0 / 11 (0.00%)	0 / 10 (0.00%)	0 / 35 (0.00%)
occurrences (all)	0	0	0
Psychiatric disorders			
Agitation			
subjects affected / exposed	1 / 11 (9.09%)	0 / 10 (0.00%)	1 / 35 (2.86%)
occurrences (all)	1	0	1
Anxiety			
subjects affected / exposed	0 / 11 (0.00%)	1 / 10 (10.00%)	1 / 35 (2.86%)
occurrences (all)	0	1	1
Confusional State			

subjects affected / exposed	0 / 11 (0.00%)	0 / 10 (0.00%)	1 / 35 (2.86%)
occurrences (all)	0	0	1
Depression			
subjects affected / exposed	0 / 11 (0.00%)	1 / 10 (10.00%)	1 / 35 (2.86%)
occurrences (all)	0	1	1
Hallucination			
subjects affected / exposed	0 / 11 (0.00%)	1 / 10 (10.00%)	1 / 35 (2.86%)
occurrences (all)	0	1	1
Insomnia			
subjects affected / exposed	0 / 11 (0.00%)	0 / 10 (0.00%)	4 / 35 (11.43%)
occurrences (all)	0	0	4
Irritability			
subjects affected / exposed	1 / 11 (9.09%)	0 / 10 (0.00%)	0 / 35 (0.00%)
occurrences (all)	1	0	0
Post-Traumatic Stress Disorder			
subjects affected / exposed	0 / 11 (0.00%)	1 / 10 (10.00%)	0 / 35 (0.00%)
occurrences (all)	0	1	0
Investigations			
Alanine Aminotransferase Increased			
subjects affected / exposed	4 / 11 (36.36%)	0 / 10 (0.00%)	7 / 35 (20.00%)
occurrences (all)	18	0	17
Amylase Increased			
subjects affected / exposed	0 / 11 (0.00%)	0 / 10 (0.00%)	1 / 35 (2.86%)
occurrences (all)	0	0	1
Antithrombin Iii Decreased			
subjects affected / exposed	1 / 11 (9.09%)	1 / 10 (10.00%)	0 / 35 (0.00%)
occurrences (all)	2	1	0
Aspartate Aminotransferase Increased			
subjects affected / exposed	5 / 11 (45.45%)	0 / 10 (0.00%)	6 / 35 (17.14%)
occurrences (all)	14	0	10
Blood Bilirubin Increased			
subjects affected / exposed	3 / 11 (27.27%)	1 / 10 (10.00%)	2 / 35 (5.71%)
occurrences (all)	3	3	2
Blood Lactate Dehydrogenase Increased			

subjects affected / exposed	1 / 11 (9.09%)	0 / 10 (0.00%)	1 / 35 (2.86%)
occurrences (all)	1	0	1
C-Reactive Protein Increased			
subjects affected / exposed	1 / 11 (9.09%)	1 / 10 (10.00%)	3 / 35 (8.57%)
occurrences (all)	1	1	8
Gamma-Glutamyltransferase Increased			
subjects affected / exposed	2 / 11 (18.18%)	1 / 10 (10.00%)	2 / 35 (5.71%)
occurrences (all)	8	1	2
Haemoglobin Decreased			
subjects affected / exposed	1 / 11 (9.09%)	0 / 10 (0.00%)	1 / 35 (2.86%)
occurrences (all)	3	0	1
International Normalised Ratio Increased			
subjects affected / exposed	0 / 11 (0.00%)	1 / 10 (10.00%)	1 / 35 (2.86%)
occurrences (all)	0	2	1
Lipase Increased			
subjects affected / exposed	0 / 11 (0.00%)	0 / 10 (0.00%)	0 / 35 (0.00%)
occurrences (all)	0	0	0
Lymphocyte Count Decreased			
subjects affected / exposed	1 / 11 (9.09%)	0 / 10 (0.00%)	4 / 35 (11.43%)
occurrences (all)	12	0	30
Neutrophil Count Decreased			
subjects affected / exposed	1 / 11 (9.09%)	2 / 10 (20.00%)	12 / 35 (34.29%)
occurrences (all)	3	9	30
Pancreatic Enzymes Decreased			
subjects affected / exposed	1 / 11 (9.09%)	0 / 10 (0.00%)	0 / 35 (0.00%)
occurrences (all)	2	0	0
Platelet Count Decreased			
subjects affected / exposed	5 / 11 (45.45%)	2 / 10 (20.00%)	12 / 35 (34.29%)
occurrences (all)	39	31	98
Staphylococcus Test Positive			
subjects affected / exposed	0 / 11 (0.00%)	0 / 10 (0.00%)	0 / 35 (0.00%)
occurrences (all)	0	0	0
Weight Decreased			

subjects affected / exposed	0 / 11 (0.00%)	1 / 10 (10.00%)	3 / 35 (8.57%)
occurrences (all)	0	1	3
Weight Increased			
subjects affected / exposed	0 / 11 (0.00%)	0 / 10 (0.00%)	1 / 35 (2.86%)
occurrences (all)	0	0	1
White Blood Cell Count Decreased			
subjects affected / exposed	1 / 11 (9.09%)	2 / 10 (20.00%)	8 / 35 (22.86%)
occurrences (all)	2	2	18
Injury, poisoning and procedural complications			
Buttock Injury			
subjects affected / exposed	0 / 11 (0.00%)	1 / 10 (10.00%)	0 / 35 (0.00%)
occurrences (all)	0	1	0
Contusion			
subjects affected / exposed	0 / 11 (0.00%)	0 / 10 (0.00%)	2 / 35 (5.71%)
occurrences (all)	0	0	2
Fall			
subjects affected / exposed	0 / 11 (0.00%)	0 / 10 (0.00%)	2 / 35 (5.71%)
occurrences (all)	0	0	2
Fractured Sacrum			
subjects affected / exposed	0 / 11 (0.00%)	1 / 10 (10.00%)	0 / 35 (0.00%)
occurrences (all)	0	1	0
Infusion Related Reaction			
subjects affected / exposed	1 / 11 (9.09%)	1 / 10 (10.00%)	4 / 35 (11.43%)
occurrences (all)	1	2	5
Procedural Pain			
subjects affected / exposed	0 / 11 (0.00%)	0 / 10 (0.00%)	4 / 35 (11.43%)
occurrences (all)	0	0	4
Transfusion Reaction			
subjects affected / exposed	0 / 11 (0.00%)	1 / 10 (10.00%)	1 / 35 (2.86%)
occurrences (all)	0	1	1
Traumatic Haematoma			
subjects affected / exposed	1 / 11 (9.09%)	0 / 10 (0.00%)	0 / 35 (0.00%)
occurrences (all)	1	0	0
Congenital, familial and genetic disorders			

Aplasia			
subjects affected / exposed	0 / 11 (0.00%)	0 / 10 (0.00%)	0 / 35 (0.00%)
occurrences (all)	0	0	0
Cardiac disorders			
Pericardial Effusion			
subjects affected / exposed	0 / 11 (0.00%)	1 / 10 (10.00%)	1 / 35 (2.86%)
occurrences (all)	0	1	1
Sinus Tachycardia			
subjects affected / exposed	0 / 11 (0.00%)	1 / 10 (10.00%)	0 / 35 (0.00%)
occurrences (all)	0	1	0
Tachycardia			
subjects affected / exposed	0 / 11 (0.00%)	1 / 10 (10.00%)	5 / 35 (14.29%)
occurrences (all)	0	1	6
Nervous system disorders			
Aphasia			
subjects affected / exposed	0 / 11 (0.00%)	0 / 10 (0.00%)	0 / 35 (0.00%)
occurrences (all)	0	0	0
Depressed Level of Consciousness			
subjects affected / exposed	0 / 11 (0.00%)	1 / 10 (10.00%)	0 / 35 (0.00%)
occurrences (all)	0	1	0
Encephalopathy			
subjects affected / exposed	0 / 11 (0.00%)	0 / 10 (0.00%)	2 / 35 (5.71%)
occurrences (all)	0	0	2
Headache			
subjects affected / exposed	1 / 11 (9.09%)	1 / 10 (10.00%)	16 / 35 (45.71%)
occurrences (all)	1	1	28
Hypersomnia			
subjects affected / exposed	0 / 11 (0.00%)	0 / 10 (0.00%)	0 / 35 (0.00%)
occurrences (all)	0	0	0
Muscle Spasticity			
subjects affected / exposed	0 / 11 (0.00%)	0 / 10 (0.00%)	0 / 35 (0.00%)
occurrences (all)	0	0	0
Myoclonus			
subjects affected / exposed	0 / 11 (0.00%)	1 / 10 (10.00%)	0 / 35 (0.00%)
occurrences (all)	0	1	0
Neuralgia			

subjects affected / exposed	0 / 11 (0.00%)	1 / 10 (10.00%)	0 / 35 (0.00%)
occurrences (all)	0	1	0
Seizure			
subjects affected / exposed	0 / 11 (0.00%)	0 / 10 (0.00%)	1 / 35 (2.86%)
occurrences (all)	0	0	1
Somnolence			
subjects affected / exposed	0 / 11 (0.00%)	1 / 10 (10.00%)	1 / 35 (2.86%)
occurrences (all)	0	1	1
Spinal Cord Haematoma			
subjects affected / exposed	0 / 11 (0.00%)	1 / 10 (10.00%)	0 / 35 (0.00%)
occurrences (all)	0	1	0
Toxic Encephalopathy			
subjects affected / exposed	0 / 11 (0.00%)	1 / 10 (10.00%)	0 / 35 (0.00%)
occurrences (all)	0	1	0
Tremor			
subjects affected / exposed	0 / 11 (0.00%)	1 / 10 (10.00%)	0 / 35 (0.00%)
occurrences (all)	0	1	0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	8 / 11 (72.73%)	9 / 10 (90.00%)	29 / 35 (82.86%)
occurrences (all)	61	80	147
Coagulopathy			
subjects affected / exposed	0 / 11 (0.00%)	1 / 10 (10.00%)	2 / 35 (5.71%)
occurrences (all)	0	2	2
Febrile Bone Marrow Aplasia			
subjects affected / exposed	0 / 11 (0.00%)	0 / 10 (0.00%)	1 / 35 (2.86%)
occurrences (all)	0	0	2
Febrile Neutropenia			
subjects affected / exposed	5 / 11 (45.45%)	2 / 10 (20.00%)	6 / 35 (17.14%)
occurrences (all)	5	2	7
Hypofibrinogenaemia			
subjects affected / exposed	1 / 11 (9.09%)	0 / 10 (0.00%)	0 / 35 (0.00%)
occurrences (all)	1	0	0
Leukopenia			
subjects affected / exposed	3 / 11 (27.27%)	1 / 10 (10.00%)	10 / 35 (28.57%)
occurrences (all)	24	2	60

Lymphopenia			
subjects affected / exposed	1 / 11 (9.09%)	0 / 10 (0.00%)	0 / 35 (0.00%)
occurrences (all)	1	0	0
Macrocytosis			
subjects affected / exposed	0 / 11 (0.00%)	0 / 10 (0.00%)	0 / 35 (0.00%)
occurrences (all)	0	0	0
Neutropenia			
subjects affected / exposed	6 / 11 (54.55%)	6 / 10 (60.00%)	14 / 35 (40.00%)
occurrences (all)	33	23	68
Thrombocytopenia			
subjects affected / exposed	6 / 11 (54.55%)	8 / 10 (80.00%)	19 / 35 (54.29%)
occurrences (all)	47	68	153
Ear and labyrinth disorders			
Ear Pain			
subjects affected / exposed	1 / 11 (9.09%)	0 / 10 (0.00%)	0 / 35 (0.00%)
occurrences (all)	1	0	0
Vertigo			
subjects affected / exposed	1 / 11 (9.09%)	0 / 10 (0.00%)	1 / 35 (2.86%)
occurrences (all)	1	0	1
Eye disorders			
Eye Pain			
subjects affected / exposed	0 / 11 (0.00%)	0 / 10 (0.00%)	0 / 35 (0.00%)
occurrences (all)	0	0	0
Eyelid Oedema			
subjects affected / exposed	1 / 11 (9.09%)	0 / 10 (0.00%)	0 / 35 (0.00%)
occurrences (all)	1	0	0
Eyelid Ptosis			
subjects affected / exposed	0 / 11 (0.00%)	1 / 10 (10.00%)	0 / 35 (0.00%)
occurrences (all)	0	1	0
Keratitis			
subjects affected / exposed	0 / 11 (0.00%)	1 / 10 (10.00%)	0 / 35 (0.00%)
occurrences (all)	0	1	0
Pupils Unequal			
subjects affected / exposed	0 / 11 (0.00%)	0 / 10 (0.00%)	0 / 35 (0.00%)
occurrences (all)	0	0	0
Vision Blurred			

subjects affected / exposed	1 / 11 (9.09%)	0 / 10 (0.00%)	0 / 35 (0.00%)
occurrences (all)	1	0	0
Xerophthalmia			
subjects affected / exposed	0 / 11 (0.00%)	1 / 10 (10.00%)	0 / 35 (0.00%)
occurrences (all)	0	1	0
Gastrointestinal disorders			
Abdominal Distension			
subjects affected / exposed	0 / 11 (0.00%)	1 / 10 (10.00%)	1 / 35 (2.86%)
occurrences (all)	0	1	1
Abdominal Pain			
subjects affected / exposed	3 / 11 (27.27%)	5 / 10 (50.00%)	12 / 35 (34.29%)
occurrences (all)	3	6	23
Abdominal Pain Upper			
subjects affected / exposed	0 / 11 (0.00%)	0 / 10 (0.00%)	6 / 35 (17.14%)
occurrences (all)	0	0	8
Anal Erythema			
subjects affected / exposed	0 / 11 (0.00%)	0 / 10 (0.00%)	1 / 35 (2.86%)
occurrences (all)	0	0	3
Anal Inflammation			
subjects affected / exposed	0 / 11 (0.00%)	1 / 10 (10.00%)	0 / 35 (0.00%)
occurrences (all)	0	1	0
Anal Ulcer			
subjects affected / exposed	0 / 11 (0.00%)	1 / 10 (10.00%)	0 / 35 (0.00%)
occurrences (all)	0	1	0
Anorectal Ulcer			
subjects affected / exposed	0 / 11 (0.00%)	1 / 10 (10.00%)	0 / 35 (0.00%)
occurrences (all)	0	1	0
Aphthous Ulcer			
subjects affected / exposed	1 / 11 (9.09%)	0 / 10 (0.00%)	2 / 35 (5.71%)
occurrences (all)	1	0	2
Chapped Lips			
subjects affected / exposed	0 / 11 (0.00%)	1 / 10 (10.00%)	0 / 35 (0.00%)
occurrences (all)	0	1	0
Colitis			
subjects affected / exposed	0 / 11 (0.00%)	0 / 10 (0.00%)	1 / 35 (2.86%)
occurrences (all)	0	0	1

Constipation			
subjects affected / exposed	1 / 11 (9.09%)	3 / 10 (30.00%)	8 / 35 (22.86%)
occurrences (all)	1	6	12
Dental Caries			
subjects affected / exposed	0 / 11 (0.00%)	0 / 10 (0.00%)	0 / 35 (0.00%)
occurrences (all)	0	0	0
Diarrhoea			
subjects affected / exposed	4 / 11 (36.36%)	6 / 10 (60.00%)	10 / 35 (28.57%)
occurrences (all)	5	11	18
Dyspepsia			
subjects affected / exposed	0 / 11 (0.00%)	0 / 10 (0.00%)	5 / 35 (14.29%)
occurrences (all)	0	0	12
Dysphagia			
subjects affected / exposed	0 / 11 (0.00%)	0 / 10 (0.00%)	3 / 35 (8.57%)
occurrences (all)	0	0	3
Enterocolitis			
subjects affected / exposed	0 / 11 (0.00%)	1 / 10 (10.00%)	1 / 35 (2.86%)
occurrences (all)	0	1	1
Flatulence			
subjects affected / exposed	0 / 11 (0.00%)	1 / 10 (10.00%)	0 / 35 (0.00%)
occurrences (all)	0	1	0
Gastrointestinal Inflammation			
subjects affected / exposed	0 / 11 (0.00%)	1 / 10 (10.00%)	2 / 35 (5.71%)
occurrences (all)	0	1	2
Gastrointestinal Motility Disorder			
subjects affected / exposed	0 / 11 (0.00%)	1 / 10 (10.00%)	0 / 35 (0.00%)
occurrences (all)	0	1	0
Gingival Bleeding			
subjects affected / exposed	0 / 11 (0.00%)	0 / 10 (0.00%)	2 / 35 (5.71%)
occurrences (all)	0	0	2
Gingival Oedema			
subjects affected / exposed	0 / 11 (0.00%)	1 / 10 (10.00%)	0 / 35 (0.00%)
occurrences (all)	0	1	0
Haematemesis			
subjects affected / exposed	0 / 11 (0.00%)	1 / 10 (10.00%)	1 / 35 (2.86%)
occurrences (all)	0	1	1

Haematochezia			
subjects affected / exposed	0 / 11 (0.00%)	0 / 10 (0.00%)	2 / 35 (5.71%)
occurrences (all)	0	0	3
Ileus			
subjects affected / exposed	0 / 11 (0.00%)	1 / 10 (10.00%)	0 / 35 (0.00%)
occurrences (all)	0	1	0
Intestinal Haemorrhage			
subjects affected / exposed	0 / 11 (0.00%)	1 / 10 (10.00%)	0 / 35 (0.00%)
occurrences (all)	0	1	0
Melaena			
subjects affected / exposed	1 / 11 (9.09%)	1 / 10 (10.00%)	0 / 35 (0.00%)
occurrences (all)	1	2	0
Mouth Haemorrhage			
subjects affected / exposed	0 / 11 (0.00%)	1 / 10 (10.00%)	1 / 35 (2.86%)
occurrences (all)	0	3	1
Mouth Ulceration			
subjects affected / exposed	1 / 11 (9.09%)	0 / 10 (0.00%)	1 / 35 (2.86%)
occurrences (all)	1	0	1
Nausea			
subjects affected / exposed	7 / 11 (63.64%)	5 / 10 (50.00%)	21 / 35 (60.00%)
occurrences (all)	8	6	45
Odynophagia			
subjects affected / exposed	1 / 11 (9.09%)	0 / 10 (0.00%)	0 / 35 (0.00%)
occurrences (all)	1	0	0
Oesophageal Pain			
subjects affected / exposed	0 / 11 (0.00%)	1 / 10 (10.00%)	0 / 35 (0.00%)
occurrences (all)	0	1	0
Oesophagitis			
subjects affected / exposed	0 / 11 (0.00%)	0 / 10 (0.00%)	0 / 35 (0.00%)
occurrences (all)	0	0	0
Proctalgia			
subjects affected / exposed	1 / 11 (9.09%)	1 / 10 (10.00%)	2 / 35 (5.71%)
occurrences (all)	1	1	4
Rectal Haemorrhage			
subjects affected / exposed	0 / 11 (0.00%)	1 / 10 (10.00%)	1 / 35 (2.86%)
occurrences (all)	0	2	1

Stomatitis			
subjects affected / exposed	0 / 11 (0.00%)	1 / 10 (10.00%)	7 / 35 (20.00%)
occurrences (all)	0	1	12
Toothache			
subjects affected / exposed	1 / 11 (9.09%)	0 / 10 (0.00%)	1 / 35 (2.86%)
occurrences (all)	1	0	1
Vomiting			
subjects affected / exposed	5 / 11 (45.45%)	5 / 10 (50.00%)	25 / 35 (71.43%)
occurrences (all)	12	11	56
Hepatobiliary disorders			
Hepatic Failure			
subjects affected / exposed	1 / 11 (9.09%)	0 / 10 (0.00%)	1 / 35 (2.86%)
occurrences (all)	1	0	1
Hypertransaminasaemia			
subjects affected / exposed	0 / 11 (0.00%)	1 / 10 (10.00%)	0 / 35 (0.00%)
occurrences (all)	0	2	0
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	1 / 11 (9.09%)	0 / 10 (0.00%)	1 / 35 (2.86%)
occurrences (all)	2	0	1
Decubitus Ulcer			
subjects affected / exposed	0 / 11 (0.00%)	0 / 10 (0.00%)	2 / 35 (5.71%)
occurrences (all)	0	0	2
Ecchymosis			
subjects affected / exposed	1 / 11 (9.09%)	0 / 10 (0.00%)	0 / 35 (0.00%)
occurrences (all)	1	0	0
Petechiae			
subjects affected / exposed	0 / 11 (0.00%)	0 / 10 (0.00%)	3 / 35 (8.57%)
occurrences (all)	0	0	3
Pruritus			
subjects affected / exposed	2 / 11 (18.18%)	1 / 10 (10.00%)	1 / 35 (2.86%)
occurrences (all)	2	1	1
Rash			
subjects affected / exposed	1 / 11 (9.09%)	1 / 10 (10.00%)	4 / 35 (11.43%)
occurrences (all)	1	1	5
Rash Maculo-Papular			

subjects affected / exposed	0 / 11 (0.00%)	0 / 10 (0.00%)	0 / 35 (0.00%)
occurrences (all)	0	0	0
Skin Lesion			
subjects affected / exposed	0 / 11 (0.00%)	0 / 10 (0.00%)	0 / 35 (0.00%)
occurrences (all)	0	0	0
Urticaria			
subjects affected / exposed	1 / 11 (9.09%)	0 / 10 (0.00%)	0 / 35 (0.00%)
occurrences (all)	1	0	0
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	0 / 11 (0.00%)	0 / 10 (0.00%)	5 / 35 (14.29%)
occurrences (all)	0	0	5
Hypotonic Urinary Bladder			
subjects affected / exposed	0 / 11 (0.00%)	1 / 10 (10.00%)	0 / 35 (0.00%)
occurrences (all)	0	1	0
Renal Impairment			
subjects affected / exposed	0 / 11 (0.00%)	0 / 10 (0.00%)	2 / 35 (5.71%)
occurrences (all)	0	0	2
Renal Tubular Injury			
subjects affected / exposed	0 / 11 (0.00%)	1 / 10 (10.00%)	0 / 35 (0.00%)
occurrences (all)	0	1	0
Urinary Retention			
subjects affected / exposed	1 / 11 (9.09%)	0 / 10 (0.00%)	0 / 35 (0.00%)
occurrences (all)	1	0	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 11 (9.09%)	0 / 10 (0.00%)	5 / 35 (14.29%)
occurrences (all)	1	0	6
Back Pain			
subjects affected / exposed	1 / 11 (9.09%)	0 / 10 (0.00%)	5 / 35 (14.29%)
occurrences (all)	1	0	5
Bone Pain			
subjects affected / exposed	1 / 11 (9.09%)	1 / 10 (10.00%)	4 / 35 (11.43%)
occurrences (all)	1	3	4
Musculoskeletal Chest Pain			

subjects affected / exposed	1 / 11 (9.09%)	0 / 10 (0.00%)	0 / 35 (0.00%)
occurrences (all)	1	0	0
Musculoskeletal Pain			
subjects affected / exposed	0 / 11 (0.00%)	0 / 10 (0.00%)	0 / 35 (0.00%)
occurrences (all)	0	0	0
Myalgia			
subjects affected / exposed	2 / 11 (18.18%)	1 / 10 (10.00%)	4 / 35 (11.43%)
occurrences (all)	2	1	5
Neck Pain			
subjects affected / exposed	0 / 11 (0.00%)	0 / 10 (0.00%)	2 / 35 (5.71%)
occurrences (all)	0	0	3
Pain in Extremity			
subjects affected / exposed	2 / 11 (18.18%)	0 / 10 (0.00%)	7 / 35 (20.00%)
occurrences (all)	3	0	7
Infections and infestations			
Anal Abscess			
subjects affected / exposed	0 / 11 (0.00%)	1 / 10 (10.00%)	0 / 35 (0.00%)
occurrences (all)	0	1	0
Aspergillus Infection			
subjects affected / exposed	0 / 11 (0.00%)	0 / 10 (0.00%)	2 / 35 (5.71%)
occurrences (all)	0	0	2
Bacteraemia			
subjects affected / exposed	0 / 11 (0.00%)	0 / 10 (0.00%)	0 / 35 (0.00%)
occurrences (all)	0	0	0
Bk Virus Infection			
subjects affected / exposed	1 / 11 (9.09%)	0 / 10 (0.00%)	0 / 35 (0.00%)
occurrences (all)	1	0	0
Conjunctivitis			
subjects affected / exposed	0 / 11 (0.00%)	1 / 10 (10.00%)	0 / 35 (0.00%)
occurrences (all)	0	1	0
Device Related Infection			
subjects affected / exposed	2 / 11 (18.18%)	0 / 10 (0.00%)	3 / 35 (8.57%)
occurrences (all)	3	0	3
Escherichia Infection			
subjects affected / exposed	0 / 11 (0.00%)	0 / 10 (0.00%)	0 / 35 (0.00%)
occurrences (all)	0	0	0

Fungal Infection			
subjects affected / exposed	0 / 11 (0.00%)	0 / 10 (0.00%)	0 / 35 (0.00%)
occurrences (all)	0	0	0
Fusarium Infection			
subjects affected / exposed	0 / 11 (0.00%)	1 / 10 (10.00%)	0 / 35 (0.00%)
occurrences (all)	0	1	0
Geotrichum Infection			
subjects affected / exposed	0 / 11 (0.00%)	1 / 10 (10.00%)	0 / 35 (0.00%)
occurrences (all)	0	2	0
Herpes Zoster			
subjects affected / exposed	0 / 11 (0.00%)	2 / 10 (20.00%)	0 / 35 (0.00%)
occurrences (all)	0	3	0
Klebsiella Infection			
subjects affected / exposed	1 / 11 (9.09%)	0 / 10 (0.00%)	0 / 35 (0.00%)
occurrences (all)	1	0	0
Nasopharyngitis			
subjects affected / exposed	0 / 11 (0.00%)	0 / 10 (0.00%)	2 / 35 (5.71%)
occurrences (all)	0	0	2
Oral Herpes			
subjects affected / exposed	0 / 11 (0.00%)	1 / 10 (10.00%)	2 / 35 (5.71%)
occurrences (all)	0	1	2
Pneumonia			
subjects affected / exposed	0 / 11 (0.00%)	2 / 10 (20.00%)	1 / 35 (2.86%)
occurrences (all)	0	2	1
Pseudomonal Bacteraemia			
subjects affected / exposed	1 / 11 (9.09%)	0 / 10 (0.00%)	1 / 35 (2.86%)
occurrences (all)	1	0	1
Rhinitis			
subjects affected / exposed	0 / 11 (0.00%)	0 / 10 (0.00%)	0 / 35 (0.00%)
occurrences (all)	0	0	0
Rhinovirus Infection			
subjects affected / exposed	0 / 11 (0.00%)	1 / 10 (10.00%)	2 / 35 (5.71%)
occurrences (all)	0	1	2
Sepsis			
subjects affected / exposed	1 / 11 (9.09%)	0 / 10 (0.00%)	0 / 35 (0.00%)
occurrences (all)	1	0	0

Sinusitis			
subjects affected / exposed	1 / 11 (9.09%)	0 / 10 (0.00%)	0 / 35 (0.00%)
occurrences (all)	1	0	0
Upper Respiratory Tract Infection			
subjects affected / exposed	0 / 11 (0.00%)	1 / 10 (10.00%)	0 / 35 (0.00%)
occurrences (all)	0	1	0
Urinary Tract Infection			
subjects affected / exposed	1 / 11 (9.09%)	0 / 10 (0.00%)	0 / 35 (0.00%)
occurrences (all)	1	0	0
Urinary Tract Infection Pseudomonal			
subjects affected / exposed	0 / 11 (0.00%)	0 / 10 (0.00%)	0 / 35 (0.00%)
occurrences (all)	0	0	0
Vascular Device Infection			
subjects affected / exposed	0 / 11 (0.00%)	1 / 10 (10.00%)	0 / 35 (0.00%)
occurrences (all)	0	1	0
Viral Upper Respiratory Tract Infection			
subjects affected / exposed	0 / 11 (0.00%)	0 / 10 (0.00%)	0 / 35 (0.00%)
occurrences (all)	0	0	0
Metabolism and nutrition disorders			
Decreased Appetite			
subjects affected / exposed	0 / 11 (0.00%)	3 / 10 (30.00%)	3 / 35 (8.57%)
occurrences (all)	0	4	4
Fluid Retention			
subjects affected / exposed	0 / 11 (0.00%)	0 / 10 (0.00%)	2 / 35 (5.71%)
occurrences (all)	0	0	5
Hyperglycaemia			
subjects affected / exposed	0 / 11 (0.00%)	1 / 10 (10.00%)	1 / 35 (2.86%)
occurrences (all)	0	2	2
Hyperkalaemia			
subjects affected / exposed	0 / 11 (0.00%)	1 / 10 (10.00%)	2 / 35 (5.71%)
occurrences (all)	0	1	2
Hypernatraemia			
subjects affected / exposed	0 / 11 (0.00%)	1 / 10 (10.00%)	1 / 35 (2.86%)
occurrences (all)	0	1	1
Hyperphosphataemia			

subjects affected / exposed	1 / 11 (9.09%)	0 / 10 (0.00%)	1 / 35 (2.86%)
occurrences (all)	1	0	1
Hypoalbuminaemia			
subjects affected / exposed	3 / 11 (27.27%)	5 / 10 (50.00%)	7 / 35 (20.00%)
occurrences (all)	4	10	13
Hypocalcaemia			
subjects affected / exposed	1 / 11 (9.09%)	3 / 10 (30.00%)	2 / 35 (5.71%)
occurrences (all)	1	9	3
Hypoglycaemia			
subjects affected / exposed	1 / 11 (9.09%)	0 / 10 (0.00%)	1 / 35 (2.86%)
occurrences (all)	1	0	1
Hypokalaemia			
subjects affected / exposed	2 / 11 (18.18%)	6 / 10 (60.00%)	12 / 35 (34.29%)
occurrences (all)	11	20	38
Hypomagnesaemia			
subjects affected / exposed	0 / 11 (0.00%)	2 / 10 (20.00%)	6 / 35 (17.14%)
occurrences (all)	0	6	21
Hyponatraemia			
subjects affected / exposed	2 / 11 (18.18%)	1 / 10 (10.00%)	4 / 35 (11.43%)
occurrences (all)	3	4	4
Hypophosphataemia			
subjects affected / exposed	1 / 11 (9.09%)	2 / 10 (20.00%)	5 / 35 (14.29%)
occurrences (all)	3	4	9

Non-serious adverse events	Part 2: CIT		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	15 / 15 (100.00%)		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Skin Papilloma			
subjects affected / exposed	0 / 15 (0.00%)		
occurrences (all)	0		
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Hypotension			

subjects affected / exposed	2 / 15 (13.33%)		
occurrences (all)	2		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 15 (0.00%)		
occurrences (all)	0		
Catheter Site Granuloma			
subjects affected / exposed	0 / 15 (0.00%)		
occurrences (all)	0		
Catheter Site Pain			
subjects affected / exposed	0 / 15 (0.00%)		
occurrences (all)	0		
Chest Pain			
subjects affected / exposed	2 / 15 (13.33%)		
occurrences (all)	2		
Chills			
subjects affected / exposed	0 / 15 (0.00%)		
occurrences (all)	0		
Device Related Thrombosis			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Face Oedema			
subjects affected / exposed	0 / 15 (0.00%)		
occurrences (all)	0		
Fatigue			
subjects affected / exposed	0 / 15 (0.00%)		
occurrences (all)	0		
Generalised Oedema			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Hypothermia			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Mucosal Inflammation			

subjects affected / exposed	3 / 15 (20.00%)		
occurrences (all)	4		
Mucosal Ulceration			
subjects affected / exposed	0 / 15 (0.00%)		
occurrences (all)	0		
Pain			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Pyrexia			
subjects affected / exposed	5 / 15 (33.33%)		
occurrences (all)	7		
Swelling			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Swelling Face			
subjects affected / exposed	0 / 15 (0.00%)		
occurrences (all)	0		
Immune system disorders			
Drug Hypersensitivity			
subjects affected / exposed	0 / 15 (0.00%)		
occurrences (all)	0		
Hypersensitivity			
subjects affected / exposed	0 / 15 (0.00%)		
occurrences (all)	0		
Hypogammaglobulinaemia			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Reproductive system and breast disorders			
Penile Swelling			
subjects affected / exposed	0 / 15 (0.00%)		
occurrences (all)	0		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	4 / 15 (26.67%)		
occurrences (all)	5		
Dyspnoea			

subjects affected / exposed	0 / 15 (0.00%)		
occurrences (all)	0		
Epistaxis			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Hypoxia			
subjects affected / exposed	0 / 15 (0.00%)		
occurrences (all)	0		
Laryngospasm			
subjects affected / exposed	0 / 15 (0.00%)		
occurrences (all)	0		
Nasal Congestion			
subjects affected / exposed	0 / 15 (0.00%)		
occurrences (all)	0		
Oropharyngeal Pain			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Respiratory Alkalosis			
subjects affected / exposed	0 / 15 (0.00%)		
occurrences (all)	0		
Rhinorrhoea			
subjects affected / exposed	2 / 15 (13.33%)		
occurrences (all)	2		
Psychiatric disorders			
Agitation			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Anxiety			
subjects affected / exposed	0 / 15 (0.00%)		
occurrences (all)	0		
Confusional State			
subjects affected / exposed	2 / 15 (13.33%)		
occurrences (all)	2		
Depression			
subjects affected / exposed	2 / 15 (13.33%)		
occurrences (all)	2		

Hallucination			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Insomnia			
subjects affected / exposed	0 / 15 (0.00%)		
occurrences (all)	0		
Irritability			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Post-Traumatic Stress Disorder			
subjects affected / exposed	0 / 15 (0.00%)		
occurrences (all)	0		
Investigations			
Alanine Aminotransferase Increased			
subjects affected / exposed	6 / 15 (40.00%)		
occurrences (all)	11		
Amylase Increased			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	2		
Antithrombin Iii Decreased			
subjects affected / exposed	0 / 15 (0.00%)		
occurrences (all)	0		
Aspartate Aminotransferase Increased			
subjects affected / exposed	5 / 15 (33.33%)		
occurrences (all)	8		
Blood Bilirubin Increased			
subjects affected / exposed	0 / 15 (0.00%)		
occurrences (all)	0		
Blood Lactate Dehydrogenase Increased			
subjects affected / exposed	0 / 15 (0.00%)		
occurrences (all)	0		
C-Reactive Protein Increased			
subjects affected / exposed	0 / 15 (0.00%)		
occurrences (all)	0		
Gamma-Glutamyltransferase Increased			

subjects affected / exposed	0 / 15 (0.00%)			
occurrences (all)	0			
Haemoglobin Decreased				
subjects affected / exposed	0 / 15 (0.00%)			
occurrences (all)	0			
International Normalised Ratio Increased				
subjects affected / exposed	2 / 15 (13.33%)			
occurrences (all)	2			
Lipase Increased				
subjects affected / exposed	1 / 15 (6.67%)			
occurrences (all)	2			
Lymphocyte Count Decreased				
subjects affected / exposed	2 / 15 (13.33%)			
occurrences (all)	8			
Neutrophil Count Decreased				
subjects affected / exposed	9 / 15 (60.00%)			
occurrences (all)	30			
Pancreatic Enzymes Decreased				
subjects affected / exposed	0 / 15 (0.00%)			
occurrences (all)	0			
Platelet Count Decreased				
subjects affected / exposed	8 / 15 (53.33%)			
occurrences (all)	27			
Staphylococcus Test Positive				
subjects affected / exposed	1 / 15 (6.67%)			
occurrences (all)	1			
Weight Decreased				
subjects affected / exposed	0 / 15 (0.00%)			
occurrences (all)	0			
Weight Increased				
subjects affected / exposed	1 / 15 (6.67%)			
occurrences (all)	3			
White Blood Cell Count Decreased				
subjects affected / exposed	6 / 15 (40.00%)			
occurrences (all)	17			

Injury, poisoning and procedural complications			
Buttock Injury			
subjects affected / exposed	0 / 15 (0.00%)		
occurrences (all)	0		
Contusion			
subjects affected / exposed	0 / 15 (0.00%)		
occurrences (all)	0		
Fall			
subjects affected / exposed	0 / 15 (0.00%)		
occurrences (all)	0		
Fractured Sacrum			
subjects affected / exposed	0 / 15 (0.00%)		
occurrences (all)	0		
Infusion Related Reaction			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Procedural Pain			
subjects affected / exposed	0 / 15 (0.00%)		
occurrences (all)	0		
Transfusion Reaction			
subjects affected / exposed	0 / 15 (0.00%)		
occurrences (all)	0		
Traumatic Haematoma			
subjects affected / exposed	0 / 15 (0.00%)		
occurrences (all)	0		
Congenital, familial and genetic disorders			
Aplasia			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	2		
Cardiac disorders			
Pericardial Effusion			
subjects affected / exposed	0 / 15 (0.00%)		
occurrences (all)	0		
Sinus Tachycardia			
subjects affected / exposed	0 / 15 (0.00%)		
occurrences (all)	0		

Tachycardia			
subjects affected / exposed	2 / 15 (13.33%)		
occurrences (all)	2		
Nervous system disorders			
Aphasia			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Depressed Level of Consciousness			
subjects affected / exposed	0 / 15 (0.00%)		
occurrences (all)	0		
Encephalopathy			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Headache			
subjects affected / exposed	3 / 15 (20.00%)		
occurrences (all)	8		
Hypersomnia			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Muscle Spasticity			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	2		
Myoclonus			
subjects affected / exposed	0 / 15 (0.00%)		
occurrences (all)	0		
Neuralgia			
subjects affected / exposed	0 / 15 (0.00%)		
occurrences (all)	0		
Seizure			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Somnolence			
subjects affected / exposed	0 / 15 (0.00%)		
occurrences (all)	0		
Spinal Cord Haematoma			

subjects affected / exposed	0 / 15 (0.00%)		
occurrences (all)	0		
Toxic Encephalopathy			
subjects affected / exposed	0 / 15 (0.00%)		
occurrences (all)	0		
Tremor			
subjects affected / exposed	0 / 15 (0.00%)		
occurrences (all)	0		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	14 / 15 (93.33%)		
occurrences (all)	45		
Coagulopathy			
subjects affected / exposed	0 / 15 (0.00%)		
occurrences (all)	0		
Febrile Bone Marrow Aplasia			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Febrile Neutropenia			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Hypofibrinogenaemia			
subjects affected / exposed	0 / 15 (0.00%)		
occurrences (all)	0		
Leukopenia			
subjects affected / exposed	3 / 15 (20.00%)		
occurrences (all)	17		
Lymphopenia			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	5		
Macrocytosis			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Neutropenia			
subjects affected / exposed	4 / 15 (26.67%)		
occurrences (all)	14		

Thrombocytopenia subjects affected / exposed occurrences (all)	4 / 15 (26.67%) 18		
Ear and labyrinth disorders Ear Pain subjects affected / exposed occurrences (all) Vertigo subjects affected / exposed occurrences (all)	 0 / 15 (0.00%) 0 0 / 15 (0.00%) 0		
Eye disorders Eye Pain subjects affected / exposed occurrences (all) Eyelid Oedema subjects affected / exposed occurrences (all) Eyelid Ptosis subjects affected / exposed occurrences (all) Keratitis subjects affected / exposed occurrences (all) Pupils Unequal subjects affected / exposed occurrences (all) Vision Blurred subjects affected / exposed occurrences (all) Xerophthalmia subjects affected / exposed occurrences (all)	 1 / 15 (6.67%) 1 0 / 15 (0.00%) 0 0 / 15 (0.00%) 0 0 / 15 (0.00%) 0 1 / 15 (6.67%) 1 0 / 15 (0.00%) 0 0 / 15 (0.00%) 0		
Gastrointestinal disorders Abdominal Distension subjects affected / exposed occurrences (all) Abdominal Pain	 0 / 15 (0.00%) 0 		

subjects affected / exposed	2 / 15 (13.33%)			
occurrences (all)	3			
Abdominal Pain Upper				
subjects affected / exposed	1 / 15 (6.67%)			
occurrences (all)	1			
Anal Erythema				
subjects affected / exposed	1 / 15 (6.67%)			
occurrences (all)	1			
Anal Inflammation				
subjects affected / exposed	0 / 15 (0.00%)			
occurrences (all)	0			
Anal Ulcer				
subjects affected / exposed	0 / 15 (0.00%)			
occurrences (all)	0			
Anorectal Ulcer				
subjects affected / exposed	0 / 15 (0.00%)			
occurrences (all)	0			
Aphthous Ulcer				
subjects affected / exposed	0 / 15 (0.00%)			
occurrences (all)	0			
Chapped Lips				
subjects affected / exposed	0 / 15 (0.00%)			
occurrences (all)	0			
Colitis				
subjects affected / exposed	1 / 15 (6.67%)			
occurrences (all)	1			
Constipation				
subjects affected / exposed	3 / 15 (20.00%)			
occurrences (all)	3			
Dental Caries				
subjects affected / exposed	1 / 15 (6.67%)			
occurrences (all)	1			
Diarrhoea				
subjects affected / exposed	3 / 15 (20.00%)			
occurrences (all)	4			
Dyspepsia				

subjects affected / exposed	2 / 15 (13.33%)			
occurrences (all)	2			
Dysphagia				
subjects affected / exposed	0 / 15 (0.00%)			
occurrences (all)	0			
Enterocolitis				
subjects affected / exposed	0 / 15 (0.00%)			
occurrences (all)	0			
Flatulence				
subjects affected / exposed	0 / 15 (0.00%)			
occurrences (all)	0			
Gastrointestinal Inflammation				
subjects affected / exposed	0 / 15 (0.00%)			
occurrences (all)	0			
Gastrointestinal Motility Disorder				
subjects affected / exposed	0 / 15 (0.00%)			
occurrences (all)	0			
Gingival Bleeding				
subjects affected / exposed	0 / 15 (0.00%)			
occurrences (all)	0			
Gingival Oedema				
subjects affected / exposed	0 / 15 (0.00%)			
occurrences (all)	0			
Haematemesis				
subjects affected / exposed	0 / 15 (0.00%)			
occurrences (all)	0			
Haematochezia				
subjects affected / exposed	0 / 15 (0.00%)			
occurrences (all)	0			
Ileus				
subjects affected / exposed	0 / 15 (0.00%)			
occurrences (all)	0			
Intestinal Haemorrhage				
subjects affected / exposed	0 / 15 (0.00%)			
occurrences (all)	0			
Melaena				

subjects affected / exposed	0 / 15 (0.00%)		
occurrences (all)	0		
Mouth Haemorrhage			
subjects affected / exposed	0 / 15 (0.00%)		
occurrences (all)	0		
Mouth Ulceration			
subjects affected / exposed	0 / 15 (0.00%)		
occurrences (all)	0		
Nausea			
subjects affected / exposed	2 / 15 (13.33%)		
occurrences (all)	8		
Odynophagia			
subjects affected / exposed	0 / 15 (0.00%)		
occurrences (all)	0		
Oesophageal Pain			
subjects affected / exposed	0 / 15 (0.00%)		
occurrences (all)	0		
Oesophagitis			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Proctalgia			
subjects affected / exposed	0 / 15 (0.00%)		
occurrences (all)	0		
Rectal Haemorrhage			
subjects affected / exposed	0 / 15 (0.00%)		
occurrences (all)	0		
Stomatitis			
subjects affected / exposed	3 / 15 (20.00%)		
occurrences (all)	3		
Toothache			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Vomiting			
subjects affected / exposed	4 / 15 (26.67%)		
occurrences (all)	7		
Hepatobiliary disorders			

Hepatic Failure subjects affected / exposed occurrences (all) Hypertransaminasaemia subjects affected / exposed occurrences (all)	 0 / 15 (0.00%) 0 0 / 15 (0.00%) 0		
Skin and subcutaneous tissue disorders Alopecia subjects affected / exposed occurrences (all) Decubitus Ulcer subjects affected / exposed occurrences (all) Ecchymosis subjects affected / exposed occurrences (all) Petechiae subjects affected / exposed occurrences (all) Pruritus subjects affected / exposed occurrences (all) Rash subjects affected / exposed occurrences (all) Rash Maculo-Papular subjects affected / exposed occurrences (all) Skin Lesion subjects affected / exposed occurrences (all) Urticaria subjects affected / exposed occurrences (all)	 0 / 15 (0.00%) 0 0 / 15 (0.00%) 0 1 / 15 (6.67%) 1 0 / 15 (0.00%) 0 0 / 15 (0.00%) 0 0 / 15 (0.00%) 0 1 / 15 (6.67%) 1 1 / 15 (6.67%) 1 0 / 15 (0.00%) 0		
Renal and urinary disorders			

Haematuria				
subjects affected / exposed	0 / 15 (0.00%)			
occurrences (all)	0			
Hypotonic Urinary Bladder				
subjects affected / exposed	0 / 15 (0.00%)			
occurrences (all)	0			
Renal Impairment				
subjects affected / exposed	1 / 15 (6.67%)			
occurrences (all)	1			
Renal Tubular Injury				
subjects affected / exposed	0 / 15 (0.00%)			
occurrences (all)	0			
Urinary Retention				
subjects affected / exposed	0 / 15 (0.00%)			
occurrences (all)	0			
Musculoskeletal and connective tissue disorders				
Arthralgia				
subjects affected / exposed	0 / 15 (0.00%)			
occurrences (all)	0			
Back Pain				
subjects affected / exposed	0 / 15 (0.00%)			
occurrences (all)	0			
Bone Pain				
subjects affected / exposed	1 / 15 (6.67%)			
occurrences (all)	1			
Musculoskeletal Chest Pain				
subjects affected / exposed	0 / 15 (0.00%)			
occurrences (all)	0			
Musculoskeletal Pain				
subjects affected / exposed	1 / 15 (6.67%)			
occurrences (all)	1			
Myalgia				
subjects affected / exposed	0 / 15 (0.00%)			
occurrences (all)	0			
Neck Pain				

subjects affected / exposed	0 / 15 (0.00%)		
occurrences (all)	0		
Pain in Extremity			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Infections and infestations			
Anal Abscess			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Aspergillus Infection			
subjects affected / exposed	0 / 15 (0.00%)		
occurrences (all)	0		
Bacteraemia			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Bk Virus Infection			
subjects affected / exposed	0 / 15 (0.00%)		
occurrences (all)	0		
Conjunctivitis			
subjects affected / exposed	0 / 15 (0.00%)		
occurrences (all)	0		
Device Related Infection			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	2		
Escherichia Infection			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Fungal Infection			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Fusarium Infection			
subjects affected / exposed	0 / 15 (0.00%)		
occurrences (all)	0		
Geotrichum Infection			
subjects affected / exposed	0 / 15 (0.00%)		
occurrences (all)	0		

Herpes Zoster				
subjects affected / exposed	0 / 15 (0.00%)			
occurrences (all)	0			
Klebsiella Infection				
subjects affected / exposed	1 / 15 (6.67%)			
occurrences (all)	1			
Nasopharyngitis				
subjects affected / exposed	0 / 15 (0.00%)			
occurrences (all)	0			
Oral Herpes				
subjects affected / exposed	1 / 15 (6.67%)			
occurrences (all)	1			
Pneumonia				
subjects affected / exposed	0 / 15 (0.00%)			
occurrences (all)	0			
Pseudomonal Bacteraemia				
subjects affected / exposed	0 / 15 (0.00%)			
occurrences (all)	0			
Rhinitis				
subjects affected / exposed	2 / 15 (13.33%)			
occurrences (all)	3			
Rhinovirus Infection				
subjects affected / exposed	0 / 15 (0.00%)			
occurrences (all)	0			
Sepsis				
subjects affected / exposed	0 / 15 (0.00%)			
occurrences (all)	0			
Sinusitis				
subjects affected / exposed	0 / 15 (0.00%)			
occurrences (all)	0			
Upper Respiratory Tract Infection				
subjects affected / exposed	1 / 15 (6.67%)			
occurrences (all)	1			
Urinary Tract Infection				
subjects affected / exposed	1 / 15 (6.67%)			
occurrences (all)	1			

Urinary Tract Infection Pseudomonal subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1		
Vascular Device Infection subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0		
Viral Upper Respiratory Tract Infection subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1		
Metabolism and nutrition disorders			
Decreased Appetite subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0		
Fluid Retention subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0		
Hyperglycaemia subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1		
Hyperkalaemia subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0		
Hypernatraemia subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0		
Hyperphosphataemia subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0		
Hypoalbuminaemia subjects affected / exposed occurrences (all)	2 / 15 (13.33%) 3		
Hypocalcaemia subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0		
Hypoglycaemia			

subjects affected / exposed	0 / 15 (0.00%)		
occurrences (all)	0		
Hypokalaemia			
subjects affected / exposed	6 / 15 (40.00%)		
occurrences (all)	10		
Hypomagnesaemia			
subjects affected / exposed	5 / 15 (33.33%)		
occurrences (all)	6		
Hyponatraemia			
subjects affected / exposed	2 / 15 (13.33%)		
occurrences (all)	3		
Hypophosphataemia			
subjects affected / exposed	0 / 15 (0.00%)		
occurrences (all)	0		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
21 June 2016	The overall reason for the Amendment 1 was to address changes requested during Health Authority review; Subjects in the 2 older age groups (6-11 years, 12-17 years) to be enrolled and treated prior to opening enrollment to subjects in the younger age group (1-5 years); Central assessment of viral serologies to be performed at screening; Tetanus and pneumococcal antibody titers were added at screening; Guidance for dosing of ibrutinib around the time of lumbar procedures were added due to risk of bleeding.
24 April 2017	The overall reason for the Amendment-2 was to address changes requested during Health Authority review; Contraception language changed to clarify length of time subjects should avoid pregnancy after the last dose of any study agent (example, year); women of childbearing potential are required to use contraceptives while taking ibrutinib and women using hormonal methods of contraception were required to add a barrier method of contraception; Added exclusion criteria for subjects with a diagnosis of post transplant lymphoproliferative disease (PTLD); and for subjects who received an allogeneic bone marrow transplant within 6 months; Recommended use of non-azole antifungal prophylaxis for aspergillosis and concomitant granulocyte colony stimulating factor added to rituximab, vincristine, idarubicin, carboplatin, ifosfamide, and dexamethasone (RVICI) regimen as prophylaxis against neutropenia; Bone marrow on Cycle 2 Day 1 (C2D1) only obtained if clinically indicated; Intrathecal therapy administered not more than 24 hours before D1 of each cycle; Lumbar puncture and bone marrow procedures may be performed the day prior to the start of a treatment cycle for logistical reasons as needed.
07 July 2017	The overall reason for the Amendment-3 was to allow for collection of additional exposure data from subjects in the 2 younger age groups (ages 1-5 and 6-11 years) to facilitate dose confirmation for Part 2; Increased the number of subjects to be enrolled into Part 1 (from 12 to up to approximately 24 subjects) to allow for collection of additional exposure data from subjects in the 2 younger age groups (ages 1-5 and 6-11 years) for dose confirmation for Part 2 in these younger age groups. Clarified that at a minimum, the first 2 subjects in each age group were to be enrolled into Part 1 before recruitment of children in that age group was to begin in Part 2.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported