# 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<br>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<br>Units: years | | | |
| arithmetic mean | 10.5 | 8.3 | 13.9 |
| standard deviation | ± 4.91 | ± 3.43 | ± 3.94 |
| Title for Gender<br>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<br>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<br>Units: years | | | |
| arithmetic mean | 13.3 | | |
| standard deviation | ± 4.51 | - | |
| Title for Gender<br>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 | | | |

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

| | | | | |
|---|---|---|---|---|
| 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<br>subjects affected / exposed<br>occurrences (all)<br><br>Hypertransaminasaemia<br>subjects affected / exposed<br>occurrences (all) | <br>0 / 15 (0.00%)<br>0<br><br><br>0 / 15 (0.00%)<br>0 | | |
| Skin and subcutaneous tissue disorders<br>Alopecia<br>subjects affected / exposed<br>occurrences (all)<br><br>Decubitus Ulcer<br>subjects affected / exposed<br>occurrences (all)<br><br>Ecchymosis<br>subjects affected / exposed<br>occurrences (all)<br><br>Petechiae<br>subjects affected / exposed<br>occurrences (all)<br><br>Pruritus<br>subjects affected / exposed<br>occurrences (all)<br><br>Rash<br>subjects affected / exposed<br>occurrences (all)<br><br>Rash Maculo-Papular<br>subjects affected / exposed<br>occurrences (all)<br><br>Skin Lesion<br>subjects affected / exposed<br>occurrences (all)<br><br>Urticaria<br>subjects affected / exposed<br>occurrences (all) | <br><br>0 / 15 (0.00%)<br>0<br><br><br>0 / 15 (0.00%)<br>0<br><br><br>1 / 15 (6.67%)<br>1<br><br><br>0 / 15 (0.00%)<br>0<br><br><br>0 / 15 (0.00%)<br>0<br><br><br>0 / 15 (0.00%)<br>0<br><br><br>1 / 15 (6.67%)<br>1<br><br><br>1 / 15 (6.67%)<br>1<br><br><br>0 / 15 (0.00%)<br>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<br>subjects affected / exposed<br>occurrences (all) | 1 / 15 (6.67%)<br>1 | | |
| Vascular Device Infection<br>subjects affected / exposed<br>occurrences (all) | 0 / 15 (0.00%)<br>0 | | |
| Viral Upper Respiratory Tract Infection<br>subjects affected / exposed<br>occurrences (all) | 1 / 15 (6.67%)<br>1 | | |
| Metabolism and nutrition disorders | | | |
| Decreased Appetite<br>subjects affected / exposed<br>occurrences (all) | 0 / 15 (0.00%)<br>0 | | |
| Fluid Retention<br>subjects affected / exposed<br>occurrences (all) | 0 / 15 (0.00%)<br>0 | | |
| Hyperglycaemia<br>subjects affected / exposed<br>occurrences (all) | 1 / 15 (6.67%)<br>1 | | |
| Hyperkalaemia<br>subjects affected / exposed<br>occurrences (all) | 0 / 15 (0.00%)<br>0 | | |
| Hypernatraemia<br>subjects affected / exposed<br>occurrences (all) | 0 / 15 (0.00%)<br>0 | | |
| Hyperphosphataemia<br>subjects affected / exposed<br>occurrences (all) | 0 / 15 (0.00%)<br>0 | | |
| Hypoalbuminaemia<br>subjects affected / exposed<br>occurrences (all) | 2 / 15 (13.33%)<br>3 | | |
| Hypocalcaemia<br>subjects affected / exposed<br>occurrences (all) | 0 / 15 (0.00%)<br>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<br>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<br>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