



## Clinical trial results:

### A Multi-Center, Open-Label, Compassionate Use Extension Study of Ublituximab (TG-1101) in Combination with Umbralisib (TGR-1202) for Patients Previously Enrolled in Protocol UTX-TGR-304

#### Summary

|                          |                |
|--------------------------|----------------|
| EudraCT number           | 2016-004339-19 |
| Trial protocol           | PL ES GB IT    |
| Global end of trial date | 11 July 2022   |

#### Results information

|                                |              |
|--------------------------------|--------------|
| Result version number          | v1 (current) |
| This version publication date  | 27 July 2023 |
| First version publication date | 27 July 2023 |

#### Trial information

##### Trial identification

|                       |             |
|-----------------------|-------------|
| Sponsor protocol code | UTX-TGR-204 |
|-----------------------|-------------|

##### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT02656303 |
| WHO universal trial number (UTN)   | -           |

Notes:

##### Sponsors

|                              |   |
|------------------------------|---|
| Sponsor organisation name    | TG Therapeutics, Inc.   |
| Sponsor organisation address | 2 Gansevoort Street, 9th Floor, New York, United States, 10014                      |
| Public contact               | Clinical Support Team, TG Therapeutics, 1 877-575-8489, Clinicalsupport@tgtxinc.com |
| Scientific contact           | Clinical Support Team, TG Therapeutics, 1 877-575-8489, Clinicalsupport@tgtxinc.com |

Notes:

##### Paediatric regulatory details

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

Notes:

## Results analysis stage

|  |              |
|--|--------------|
| Analysis stage                                       | Final        |
| Date of interim/final analysis                       | 11 July 2022 |
| Is this the analysis of the primary completion data? | No           |
| Global end of trial reached?                         | Yes          |
| Global end of trial date                             | 11 July 2022 |
| Was the trial ended prematurely?                     | Yes          |

Notes:

## General information about the trial

Main objective of the trial:

The purpose of this study was to provide the opportunity to the subjects who progressed on treatment arm previously in the study UTX-TGR-304 (2015-005758-36) to receive ublituximab (TG-1101) treatment in combination with umbralisib (TGR-1202).

Protection of trial subjects:

This study was conducted in accordance with the protocol and consensus ethical principles originating in or derived from the Declaration of Helsinki and in compliance with all ICH GCP Guidelines. The Investigator or his/her representative explained the nature of the study to the subject or his/her legally authorized representative and answered all questions regarding the study. Subjects and/or their legally authorized representative were informed that their participation was voluntary. Subjects or their legally authorized representative were required to sign a statement of informed consent that met the requirements of 21 CFR 31.27, local regulations, ICH guidelines, HIPAA requirements, where applicable, and the IRB/IEC or study center. Investigative sites were instructed to obtain written informed consent before the subject was enrolled in the study and document the date the written consent was obtained. The authorized person obtaining the informed consent was also instructed to sign the ICF.

Background therapy: -

Evidence for comparator: -

|   |                 |
|---|-----------------|
| Actual start date of recruitment                          | 03 January 2017 |
| Long term follow-up planned                               | No              |
| Independent data monitoring committee (IDMC) involvement? | No              |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |                   |
|--------------------------------------|-------------------|
| Country: Number of subjects enrolled | Poland: 43        |
| Country: Number of subjects enrolled | United Kingdom: 1 |
| Country: Number of subjects enrolled | Italy: 4          |
| Country: Number of subjects enrolled | United States: 68 |
| Worldwide total number of subjects   | 116               |
| EEA total number of subjects         | 47                |

Notes:

### Subjects enrolled per age group

|   |   |
|---|---|
| In utero                                  | 0 |
| Preterm newborn - gestational age < 37 wk | 0 |
| Newborns (0-27 days)                      | 0 |

|  |    |
|--|----|
| Infants and toddlers (28 days-23 months) | 0  |
| Children (2-11 years)                    | 0  |
| Adolescents (12-17 years)                | 0  |
| Adults (18-64 years)                     | 47 |
| From 65 to 84 years                      | 67 |
| 85 years and over                        | 2  |

## Subject disposition

### Recruitment

Recruitment details:

A total of 116 subjects took part across 50 investigative sites in the United States, United Kingdom, Italy, and Poland from 03 January 2017 to 28 June 2022.

### Pre-assignment

Screening details:

Subjects previously enrolled in the parent study UTX-TGR-304 (2015-005758-36) were enrolled in this study.

### Period 1

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

### Arms

|                              |                    |
|------------------------------|--------------------|
| Are arms mutually exclusive? | Yes                |
| <b>Arm title</b>             | Parent Study Arm B |

Arm description:

Subjects from Arm B of the parent trial (UTX-TGR-304) received ublituximab, 150 milligrams (mg), intravenously (IV), on Day 1, 750 mg on Day 2, followed by 900 mg on Days 8 and 15 of Cycle 1, Day 1 of Cycles 2-6 (cycle length=28 days), and once every 3 months thereafter, along with umbralisib, 800 mg, orally, once daily during each cycle (cycle length=28 days) until disease progression, lack of tolerability, or until the treatment is commercially available or up to 78 months.

|  |                 |
|--|-----------------|
| Arm type                               | Experimental    |
| Investigational medicinal product name | Ublituximab     |
| Investigational medicinal product code |                 |
| Other name                             | TG-1101         |
| Pharmaceutical forms                   | Infusion        |
| Routes of administration               | Intravenous use |

Dosage and administration details:

Ublituximab 150 mg was administered as an IV on Day 1, 750 mg on Day 2, followed by 900 mg on Days 8 and 15 of Cycle 1, Day 1 of Cycles 2-6 (cycle length=28 days), and once every 3 months thereafter.

|  |            |
|--|------------|
| Investigational medicinal product name | Umbralisib |
| Investigational medicinal product code |            |
| Other name                             | TGR-1202   |
| Pharmaceutical forms                   | Tablet     |
| Routes of administration               | Oral use   |

Dosage and administration details:

Umbralisib 800 mg was administered orally, once daily during each cycle (cycle length=28 days) until disease progression, lack of tolerability, or until the treatment is commercially available or up to 78 months.

|                  |                    |
|------------------|--------------------|
| <b>Arm title</b> | Parent Study Arm C |
|------------------|--------------------|

Arm description:

Subjects from Arm C of the parent trial (UTX-TGR-304) received ublituximab, 900 mg, IV, on Day 1 of Cycles 1-6 (cycle length=28 days), and once every 3 months thereafter, along with umbralisib, 800 mg, orally, once daily during each cycle (cycle length=28 days) until disease progression, lack of tolerability, or until the treatment is commercially available or up to 78 months.

|          |              |
|----------|--------------|
| Arm type | Experimental |
|----------|--------------|

|  |                 |
|--|-----------------|
| Investigational medicinal product name | Ublituximab     |
| Investigational medicinal product code |                 |
| Other name                             | TG-1101         |
| Pharmaceutical forms                   | Infusion        |
| Routes of administration               | Intravenous use |

**Dosage and administration details:**

Ublituximab 900 mg was administered as an IV on Day 1 of Cycles 1-6 (cycle length=28 days), and once every 3 months thereafter.

|  |            |
|--|------------|
| Investigational medicinal product name | Umbralisib |
| Investigational medicinal product code |            |
| Other name                             | TGR-1202   |
| Pharmaceutical forms                   | Tablet     |
| Routes of administration               | Oral use   |

**Dosage and administration details:**

Umbralisib 800 mg was administered orally, once daily during each cycle (cycle length=28 days) until disease progression, lack of tolerability, or until the treatment is commercially available or up to 78 months.

|                  |                    |
|------------------|--------------------|
| <b>Arm title</b> | Parent Study Arm D |
|------------------|--------------------|

**Arm description:**

Subjects from Arm D of the parent trial (UTX-TGR-304) received ublituximab, 150 mg, IV, on Day 1, 750 mg on Day 2, followed by 900 mg on Days 8 and 15 of Cycle 1, Day 1 of Cycles 2-6 (cycle length=28 days), and once every 3 months thereafter, along with umbralisib, 800 mg, orally, once daily during each cycle (cycle length=28 days) until disease progression, lack of tolerability, or until the treatment is commercially available or up to 78 months.

|  |                 |
|--|-----------------|
| Arm type                               | Experimental    |
| Investigational medicinal product name | Ublituximab     |
| Investigational medicinal product code |                 |
| Other name                             | TG-1101         |
| Pharmaceutical forms                   | Infusion        |
| Routes of administration               | Intravenous use |

**Dosage and administration details:**

Ublituximab 150 mg was administered as an IV on Day 1, 750 mg on Day 2, followed by 900 mg on Days 8 and 15 of Cycle 1, Day 1 of Cycles 2-6 (cycle length=28 days), and once every 3 months thereafter.

|  |            |
|--|------------|
| Investigational medicinal product name | Umbralisib |
| Investigational medicinal product code |            |
| Other name                             | TGR-1202   |
| Pharmaceutical forms                   | Tablet     |
| Routes of administration               | Oral use   |

**Dosage and administration details:**

Umbralisib 800 mg was administered, orally, once daily during each cycle (cycle length=28 days) until disease progression, lack of tolerability, or until the treatment is commercially available or up to 78 months.

| <b>Number of subjects in period 1</b> | Parent Study Arm B | Parent Study Arm C | Parent Study Arm D |
|---------------------------------------|--------------------|--------------------|--------------------|
| Started                               | 67                 | 31                 | 18                 |
| Completed                             | 0                  | 0                  | 0                  |
| Not completed                         | 67                 | 31                 | 18                 |
| Non-compliance with study             | 1                  | 1                  | -                  |
| Death                                 | 12                 | 4                  | 1                  |

|   |    |    |    |
|---|----|----|----|
| Initiation of non-protocol intervention | 1  | -  | -  |
| Adverse event                           | 3  | 2  | -  |
| Investigator decision                   | 2  | 1  | -  |
| Study terminated by sponsor             | 20 | 7  | 5  |
| Progressive disease                     | 25 | 14 | 10 |
| Reason not specified                    | 1  | 1  | 2  |
| Lack of efficacy                        | 1  | -  | -  |
| Withdrawal of consent by subject        | 1  | 1  | -  |

## Baseline characteristics

### Reporting groups

|  |                    |
|--|--------------------|
| Reporting group title  | Parent Study Arm B |
| Reporting group description:   |                    |
| Subjects from Arm B of the parent trial (UTX-TGR-304) received ublituximab, 150 milligrams (mg), intravenously (IV), on Day 1, 750 mg on Day 2, followed by 900 mg on Days 8 and 15 of Cycle 1, Day 1 of Cycles 2-6 (cycle length=28 days), and once every 3 months thereafter, along with umbralisib, 800 mg, orally, once daily during each cycle (cycle length=28 days) until disease progression, lack of tolerability, or until the treatment is commercially available or up to 78 months. |                    |
| Reporting group title  | Parent Study Arm C |
| Reporting group description:   |                    |
| Subjects from Arm C of the parent trial (UTX-TGR-304) received ublituximab, 900 mg, IV, on Day 1 of Cycles 1-6 (cycle length=28 days), and once every 3 months thereafter, along with umbralisib, 800 mg, orally, once daily during each cycle (cycle length=28 days) until disease progression, lack of tolerability, or until the treatment is commercially available or up to 78 months.  |                    |
| Reporting group title  | Parent Study Arm D |
| Reporting group description:   |                    |
| Subjects from Arm D of the parent trial (UTX-TGR-304) received ublituximab, 150 mg, IV, on Day 1, 750 mg on Day 2, followed by 900 mg on Days 8 and 15 of Cycle 1, Day 1 of Cycles 2-6 (cycle length=28 days), and once every 3 months thereafter, along with umbralisib, 800 mg, orally, once daily during each cycle (cycle length=28 days) until disease progression, lack of tolerability, or until the treatment is commercially available or up to 78 months.                              |                    |

| Reporting group values                             | Parent Study Arm B | Parent Study Arm C | Parent Study Arm D |
|--|--------------------|--------------------|--------------------|
| Number of subjects                                 | 67                 | 31                 | 18                 |
| Age categorical                                    |                    |                    |                    |
| Units: Subjects                                    |                    |                    |                    |
| In utero   |                    |                    |                    |
| Preterm newborn infants (gestational age < 37 wks) |                    |                    |                    |
| Newborns (0-27 days)                               |                    |                    |                    |
| Infants and toddlers (28 days-23 months)           |                    |                    |                    |
| Children (2-11 years)                              |                    |                    |                    |
| Adolescents (12-17 years)                          |                    |                    |                    |
| Adults (18-64 years)                               |                    |                    |                    |
| From 65-84 years                                   |                    |                    |                    |
| 85 years and over                                  |                    |                    |                    |
| Age continuous                                     |                    |                    |                    |
| Units: years                                       |                    |                    |                    |
| arithmetic mean                                    | 65.6               | 66.7               | 65.7               |
| standard deviation                                 | ± 8.18             | ± 9.41             | ± 8.79             |
| Gender categorical                                 |                    |                    |                    |
| Units: Subjects                                    |                    |                    |                    |
| Female   | 19                 | 5                  | 5                  |
| Male   | 48                 | 26                 | 13                 |
| Race   |                    |                    |                    |
| Units: Subjects                                    |                    |                    |                    |
| White  | 65                 | 30                 | 15                 |
| Black or African American                          | 2                  | 0                  | 1                  |
| Other  | 0                  | 0                  | 2                  |
| Not Reported                                       | 0                  | 1                  | 0                  |

|                         |    |    |    |
|-------------------------|----|----|----|
| Ethnicity               |    |    |    |
| Units: Subjects         |    |    |    |
| Hispanic or Latino      | 1  | 0  | 1  |
| Not Hispanic or Latino  | 66 | 30 | 16 |
| Unknown or Not Reported | 0  | 1  | 1  |

|   |       |  |  |
|---|-------|--|--|
| <b>Reporting group values</b>                         | Total |  |  |
| Number of subjects                                    | 116   |  |  |
| Age categorical                                       |       |  |  |
| Units: Subjects                                       |       |  |  |
| In utero  | 0     |  |  |
| Preterm newborn infants<br>(gestational age < 37 wks) | 0     |  |  |
| Newborns (0-27 days)                                  | 0     |  |  |
| Infants and toddlers (28 days-23<br>months)           | 0     |  |  |
| Children (2-11 years)                                 | 0     |  |  |
| Adolescents (12-17 years)                             | 0     |  |  |
| Adults (18-64 years)                                  | 0     |  |  |
| From 65-84 years                                      | 0     |  |  |
| 85 years and over                                     | 0     |  |  |
| Age continuous  |       |  |  |
| Units: years  |       |  |  |
| arithmetic mean                                       |       |  |  |
| standard deviation                                    | -     |  |  |
| Gender categorical                                    |       |  |  |
| Units: Subjects                                       |       |  |  |
| Female  | 29    |  |  |
| Male  | 87    |  |  |
| Race  |       |  |  |
| Units: Subjects                                       |       |  |  |
| White   | 110   |  |  |
| Black or African American                             | 3     |  |  |
| Other   | 2     |  |  |
| Not Reported  | 1     |  |  |
| Ethnicity   |       |  |  |
| Units: Subjects                                       |       |  |  |
| Hispanic or Latino                                    | 2     |  |  |
| Not Hispanic or Latino                                | 112   |  |  |
| Unknown or Not Reported                               | 2     |  |  |



## End points

### End points reporting groups

|  |                    |
|--|--------------------|
| Reporting group title  | Parent Study Arm B |
| Reporting group description:   |                    |
| Subjects from Arm B of the parent trial (UTX-TGR-304) received ublituximab, 150 milligrams (mg), intravenously (IV), on Day 1, 750 mg on Day 2, followed by 900 mg on Days 8 and 15 of Cycle 1, Day 1 of Cycles 2-6 (cycle length=28 days), and once every 3 months thereafter, along with umbralisib, 800 mg, orally, once daily during each cycle (cycle length=28 days) until disease progression, lack of tolerability, or until the treatment is commercially available or up to 78 months. |                    |
| Reporting group title  | Parent Study Arm C |
| Reporting group description:   |                    |
| Subjects from Arm C of the parent trial (UTX-TGR-304) received ublituximab, 900 mg, IV, on Day 1 of Cycles 1-6 (cycle length=28 days), and once every 3 months thereafter, along with umbralisib, 800 mg, orally, once daily during each cycle (cycle length=28 days) until disease progression, lack of tolerability, or until the treatment is commercially available or up to 78 months.  |                    |
| Reporting group title  | Parent Study Arm D |
| Reporting group description:   |                    |
| Subjects from Arm D of the parent trial (UTX-TGR-304) received ublituximab, 150 mg, IV, on Day 1, 750 mg on Day 2, followed by 900 mg on Days 8 and 15 of Cycle 1, Day 1 of Cycles 2-6 (cycle length=28 days), and once every 3 months thereafter, along with umbralisib, 800 mg, orally, once daily during each cycle (cycle length=28 days) until disease progression, lack of tolerability, or until the treatment is commercially available or up to 78 months.                              |                    |

### Primary: Overall Response Rate (ORR) as Per International Workshop on Chronic Lymphocytic Leukemia (iwCLL) Criteria

|  |   |
|--|---|
| End point title  | Overall Response Rate (ORR) as Per International Workshop on Chronic Lymphocytic Leukemia (iwCLL) Criteria <sup>[1]</sup> |
| End point description:   |   |
| ORR was defined as sum of subjects with partial response (PR) and complete response (CR). CR: No evidence of new disease; Absolute lymphocyte count (ALC)<4x10 <sup>9</sup> /litre(L); Regression of all target nodal masses to ≤1.5 centimetres (cm) in longest diameter(LD); Normal spleen, liver size; Regression to normal of all nodal non-target disease and disappearance of all detectable; Non-nodal, non-target disease; Morphologically negative bone marrow; No lymphoid nodules; Absolute neutrophil count (ANC)>1.5x10 <sup>9</sup> /L, platelets≥100x10 <sup>9</sup> /L, hemoglobin (Hgb)≥110 gram per litre(g/L). PR: No evidence of new disease; Response in 2 of following if abnormal at baseline: ALC<4x10 <sup>9</sup> /L or ≥50% decrease from baseline in sum of products (SPD) of target nodal lesions; splenomegaly; hepatomegaly; ≥50% decrease from baseline in CLL marrow infiltrate/B-lymphoid nodules; response in any 1: ANC>1.5x10 <sup>9</sup> /L, platelets>100x10 <sup>9</sup> /L, Hgb>110g/L or ≥50% increase over baseline in any of these. |   |
| End point type   | Primary   |
| End point timeframe:   |   |
| Up to 76 months  |   |

#### 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: Data was not collected or analysed for this endpoint as the study was terminated due to sponsor's business decision.

| End point values            | Parent Study Arm B | Parent Study Arm C | Parent Study Arm D |  |
|-----------------------------|--------------------|--------------------|--------------------|--|
| Subject group type          | Reporting group    | Reporting group    | Reporting group    |  |
| Number of subjects analysed | 0 <sup>[2]</sup>   | 0 <sup>[3]</sup>   | 0 <sup>[4]</sup>   |  |
| Units: subjects             |                    |                    |                    |  |

Notes:

[2] - Data was not collected or analysed as the study was terminated due to sponsor's business decision.

[3] - Data was not collected or analysed as the study was terminated due to sponsor's business decision.

[4] - Data was not collected or analysed as the study was terminated due to sponsor's business decision.

## Statistical analyses

No statistical analyses for this end point

### Primary: Complete Response (CR) Rate Per iwCLL Criteria

|                 |   |
|-----------------|---|
| End point title | Complete Response (CR) Rate Per iwCLL Criteria <sup>[5]</sup> |
|-----------------|---|

End point description:

The CR rate was defined as the percentage of subjects who achieved CR. CR: No evidence of new disease; ALC  $<4 \times 10^9/L$ ; Regression of all target nodal masses to normal size  $\leq 1.5$  cm in the LD; Normal spleen and liver size; Regression to normal of all nodal non-target disease and disappearance of all detectable; Non-nodal, non-target disease; Morphologically negative bone marrow; No lymphoid nodules; ANC  $>1.5 \times 10^9/L$ , platelets  $\geq 100 \times 10^9/L$ , Hgb  $\geq 110$  g/L.

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Up to 76 months

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: Data was not collected or analysed for this endpoint as the study was terminated due to sponsor's business decision.

| End point values            | Parent Study Arm B | Parent Study Arm C | Parent Study Arm D |  |
|-----------------------------|--------------------|--------------------|--------------------|--|
| Subject group type          | Reporting group    | Reporting group    | Reporting group    |  |
| Number of subjects analysed | 0 <sup>[6]</sup>   | 0 <sup>[7]</sup>   | 0 <sup>[8]</sup>   |  |
| Units: subjects             |                    |                    |                    |  |

Notes:

[6] - Data was not collected or analysed as the study was terminated due to sponsor's business decision.

[7] - Data was not collected or analysed as the study was terminated due to sponsor's business decision.

[8] - Data was not collected or analysed as the study was terminated due to sponsor's business decision.

## Statistical analyses

No statistical analyses for this end point

### Primary: Progression-Free Survival (PFS) Per iwCLL Criteria

|                 |   |
|-----------------|---|
| End point title | Progression-Free Survival (PFS) Per iwCLL Criteria <sup>[9]</sup> |
|-----------------|---|

End point description:

PFS was defined as the interval from enrollment to the earlier of the first documentation of definitive disease progression (PD) or death from any cause. PD was appearance of new nodes  $>1.5$  cm in the LD and  $>1.0$  in longest perpendicular diameter (LPD), new or recurrent hepatomegaly or splenomegaly, new or reappearance of an unequivocal extra-nodal lesion,  $\geq 50\%$  increase from the nadir in the SPD of target lesions,  $\geq 50\%$  increase in the LD of an individual node or extra-nodal mass, splenic/hepatic enlargement of  $\geq 50\%$  from nadir, unequivocal increase in the size of non-target disease, transformation to a more aggressive histology, decrease in platelet count or Hgb,  $>50\%$  decrease from the highest on-study platelet count,  $>20$  g/L decrease from the highest on-study Hgb.

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Up to 76 months

Notes:

[9] - 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: Data was not collected or analysed for this endpoint as the study was terminated due to sponsor's business decision.

| End point values            | Parent Study Arm B | Parent Study Arm C | Parent Study Arm D |  |
|-----------------------------|--------------------|--------------------|--------------------|--|
| Subject group type          | Reporting group    | Reporting group    | Reporting group    |  |
| Number of subjects analysed | 0 <sup>[10]</sup>  | 0 <sup>[11]</sup>  | 0 <sup>[12]</sup>  |  |
| Units: months               |                    |                    |                    |  |

Notes:

[10] - Data was not collected or analysed as the study was terminated due to sponsor's business decision.

[11] - Data was not collected or analysed as the study was terminated due to sponsor's business decision.

[12] - Data was not collected or analysed as the study was terminated due to sponsor's business decision.

## Statistical analyses

No statistical analyses for this end point

## Primary: Duration of Response (DOR)

|                 |  |
|-----------------|--|
| End point title | Duration of Response (DOR) <sup>[13]</sup> |
|-----------------|--|

End point description:

DOR: Interval from first documentation of CR/PR to first documentation of PD or death from any cause. CR: ALC<4x10<sup>9</sup>/L; Regression to normal of target nodal masses,nodal non-target disease,and no detectable non-nodal,non-target disease; Normal spleen,liver size; Morphologically negative bone marrow,No lymphoid nodules;ANC>1.5x10<sup>9</sup>/L,Platelets≥100x10<sup>9</sup>/L,Hgb≥110 g/L. PR: Response in 2 or more:ALC<4x10<sup>9</sup>/L, ≥50% drop from baseline in ALC or SPD of target nodal lesions,Hepatosplenomegaly,≥50% decrease from baseline in CLL marrow infiltrate/B-lymphoid nodules;Response in 1 or more:ANC>1.5x10<sup>9</sup>/L,Platelets>100x10<sup>9</sup>/L,Hgb>110 g/L or ≥50% increase over baseline in any. PD: Response in 1 or more:new nodes,Hepatosplenomegaly,unequivocal extra-nodal lesion;≥50% increase from nadir in SPD of target lesions or LD of node/extr-nodal mass or Splenic/Hepatic size,Unequivocal increase in non-target disease,More aggressive histology;Drop of >50% in platelets/>20g/L in Hgb from highest on-study count.

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Up to 76 months

Notes:

[13] - 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: Data was not collected or analysed for this endpoint as the study was terminated due to sponsor's business decision.

| End point values            | Parent Study Arm B | Parent Study Arm C | Parent Study Arm D |  |
|-----------------------------|--------------------|--------------------|--------------------|--|
| Subject group type          | Reporting group    | Reporting group    | Reporting group    |  |
| Number of subjects analysed | 0 <sup>[14]</sup>  | 0 <sup>[15]</sup>  | 0 <sup>[16]</sup>  |  |
| Units: months               |                    |                    |                    |  |

Notes:

[14] - Data was not collected or analysed as the study was terminated due to sponsor's business decision.

[15] - Data was not collected or analysed as the study was terminated due to sponsor's business decision.

[16] - Data was not collected or analysed as the study was terminated due to sponsor's business decision.

## Statistical analyses

No statistical analyses for this end point

### Secondary: Minimal Residual Disease (MRD) Negativity Rate

|  |  |
|--|--|
| End point title  | Minimal Residual Disease (MRD) Negativity Rate |
| End point description:<br>MRD negativity rate is defined as the percentage of subjects who are MRD negative. If a subject was determined to be MRD negative by peripheral blood, a bone marrow aspirate was obtained to assess MRD in the bone marrow. |  |
| End point type   | Secondary                                      |
| End point timeframe:<br>From Cycle 6 until Cycle 15 (cycle length=28 days) (Up to approximately 76 months)   |  |

| End point values            | Parent Study Arm B | Parent Study Arm C | Parent Study Arm D |  |
|-----------------------------|--------------------|--------------------|--------------------|--|
| Subject group type          | Reporting group    | Reporting group    | Reporting group    |  |
| Number of subjects analysed | 0 <sup>[17]</sup>  | 0 <sup>[18]</sup>  | 0 <sup>[19]</sup>  |  |
| Units: subjects             |                    |                    |                    |  |

Notes:

[17] - Data was not collected or analysed as the study was terminated due to sponsor's business decision.

[18] - Data was not collected or analysed as the study was terminated due to sponsor's business decision.

[19] - Data was not collected or analysed as the study was terminated due to sponsor's business decision.

## Statistical analyses

No statistical analyses for this end point

### Secondary: Number of Subjects Experiencing at Least One Treatment-Emergent Adverse Event (TEAE)

|   |  |
|---|--|
| End point title   | Number of Subjects Experiencing at Least One Treatment-Emergent Adverse Event (TEAE) |
| End point description:<br>An adverse event (AE) is any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product. An AE does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporarily associated with the use of a medicinal product, whether or not considered related to the medicinal product. TEAE is any AE that occur after first dosing of study medication and through the end of the study or through 30 days after the last dose of study treatment, or is considered treatment-related regardless of the start date of the event, or is present before first dosing of study medication but worsens in intensity or the investigator subsequently considers treatment-related. Safety population included all subjects who were enrolled and received at least one dose of study drug. |  |
| End point type  | Secondary  |

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End point timeframe:

Up to 78 months

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| <b>End point values</b>     | Parent Study<br>Arm B | Parent Study<br>Arm C | Parent Study<br>Arm D |  |
|-----------------------------|-----------------------|-----------------------|-----------------------|--|
| Subject group type          | Reporting group       | Reporting group       | Reporting group       |  |
| Number of subjects analysed | 67                    | 31                    | 18                    |  |
| Units: subjects             | 66                    | 30                    | 18                    |  |

### **Statistical analyses**

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No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Up to approximately 78 months

Adverse event reporting additional description:

Safety population included all subjects who were enrolled and received at least one dose of study drug.

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

### Dictionary used

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

|                    |      |
|--------------------|------|
| Dictionary version | 23.0 |
|--------------------|------|

### Reporting groups

|                       |                    |
|-----------------------|--------------------|
| Reporting group title | Parent Study Arm B |
|-----------------------|--------------------|

Reporting group description:

Subjects from Arm B of the parent trial (UTX-TGR-304) received ublituximab, 150 mg, IV, on Day 1, 750 mg on Day 2, followed by 900 mg on Days 8 and 15 of Cycle 1, Day 1 of Cycles 2-6 (cycle length=28 days), and once every 3 months thereafter, along with umbralisib, 800 mg, orally, once daily during each cycle (cycle length=28 days) until disease progression, lack of tolerability, or until the treatment is commercially available or up to 78 months.

|                       |                    |
|-----------------------|--------------------|
| Reporting group title | Parent Study Arm C |
|-----------------------|--------------------|

Reporting group description:

Subjects from Arm C of the parent trial (UTX-TGR-304) received ublituximab, 900 mg, IV, on Day 1 of Cycles 1-6 (cycle length=28 days), and once every 3 months thereafter, along with umbralisib, 800 mg, orally, once daily during each cycle (cycle length=28 days) until disease progression, lack of tolerability, or until the treatment is commercially available or up to 78 months.

|                       |                    |
|-----------------------|--------------------|
| Reporting group title | Parent Study Arm D |
|-----------------------|--------------------|

Reporting group description:

Subjects from Arm D of the parent trial (UTX-TGR-304) received ublituximab, 150 mg, IV, on Day 1, 750 mg on Day 2, followed by 900 mg on Days 8 and 15 of Cycle 1, Day 1 of Cycles 2-6 (cycle length=28 days), and once every 3 months thereafter, along with umbralisib, 800 mg, orally, once daily during each cycle (cycle length=28 days) until disease progression, lack of tolerability, or until the treatment is commercially available or up to 78 months.

| Serious adverse events  | Parent Study Arm B | Parent Study Arm C | Parent Study Arm D |
|---|--------------------|--------------------|--------------------|
| Total subjects affected by serious adverse events                   |                    |                    |                    |
| subjects affected / exposed   | 36 / 67 (53.73%)   | 13 / 31 (41.94%)   | 8 / 18 (44.44%)    |
| number of deaths (all causes)                                       | 23                 | 9                  | 7                  |
| number of deaths resulting from adverse events                      | 9                  | 3                  | 1                  |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                    |                    |                    |
| Colon cancer  |                    |                    |                    |
| subjects affected / exposed   | 0 / 67 (0.00%)     | 1 / 31 (3.23%)     | 0 / 18 (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              |
| Lung adenocarcinoma   |                    |                    |                    |

|  |                |                |                |
|--|----------------|----------------|----------------|
| subjects affected / exposed                          | 1 / 67 (1.49%) | 0 / 31 (0.00%) | 0 / 18 (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          |
| Malignant melanoma in situ                           |                |                |                |
| subjects affected / exposed                          | 1 / 67 (1.49%) | 0 / 31 (0.00%) | 0 / 18 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 1          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          | 0 / 0          |
| Vascular disorders                                   |                |                |                |
| Hypertension   |                |                |                |
| subjects affected / exposed                          | 0 / 67 (0.00%) | 0 / 31 (0.00%) | 1 / 18 (5.56%) |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 0          | 1 / 1          |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          | 0 / 0          |
| General disorders and administration site conditions |                |                |                |
| Chest pain   |                |                |                |
| subjects affected / exposed                          | 1 / 67 (1.49%) | 0 / 31 (0.00%) | 0 / 18 (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          |
| Death  |                |                |                |
| subjects affected / exposed                          | 1 / 67 (1.49%) | 0 / 31 (0.00%) | 0 / 18 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 1          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all           | 0 / 1          | 0 / 0          | 0 / 0          |
| Malaise  |                |                |                |
| subjects affected / exposed                          | 1 / 67 (1.49%) | 0 / 31 (0.00%) | 0 / 18 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 1          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          | 0 / 0          |
| Pyrexia  |                |                |                |
| subjects affected / exposed                          | 1 / 67 (1.49%) | 0 / 31 (0.00%) | 0 / 18 (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          |
| Sudden cardiac death                                 |                |                |                |
| subjects affected / exposed                          | 1 / 67 (1.49%) | 0 / 31 (0.00%) | 0 / 18 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 1          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all           | 0 / 1          | 0 / 0          | 0 / 0          |

|   |                |                |                 |
|---|----------------|----------------|-----------------|
| Immune system disorders                         |                |                |                 |
| Anaphylactic shock                              |                |                |                 |
| subjects affected / exposed                     | 0 / 67 (0.00%) | 1 / 31 (3.23%) | 0 / 18 (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           |
| Reproductive system and breast disorders        |                |                |                 |
| Prostatitis                                     |                |                |                 |
| subjects affected / exposed                     | 1 / 67 (1.49%) | 0 / 31 (0.00%) | 0 / 18 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Respiratory, thoracic and mediastinal disorders |                |                |                 |
| Acute respiratory failure                       |                |                |                 |
| subjects affected / exposed                     | 1 / 67 (1.49%) | 0 / 31 (0.00%) | 0 / 18 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 3          | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Chronic obstructive pulmonary disease           |                |                |                 |
| subjects affected / exposed                     | 1 / 67 (1.49%) | 0 / 31 (0.00%) | 0 / 18 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 2          | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Lung disorder                                   |                |                |                 |
| subjects affected / exposed                     | 1 / 67 (1.49%) | 0 / 31 (0.00%) | 0 / 18 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Pleural effusion                                |                |                |                 |
| subjects affected / exposed                     | 1 / 67 (1.49%) | 0 / 31 (0.00%) | 1 / 18 (5.56%)  |
| occurrences causally related to treatment / all | 1 / 1          | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Pneumonitis                                     |                |                |                 |
| subjects affected / exposed                     | 1 / 67 (1.49%) | 0 / 31 (0.00%) | 2 / 18 (11.11%) |
| occurrences causally related to treatment / all | 1 / 1          | 0 / 0          | 1 / 2           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Pulmonary embolism                              |                |                |                 |



|   |                |                |                |
|---|----------------|----------------|----------------|
| subjects affected / exposed                           | 1 / 67 (1.49%) | 0 / 31 (0.00%) | 1 / 18 (5.56%) |
| occurrences causally related to treatment / all       | 0 / 1          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all            | 0 / 0          | 0 / 0          | 0 / 0          |
| <b>Investigations</b>                                 |                |                |                |
| Aspartate aminotransferase increased                  |                |                |                |
| subjects affected / exposed                           | 1 / 67 (1.49%) | 0 / 31 (0.00%) | 0 / 18 (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          |
| Blood creatinine increased                            |                |                |                |
| subjects affected / exposed                           | 0 / 67 (0.00%) | 1 / 31 (3.23%) | 0 / 18 (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          |
| <b>Injury, poisoning and procedural complications</b> |                |                |                |
| Compression fracture                                  |                |                |                |
| subjects affected / exposed                           | 0 / 67 (0.00%) | 1 / 31 (3.23%) | 0 / 18 (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          |
| Hip fracture  |                |                |                |
| subjects affected / exposed                           | 1 / 67 (1.49%) | 0 / 31 (0.00%) | 0 / 18 (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          |
| Infusion related reaction                             |                |                |                |
| subjects affected / exposed                           | 0 / 67 (0.00%) | 0 / 31 (0.00%) | 1 / 18 (5.56%) |
| occurrences causally related to treatment / all       | 0 / 0          | 0 / 0          | 1 / 1          |
| deaths causally related to treatment / all            | 0 / 0          | 0 / 0          | 0 / 0          |
| Overdose  |                |                |                |
| subjects affected / exposed                           | 1 / 67 (1.49%) | 0 / 31 (0.00%) | 0 / 18 (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          |
| Radius fracture                                       |                |                |                |
| subjects affected / exposed                           | 2 / 67 (2.99%) | 0 / 31 (0.00%) | 0 / 18 (0.00%) |
| occurrences causally related to treatment / all       | 0 / 2          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all            | 0 / 0          | 0 / 0          | 0 / 0          |

|   |                |                |                |
|---|----------------|----------------|----------------|
| Cardiac disorders                               |                |                |                |
| Atrial fibrillation                             |                |                |                |
| subjects affected / exposed                     | 2 / 67 (2.99%) | 0 / 31 (0.00%) | 0 / 18 (0.00%) |
| occurrences causally related to treatment / all | 0 / 3          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Nervous system disorders                        |                |                |                |
| Cerebral infarction                             |                |                |                |
| subjects affected / exposed                     | 0 / 67 (0.00%) | 1 / 31 (3.23%) | 0 / 18 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 1          | 0 / 0          |
| Ischaemic stroke                                |                |                |                |
| subjects affected / exposed                     | 1 / 67 (1.49%) | 0 / 31 (0.00%) | 0 / 18 (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          |
| Paraparesis                                     |                |                |                |
| subjects affected / exposed                     | 1 / 67 (1.49%) | 0 / 31 (0.00%) | 0 / 18 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Blood and lymphatic system disorders            |                |                |                |
| Anaemia   |                |                |                |
| subjects affected / exposed                     | 2 / 67 (2.99%) | 1 / 31 (3.23%) | 0 / 18 (0.00%) |
| occurrences causally related to treatment / all | 2 / 2          | 0 / 3          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Febrile neutropenia                             |                |                |                |
| subjects affected / exposed                     | 3 / 67 (4.48%) | 0 / 31 (0.00%) | 0 / 18 (0.00%) |
| occurrences causally related to treatment / all | 3 / 3          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Lymph node haemorrhage                          |                |                |                |
| subjects affected / exposed                     | 0 / 67 (0.00%) | 1 / 31 (3.23%) | 0 / 18 (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          |
| Neutropenia                                     |                |                |                |

|   |                |                |                |
|---|----------------|----------------|----------------|
| subjects affected / exposed                     | 2 / 67 (2.99%) | 0 / 31 (0.00%) | 0 / 18 (0.00%) |
| occurrences causally related to treatment / all | 3 / 3          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Gastrointestinal disorders                      |                |                |                |
| Colitis   |                |                |                |
| subjects affected / exposed                     | 2 / 67 (2.99%) | 1 / 31 (3.23%) | 0 / 18 (0.00%) |
| occurrences causally related to treatment / all | 1 / 2          | 1 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Diarrhoea                                       |                |                |                |
| subjects affected / exposed                     | 1 / 67 (1.49%) | 1 / 31 (3.23%) | 0 / 18 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1          | 1 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Enterocolitis                                   |                |                |                |
| subjects affected / exposed                     | 0 / 67 (0.00%) | 1 / 31 (3.23%) | 0 / 18 (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          |
| Hepatobiliary disorders                         |                |                |                |
| Cholecystitis                                   |                |                |                |
| subjects affected / exposed                     | 1 / 67 (1.49%) | 0 / 31 (0.00%) | 0 / 18 (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          |
| Cholelithiasis                                  |                |                |                |
| subjects affected / exposed                     | 1 / 67 (1.49%) | 0 / 31 (0.00%) | 0 / 18 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Renal and urinary disorders                     |                |                |                |
| Acute kidney injury                             |                |                |                |
| subjects affected / exposed                     | 1 / 67 (1.49%) | 0 / 31 (0.00%) | 0 / 18 (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          |
| Musculoskeletal and connective tissue disorders |                |                |                |
| Pain in extremity                               |                |                |                |

|   |                |                |                 |
|---|----------------|----------------|-----------------|
| subjects affected / exposed                     | 1 / 67 (1.49%) | 0 / 31 (0.00%) | 0 / 18 (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           |
| Infections and infestations                     |                |                |                 |
| Aspergillus infection                           |                |                |                 |
| subjects affected / exposed                     | 0 / 67 (0.00%) | 0 / 31 (0.00%) | 1 / 18 (5.56%)  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 1 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Babesiosis                                      |                |                |                 |
| subjects affected / exposed                     | 1 / 67 (1.49%) | 0 / 31 (0.00%) | 0 / 18 (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           |
| Bronchitis                                      |                |                |                 |
| subjects affected / exposed                     | 1 / 67 (1.49%) | 0 / 31 (0.00%) | 0 / 18 (0.00%)  |
| occurrences causally related to treatment / all | 2 / 2          | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| COVID-19  |                |                |                 |
| subjects affected / exposed                     | 4 / 67 (5.97%) | 1 / 31 (3.23%) | 2 / 18 (11.11%) |
| occurrences causally related to treatment / all | 1 / 5          | 0 / 1          | 1 / 2           |
| deaths causally related to treatment / all      | 0 / 3          | 0 / 0          | 0 / 1           |
| COVID-19 pneumonia                              |                |                |                 |
| subjects affected / exposed                     | 5 / 67 (7.46%) | 2 / 31 (6.45%) | 2 / 18 (11.11%) |
| occurrences causally related to treatment / all | 0 / 5          | 0 / 3          | 1 / 2           |
| deaths causally related to treatment / all      | 0 / 3          | 0 / 1          | 0 / 0           |
| Cytomegalovirus infection                       |                |                |                 |
| subjects affected / exposed                     | 0 / 67 (0.00%) | 1 / 31 (3.23%) | 0 / 18 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 1          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 1 / 1          | 0 / 0           |
| Pneumocystis jirovecii pneumonia                |                |                |                 |
| subjects affected / exposed                     | 1 / 67 (1.49%) | 0 / 31 (0.00%) | 0 / 18 (0.00%)  |
| occurrences causally related to treatment / all | 1 / 1          | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Pneumonia                                       |                |                |                 |

|   |                 |                |                |
|---|-----------------|----------------|----------------|
| subjects affected / exposed                     | 8 / 67 (11.94%) | 2 / 31 (6.45%) | 1 / 18 (5.56%) |
| occurrences causally related to treatment / all | 6 / 13          | 1 / 2          | 1 / 1          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0          |
| Rectal abscess                                  |                 |                |                |
| subjects affected / exposed                     | 0 / 67 (0.00%)  | 1 / 31 (3.23%) | 0 / 18 (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          |
| Respiratory tract infection                     |                 |                |                |
| subjects affected / exposed                     | 1 / 67 (1.49%)  | 0 / 31 (0.00%) | 0 / 18 (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          |
| Sepsis  |                 |                |                |
| subjects affected / exposed                     | 1 / 67 (1.49%)  | 0 / 31 (0.00%) | 0 / 18 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0          | 0 / 0          |
| Septic shock                                    |                 |                |                |
| subjects affected / exposed                     | 2 / 67 (2.99%)  | 0 / 31 (0.00%) | 0 / 18 (0.00%) |
| occurrences causally related to treatment / all | 1 / 2           | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0          |
| Metabolism and nutrition disorders              |                 |                |                |
| Hypertriglyceridaemia                           |                 |                |                |
| subjects affected / exposed                     | 1 / 67 (1.49%)  | 0 / 31 (0.00%) | 0 / 18 (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          |
| Hypokalaemia                                    |                 |                |                |
| subjects affected / exposed                     | 1 / 67 (1.49%)  | 0 / 31 (0.00%) | 0 / 18 (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          |

Frequency threshold for reporting non-serious adverse events: 0 %

| <b>Non-serious adverse events</b>                                   | Parent Study Arm B | Parent Study Arm C | Parent Study Arm D |
|---|--------------------|--------------------|--------------------|
| Total subjects affected by non-serious adverse events               |                    |                    |                    |
| subjects affected / exposed   | 65 / 67 (97.01%)   | 30 / 31 (96.77%)   | 17 / 18 (94.44%)   |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                    |                    |                    |
| Acrochordon   |                    |                    |                    |
| subjects affected / exposed   | 1 / 67 (1.49%)     | 0 / 31 (0.00%)     | 0 / 18 (0.00%)     |
| occurrences (all)   | 1                  | 0                  | 0                  |
| Adenocarcinoma  |                    |                    |                    |
| subjects affected / exposed   | 0 / 67 (0.00%)     | 1 / 31 (3.23%)     | 0 / 18 (0.00%)     |
| occurrences (all)   | 0                  | 1                  | 0                  |
| Adenocarcinoma of colon   |                    |                    |                    |
| subjects affected / exposed   | 0 / 67 (0.00%)     | 1 / 31 (3.23%)     | 0 / 18 (0.00%)     |
| occurrences (all)   | 0                  | 1                  | 0                  |
| Basal cell carcinoma  |                    |                    |                    |
| subjects affected / exposed   | 2 / 67 (2.99%)     | 0 / 31 (0.00%)     | 0 / 18 (0.00%)     |
| occurrences (all)   | 2                  | 0                  | 0                  |
| Lipoma  |                    |                    |                    |
| subjects affected / exposed   | 1 / 67 (1.49%)     | 0 / 31 (0.00%)     | 0 / 18 (0.00%)     |
| occurrences (all)   | 1                  | 0                  | 0                  |
| Malignant melanoma  |                    |                    |                    |
| subjects affected / exposed   | 1 / 67 (1.49%)     | 0 / 31 (0.00%)     | 0 / 18 (0.00%)     |
| occurrences (all)   | 1                  | 0                  | 0                  |
| Renal neoplasm  |                    |                    |                    |
| subjects affected / exposed   | 1 / 67 (1.49%)     | 0 / 31 (0.00%)     | 0 / 18 (0.00%)     |
| occurrences (all)   | 1                  | 0                  | 0                  |
| Seborrhoeic keratosis   |                    |                    |                    |
| subjects affected / exposed   | 0 / 67 (0.00%)     | 0 / 31 (0.00%)     | 1 / 18 (5.56%)     |
| occurrences (all)   | 0                  | 0                  | 1                  |
| Skin papilloma  |                    |                    |                    |
| subjects affected / exposed   | 1 / 67 (1.49%)     | 0 / 31 (0.00%)     | 0 / 18 (0.00%)     |
| occurrences (all)   | 3                  | 0                  | 0                  |
| Squamous cell carcinoma   |                    |                    |                    |
| subjects affected / exposed   | 1 / 67 (1.49%)     | 0 / 31 (0.00%)     | 0 / 18 (0.00%)     |
| occurrences (all)   | 1                  | 0                  | 0                  |
| Squamous cell carcinoma of skin                                     |                    |                    |                    |

|  |                     |                     |                     |
|--|---------------------|---------------------|---------------------|
| subjects affected / exposed<br>occurrences (all) | 0 / 67 (0.00%)<br>0 | 1 / 31 (3.23%)<br>1 | 0 / 18 (0.00%)<br>0 |
| Vascular disorders                               |                     |                     |                     |
| Aortic stenosis                                  |                     |                     |                     |
| subjects affected / exposed                      | 2 / 67 (2.99%)      | 0 / 31 (0.00%)      | 0 / 18 (0.00%)      |
| occurrences (all)                                | 2                   | 0                   | 0                   |
| Arteriosclerosis                                 |                     |                     |                     |
| subjects affected / exposed                      | 1 / 67 (1.49%)      | 0 / 31 (0.00%)      | 0 / 18 (0.00%)      |
| occurrences (all)                                | 1                   | 0                   | 0                   |
| Deep vein thrombosis                             |                     |                     |                     |
| subjects affected / exposed                      | 2 / 67 (2.99%)      | 0 / 31 (0.00%)      | 0 / 18 (0.00%)      |
| occurrences (all)                                | 2                   | 0                   | 0                   |
| Flushing   |                     |                     |                     |
| subjects affected / exposed                      | 3 / 67 (4.48%)      | 1 / 31 (3.23%)      | 1 / 18 (5.56%)      |
| occurrences (all)                                | 4                   | 1                   | 1                   |
| Hot flush  |                     |                     |                     |
| subjects affected / exposed                      | 0 / 67 (0.00%)      | 2 / 31 (6.45%)      | 0 / 18 (0.00%)      |
| occurrences (all)                                | 0                   | 2                   | 0                   |
| Hypertension                                     |                     |                     |                     |
| subjects affected / exposed                      | 6 / 67 (8.96%)      | 3 / 31 (9.68%)      | 2 / 18 (11.11%)     |
| occurrences (all)                                | 8                   | 10                  | 8                   |
| Hypotension                                      |                     |                     |                     |
| subjects affected / exposed                      | 3 / 67 (4.48%)      | 1 / 31 (3.23%)      | 1 / 18 (5.56%)      |
| occurrences (all)                                | 3                   | 2                   | 1                   |
| Pallor   |                     |                     |                     |
| subjects affected / exposed                      | 0 / 67 (0.00%)      | 1 / 31 (3.23%)      | 0 / 18 (0.00%)      |
| occurrences (all)                                | 0                   | 1                   | 0                   |
| Thrombophlebitis                                 |                     |                     |                     |
| subjects affected / exposed                      | 0 / 67 (0.00%)      | 0 / 31 (0.00%)      | 1 / 18 (5.56%)      |
| occurrences (all)                                | 0                   | 0                   | 1                   |
| Thrombosis                                       |                     |                     |                     |
| subjects affected / exposed                      | 0 / 67 (0.00%)      | 1 / 31 (3.23%)      | 0 / 18 (0.00%)      |
| occurrences (all)                                | 0                   | 1                   | 0                   |
| Varicose vein                                    |                     |                     |                     |
| subjects affected / exposed                      | 0 / 67 (0.00%)      | 0 / 31 (0.00%)      | 1 / 18 (5.56%)      |
| occurrences (all)                                | 0                   | 0                   | 1                   |

|  |                  |                  |                 |
|--|------------------|------------------|-----------------|
| Surgical and medical procedures                      |                  |                  |                 |
| Pleurodesis  |                  |                  |                 |
| subjects affected / exposed                          | 0 / 67 (0.00%)   | 0 / 31 (0.00%)   | 1 / 18 (5.56%)  |
| occurrences (all)                                    | 0                | 0                | 1               |
| General disorders and administration site conditions |                  |                  |                 |
| Adverse drug reaction                                |                  |                  |                 |
| subjects affected / exposed                          | 0 / 67 (0.00%)   | 0 / 31 (0.00%)   | 1 / 18 (5.56%)  |
| occurrences (all)                                    | 0                | 0                | 1               |
| Asthenia   |                  |                  |                 |
| subjects affected / exposed                          | 11 / 67 (16.42%) | 4 / 31 (12.90%)  | 2 / 18 (11.11%) |
| occurrences (all)                                    | 14               | 11               | 2               |
| Axillary pain  |                  |                  |                 |
| subjects affected / exposed                          | 1 / 67 (1.49%)   | 0 / 31 (0.00%)   | 0 / 18 (0.00%)  |
| occurrences (all)                                    | 1                | 0                | 0               |
| Catheter site erythema                               |                  |                  |                 |
| subjects affected / exposed                          | 1 / 67 (1.49%)   | 0 / 31 (0.00%)   | 0 / 18 (0.00%)  |
| occurrences (all)                                    | 1                | 0                | 0               |
| Chest discomfort                                     |                  |                  |                 |
| subjects affected / exposed                          | 0 / 67 (0.00%)   | 0 / 31 (0.00%)   | 1 / 18 (5.56%)  |
| occurrences (all)                                    | 0                | 0                | 1               |
| Chills   |                  |                  |                 |
| subjects affected / exposed                          | 13 / 67 (19.40%) | 3 / 31 (9.68%)   | 0 / 18 (0.00%)  |
| occurrences (all)                                    | 19               | 3                | 0               |
| Face oedema  |                  |                  |                 |
| subjects affected / exposed                          | 0 / 67 (0.00%)   | 1 / 31 (3.23%)   | 0 / 18 (0.00%)  |
| occurrences (all)                                    | 0                | 1                | 0               |
| Fatigue  |                  |                  |                 |
| subjects affected / exposed                          | 23 / 67 (34.33%) | 12 / 31 (38.71%) | 2 / 18 (11.11%) |
| occurrences (all)                                    | 41               | 20               | 2               |
| Feeling abnormal                                     |                  |                  |                 |
| subjects affected / exposed                          | 2 / 67 (2.99%)   | 0 / 31 (0.00%)   | 0 / 18 (0.00%)  |
| occurrences (all)                                    | 3                | 0                | 0               |
| Feeling cold   |                  |                  |                 |
| subjects affected / exposed                          | 0 / 67 (0.00%)   | 1 / 31 (3.23%)   | 1 / 18 (5.56%)  |
| occurrences (all)                                    | 0                | 1                | 1               |
| Gait disturbance                                     |                  |                  |                 |



|                             |                  |                 |                 |
|-----------------------------|------------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 67 (1.49%)   | 1 / 31 (3.23%)  | 1 / 18 (5.56%)  |
| occurrences (all)           | 1                | 1               | 1               |
| Hypothermia                 |                  |                 |                 |
| subjects affected / exposed | 1 / 67 (1.49%)   | 0 / 31 (0.00%)  | 0 / 18 (0.00%)  |
| occurrences (all)           | 1                | 0               | 0               |
| Localised oedema            |                  |                 |                 |
| subjects affected / exposed | 1 / 67 (1.49%)   | 0 / 31 (0.00%)  | 0 / 18 (0.00%)  |
| occurrences (all)           | 1                | 0               | 0               |
| Malaise                     |                  |                 |                 |
| subjects affected / exposed | 2 / 67 (2.99%)   | 0 / 31 (0.00%)  | 0 / 18 (0.00%)  |
| occurrences (all)           | 2                | 0               | 0               |
| Non-cardiac chest pain      |                  |                 |                 |
| subjects affected / exposed | 2 / 67 (2.99%)   | 1 / 31 (3.23%)  | 0 / 18 (0.00%)  |
| occurrences (all)           | 2                | 1               | 0               |
| Oedema peripheral           |                  |                 |                 |
| subjects affected / exposed | 14 / 67 (20.90%) | 6 / 31 (19.35%) | 3 / 18 (16.67%) |
| occurrences (all)           | 18               | 7               | 7               |
| Peripheral swelling         |                  |                 |                 |
| subjects affected / exposed | 1 / 67 (1.49%)   | 0 / 31 (0.00%)  | 0 / 18 (0.00%)  |
| occurrences (all)           | 1                | 0               | 0               |
| Pyrexia                     |                  |                 |                 |
| subjects affected / exposed | 14 / 67 (20.90%) | 1 / 31 (3.23%)  | 4 / 18 (22.22%) |
| occurrences (all)           | 22               | 1               | 4               |
| Secretion discharge         |                  |                 |                 |
| subjects affected / exposed | 0 / 67 (0.00%)   | 0 / 31 (0.00%)  | 1 / 18 (5.56%)  |
| occurrences (all)           | 0                | 0               | 1               |
| Swelling                    |                  |                 |                 |
| subjects affected / exposed | 1 / 67 (1.49%)   | 0 / 31 (0.00%)  | 0 / 18 (0.00%)  |
| occurrences (all)           | 1                | 0               | 0               |
| Swelling face               |                  |                 |                 |
| subjects affected / exposed | 1 / 67 (1.49%)   | 0 / 31 (0.00%)  | 0 / 18 (0.00%)  |
| occurrences (all)           | 1                | 0               | 0               |
| Immune system disorders     |                  |                 |                 |
| Allergy to arthropod bite   |                  |                 |                 |
| subjects affected / exposed | 1 / 67 (1.49%)   | 0 / 31 (0.00%)  | 0 / 18 (0.00%)  |
| occurrences (all)           | 1                | 0               | 0               |

|  |                     |                     |                      |
|--|---------------------|---------------------|----------------------|
| Contrast media allergy<br>subjects affected / exposed<br>occurrences (all)       | 2 / 67 (2.99%)<br>2 | 0 / 31 (0.00%)<br>0 | 0 / 18 (0.00%)<br>0  |
| Hypogammaglobulinaemia<br>subjects affected / exposed<br>occurrences (all)       | 3 / 67 (4.48%)<br>3 | 2 / 31 (6.45%)<br>2 | 2 / 18 (11.11%)<br>2 |
| Seasonal allergy<br>subjects affected / exposed<br>occurrences (all)             | 0 / 67 (0.00%)<br>0 | 0 / 31 (0.00%)<br>0 | 1 / 18 (5.56%)<br>1  |
| Reproductive system and breast disorders   |                     |                     |                      |
| Benign prostatic hyperplasia<br>subjects affected / exposed<br>occurrences (all) | 1 / 67 (1.49%)<br>1 | 0 / 31 (0.00%)<br>0 | 0 / 18 (0.00%)<br>0  |
| Cervical dysplasia<br>subjects affected / exposed<br>occurrences (all)           | 1 / 67 (1.49%)<br>1 | 0 / 31 (0.00%)<br>0 | 0 / 18 (0.00%)<br>0  |
| Haematospermia<br>subjects affected / exposed<br>occurrences (all)               | 1 / 67 (1.49%)<br>1 | 0 / 31 (0.00%)<br>0 | 0 / 18 (0.00%)<br>0  |
| Pelvic discomfort<br>subjects affected / exposed<br>occurrences (all)            | 1 / 67 (1.49%)<br>1 | 0 / 31 (0.00%)<br>0 | 0 / 18 (0.00%)<br>0  |
| Prostatomegaly<br>subjects affected / exposed<br>occurrences (all)               | 1 / 67 (1.49%)<br>1 | 0 / 31 (0.00%)<br>0 | 0 / 18 (0.00%)<br>0  |
| Testicular oedema<br>subjects affected / exposed<br>occurrences (all)            | 0 / 67 (0.00%)<br>0 | 1 / 31 (3.23%)<br>1 | 0 / 18 (0.00%)<br>0  |
| Respiratory, thoracic and mediastinal disorders                                  |                     |                     |                      |
| Bronchospasm<br>subjects affected / exposed<br>occurrences (all)                 | 1 / 67 (1.49%)<br>1 | 0 / 31 (0.00%)<br>0 | 0 / 18 (0.00%)<br>0  |
| Choking<br>subjects affected / exposed<br>occurrences (all)                      | 1 / 67 (1.49%)<br>1 | 0 / 31 (0.00%)<br>0 | 0 / 18 (0.00%)<br>0  |
| Cough  |                     |                     |                      |

|   |                  |                 |                 |
|---|------------------|-----------------|-----------------|
| subjects affected / exposed                           | 22 / 67 (32.84%) | 5 / 31 (16.13%) | 3 / 18 (16.67%) |
| occurrences (all)                                     | 32               | 7               | 3               |
| Dysphonia   |                  |                 |                 |
| subjects affected / exposed                           | 0 / 67 (0.00%)   | 0 / 31 (0.00%)  | 2 / 18 (11.11%) |
| occurrences (all)                                     | 0                | 0               | 2               |
| Dyspnoea  |                  |                 |                 |
| subjects affected / exposed                           | 10 / 67 (14.93%) | 4 / 31 (12.90%) | 3 / 18 (16.67%) |
| occurrences (all)                                     | 14               | 5               | 3               |
| Dyspnoea exertional                                   |                  |                 |                 |
| subjects affected / exposed                           | 1 / 67 (1.49%)   | 0 / 31 (0.00%)  | 0 / 18 (0.00%)  |
| occurrences (all)                                     | 1                | 0               | 0               |
| Epistaxis   |                  |                 |                 |
| subjects affected / exposed                           | 1 / 67 (1.49%)   | 1 / 31 (3.23%)  | 1 / 18 (5.56%)  |
| occurrences (all)                                     | 1                | 1               | 1               |
| Haemoptysis   |                  |                 |                 |
| subjects affected / exposed                           | 0 / 67 (0.00%)   | 0 / 31 (0.00%)  | 1 / 18 (5.56%)  |
| occurrences (all)                                     | 0                | 0               | 1               |
| Hypercapnia   |                  |                 |                 |
| subjects affected / exposed                           | 0 / 67 (0.00%)   | 0 / 31 (0.00%)  | 1 / 18 (5.56%)  |
| occurrences (all)                                     | 0                | 0               | 1               |
| Hypoxia   |                  |                 |                 |
| subjects affected / exposed                           | 0 / 67 (0.00%)   | 0 / 31 (0.00%)  | 1 / 18 (5.56%)  |
| occurrences (all)                                     | 0                | 0               | 1               |
| Increased viscosity of upper<br>respiratory secretion |                  |                 |                 |
| subjects affected / exposed                           | 1 / 67 (1.49%)   | 0 / 31 (0.00%)  | 0 / 18 (0.00%)  |
| occurrences (all)                                     | 1                | 0               | 0               |
| Laryngeal inflammation                                |                  |                 |                 |
| subjects affected / exposed                           | 0 / 67 (0.00%)   | 1 / 31 (3.23%)  | 0 / 18 (0.00%)  |
| occurrences (all)                                     | 0                | 1               | 0               |
| Lower respiratory tract congestion                    |                  |                 |                 |
| subjects affected / exposed                           | 1 / 67 (1.49%)   | 1 / 31 (3.23%)  | 0 / 18 (0.00%)  |
| occurrences (all)                                     | 1                | 1               | 0               |
| Lung consolidation                                    |                  |                 |                 |
| subjects affected / exposed                           | 0 / 67 (0.00%)   | 0 / 31 (0.00%)  | 1 / 18 (5.56%)  |
| occurrences (all)                                     | 0                | 0               | 1               |

|                             |                |                |                 |
|-----------------------------|----------------|----------------|-----------------|
| Lung infiltration           |                |                |                 |
| subjects affected / exposed | 1 / 67 (1.49%) | 0 / 31 (0.00%) | 1 / 18 (5.56%)  |
| occurrences (all)           | 1              | 0              | 1               |
| Lung opacity                |                |                |                 |
| subjects affected / exposed | 1 / 67 (1.49%) | 0 / 31 (0.00%) | 0 / 18 (0.00%)  |
| occurrences (all)           | 1              | 0              | 0               |
| Nasal congestion            |                |                |                 |
| subjects affected / exposed | 4 / 67 (5.97%) | 2 / 31 (6.45%) | 0 / 18 (0.00%)  |
| occurrences (all)           | 4              | 2              | 0               |
| Oropharyngeal pain          |                |                |                 |
| subjects affected / exposed | 2 / 67 (2.99%) | 1 / 31 (3.23%) | 0 / 18 (0.00%)  |
| occurrences (all)           | 3              | 1              | 0               |
| Paranasal sinus discomfort  |                |                |                 |
| subjects affected / exposed | 1 / 67 (1.49%) | 0 / 31 (0.00%) | 0 / 18 (0.00%)  |
| occurrences (all)           | 1              | 0              | 0               |
| Pleural effusion            |                |                |                 |
| subjects affected / exposed | 1 / 67 (1.49%) | 0 / 31 (0.00%) | 0 / 18 (0.00%)  |
| occurrences (all)           | 1              | 0              | 0               |
| Pneumonitis                 |                |                |                 |
| subjects affected / exposed | 2 / 67 (2.99%) | 1 / 31 (3.23%) | 2 / 18 (11.11%) |
| occurrences (all)           | 3              | 1              | 4               |
| Pneumothorax                |                |                |                 |
| subjects affected / exposed | 0 / 67 (0.00%) | 0 / 31 (0.00%) | 1 / 18 (5.56%)  |
| occurrences (all)           | 0              | 0              | 1               |
| Productive cough            |                |                |                 |
| subjects affected / exposed | 5 / 67 (7.46%) | 2 / 31 (6.45%) | 0 / 18 (0.00%)  |
| occurrences (all)           | 8              | 3              | 0               |
| Pulmonary embolism          |                |                |                 |
| subjects affected / exposed | 0 / 67 (0.00%) | 0 / 31 (0.00%) | 1 / 18 (5.56%)  |
| occurrences (all)           | 0              | 0              | 1               |
| Pulmonary oedema            |                |                |                 |
| subjects affected / exposed | 0 / 67 (0.00%) | 1 / 31 (3.23%) | 0 / 18 (0.00%)  |
| occurrences (all)           | 0              | 1              | 0               |
| Rales                       |                |                |                 |
| subjects affected / exposed | 2 / 67 (2.99%) | 0 / 31 (0.00%) | 0 / 18 (0.00%)  |
| occurrences (all)           | 4              | 0              | 0               |

|  |                     |                     |                     |
|--|---------------------|---------------------|---------------------|
| Respiratory tract congestion<br>subjects affected / exposed<br>occurrences (all)   | 1 / 67 (1.49%)<br>1 | 0 / 31 (0.00%)<br>0 | 0 / 18 (0.00%)<br>0 |
| Respiratory tract inflammation<br>subjects affected / exposed<br>occurrences (all) | 1 / 67 (1.49%)<br>1 | 0 / 31 (0.00%)<br>0 | 0 / 18 (0.00%)<br>0 |
| Respiratory tract irritation<br>subjects affected / exposed<br>occurrences (all)   | 2 / 67 (2.99%)<br>2 | 0 / 31 (0.00%)<br>0 | 0 / 18 (0.00%)<br>0 |
| Rhinitis allergic<br>subjects affected / exposed<br>occurrences (all)              | 5 / 67 (7.46%)<br>5 | 2 / 31 (6.45%)<br>2 | 1 / 18 (5.56%)<br>2 |
| Rhinorrhoea<br>subjects affected / exposed<br>occurrences (all)                    | 1 / 67 (1.49%)<br>1 | 0 / 31 (0.00%)<br>0 | 0 / 18 (0.00%)<br>0 |
| Sinus congestion<br>subjects affected / exposed<br>occurrences (all)               | 1 / 67 (1.49%)<br>2 | 0 / 31 (0.00%)<br>0 | 0 / 18 (0.00%)<br>0 |
| Sleep apnoea syndrome<br>subjects affected / exposed<br>occurrences (all)          | 1 / 67 (1.49%)<br>1 | 0 / 31 (0.00%)<br>0 | 0 / 18 (0.00%)<br>0 |
| Throat irritation<br>subjects affected / exposed<br>occurrences (all)              | 1 / 67 (1.49%)<br>1 | 0 / 31 (0.00%)<br>0 | 0 / 18 (0.00%)<br>0 |
| Throat tightness<br>subjects affected / exposed<br>occurrences (all)               | 1 / 67 (1.49%)<br>1 | 0 / 31 (0.00%)<br>0 | 0 / 18 (0.00%)<br>0 |
| Tracheomalacia<br>subjects affected / exposed<br>occurrences (all)                 | 1 / 67 (1.49%)<br>1 | 0 / 31 (0.00%)<br>0 | 0 / 18 (0.00%)<br>0 |
| Upper-airway cough syndrome<br>subjects affected / exposed<br>occurrences (all)    | 3 / 67 (4.48%)<br>4 | 1 / 31 (3.23%)<br>1 | 1 / 18 (5.56%)<br>1 |
| Wheezing<br>subjects affected / exposed<br>occurrences (all)                       | 1 / 67 (1.49%)<br>1 | 2 / 31 (6.45%)<br>2 | 1 / 18 (5.56%)<br>1 |

|                             |                  |                 |                 |
|-----------------------------|------------------|-----------------|-----------------|
| Psychiatric disorders       |                  |                 |                 |
| Abnormal dreams             |                  |                 |                 |
| subjects affected / exposed | 1 / 67 (1.49%)   | 0 / 31 (0.00%)  | 0 / 18 (0.00%)  |
| occurrences (all)           | 1                | 0               | 0               |
| Agitation                   |                  |                 |                 |
| subjects affected / exposed | 1 / 67 (1.49%)   | 0 / 31 (0.00%)  | 0 / 18 (0.00%)  |
| occurrences (all)           | 1                | 0               | 0               |
| Anxiety                     |                  |                 |                 |
| subjects affected / exposed | 7 / 67 (10.45%)  | 3 / 31 (9.68%)  | 0 / 18 (0.00%)  |
| occurrences (all)           | 8                | 3               | 0               |
| Confusional state           |                  |                 |                 |
| subjects affected / exposed | 6 / 67 (8.96%)   | 1 / 31 (3.23%)  | 0 / 18 (0.00%)  |
| occurrences (all)           | 6                | 4               | 0               |
| Delirium                    |                  |                 |                 |
| subjects affected / exposed | 1 / 67 (1.49%)   | 0 / 31 (0.00%)  | 0 / 18 (0.00%)  |
| occurrences (all)           | 1                | 0               | 0               |
| Depression                  |                  |                 |                 |
| subjects affected / exposed | 1 / 67 (1.49%)   | 1 / 31 (3.23%)  | 1 / 18 (5.56%)  |
| occurrences (all)           | 1                | 1               | 1               |
| Hallucination               |                  |                 |                 |
| subjects affected / exposed | 1 / 67 (1.49%)   | 0 / 31 (0.00%)  | 0 / 18 (0.00%)  |
| occurrences (all)           | 1                | 0               | 0               |
| Insomnia                    |                  |                 |                 |
| subjects affected / exposed | 16 / 67 (23.88%) | 5 / 31 (16.13%) | 3 / 18 (16.67%) |
| occurrences (all)           | 19               | 5               | 4               |
| Mental status changes       |                  |                 |                 |
| subjects affected / exposed | 0 / 67 (0.00%)   | 0 / 31 (0.00%)  | 1 / 18 (5.56%)  |
| occurrences (all)           | 0                | 0               | 1               |
| Mood altered                |                  |                 |                 |
| subjects affected / exposed | 0 / 67 (0.00%)   | 0 / 31 (0.00%)  | 1 / 18 (5.56%)  |
| occurrences (all)           | 0                | 0               | 1               |
| Personality change          |                  |                 |                 |
| subjects affected / exposed | 1 / 67 (1.49%)   | 0 / 31 (0.00%)  | 0 / 18 (0.00%)  |
| occurrences (all)           | 1                | 0               | 0               |
| Restlessness                |                  |                 |                 |

|                                       |                  |                 |                 |
|---------------------------------------|------------------|-----------------|-----------------|
| subjects affected / exposed           | 1 / 67 (1.49%)   | 0 / 31 (0.00%)  | 0 / 18 (0.00%)  |
| occurrences (all)                     | 1                | 0               | 0               |
| Somatic symptom disorder              |                  |                 |                 |
| subjects affected / exposed           | 0 / 67 (0.00%)   | 0 / 31 (0.00%)  | 1 / 18 (5.56%)  |
| occurrences (all)                     | 0                | 0               | 3               |
| Investigations                        |                  |                 |                 |
| Alanine aminotransferase increased    |                  |                 |                 |
| subjects affected / exposed           | 15 / 67 (22.39%) | 6 / 31 (19.35%) | 3 / 18 (16.67%) |
| occurrences (all)                     | 25               | 16              | 9               |
| Aspartate aminotransferase increased  |                  |                 |                 |
| subjects affected / exposed           | 15 / 67 (22.39%) | 4 / 31 (12.90%) | 2 / 18 (11.11%) |
| occurrences (all)                     | 24               | 11              | 2               |
| Blood alkaline phosphatase increased  |                  |                 |                 |
| subjects affected / exposed           | 7 / 67 (10.45%)  | 0 / 31 (0.00%)  | 1 / 18 (5.56%)  |
| occurrences (all)                     | 11               | 0               | 1               |
| Blood bicarbonate decreased           |                  |                 |                 |
| subjects affected / exposed           | 0 / 67 (0.00%)   | 1 / 31 (3.23%)  | 0 / 18 (0.00%)  |
| occurrences (all)                     | 0                | 1               | 0               |
| Blood bilirubin increased             |                  |                 |                 |
| subjects affected / exposed           | 3 / 67 (4.48%)   | 3 / 31 (9.68%)  | 0 / 18 (0.00%)  |
| occurrences (all)                     | 3                | 3               | 0               |
| Blood creatine increased              |                  |                 |                 |
| subjects affected / exposed           | 6 / 67 (8.96%)   | 3 / 31 (9.68%)  | 0 / 18 (0.00%)  |
| occurrences (all)                     | 10               | 6               | 0               |
| Blood lactate dehydrogenase increased |                  |                 |                 |
| subjects affected / exposed           | 1 / 67 (1.49%)   | 1 / 31 (3.23%)  | 1 / 18 (5.56%)  |
| occurrences (all)                     | 1                | 1               | 1               |
| Blood potassium decreased             |                  |                 |                 |
| subjects affected / exposed           | 0 / 67 (0.00%)   | 1 / 31 (3.23%)  | 1 / 18 (5.56%)  |
| occurrences (all)                     | 0                | 1               | 1               |
| Blood pressure increased              |                  |                 |                 |
| subjects affected / exposed           | 1 / 67 (1.49%)   | 1 / 31 (3.23%)  | 0 / 18 (0.00%)  |
| occurrences (all)                     | 1                | 2               | 0               |
| Blood sodium decreased                |                  |                 |                 |

|                                      |                |                |                 |
|--------------------------------------|----------------|----------------|-----------------|
| subjects affected / exposed          | 1 / 67 (1.49%) | 0 / 31 (0.00%) | 0 / 18 (0.00%)  |
| occurrences (all)                    | 8              | 0              | 0               |
| Blood urea increased                 |                |                |                 |
| subjects affected / exposed          | 1 / 67 (1.49%) | 0 / 31 (0.00%) | 0 / 18 (0.00%)  |
| occurrences (all)                    | 2              | 0              | 0               |
| Blood uric acid increased            |                |                |                 |
| subjects affected / exposed          | 0 / 67 (0.00%) | 2 / 31 (6.45%) | 0 / 18 (0.00%)  |
| occurrences (all)                    | 0              | 2              | 0               |
| Blood urine present                  |                |                |                 |
| subjects affected / exposed          | 0 / 67 (0.00%) | 1 / 31 (3.23%) | 0 / 18 (0.00%)  |
| occurrences (all)                    | 0              | 1              | 0               |
| Cardiac murmur                       |                |                |                 |
| subjects affected / exposed          | 2 / 67 (2.99%) | 0 / 31 (0.00%) | 0 / 18 (0.00%)  |
| occurrences (all)                    | 2              | 0              | 0               |
| Gamma-glutamyltransferase increased  |                |                |                 |
| subjects affected / exposed          | 2 / 67 (2.99%) | 0 / 31 (0.00%) | 0 / 18 (0.00%)  |
| occurrences (all)                    | 3              | 0              | 0               |
| Glomerular filtration rate decreased |                |                |                 |
| subjects affected / exposed          | 1 / 67 (1.49%) | 0 / 31 (0.00%) | 0 / 18 (0.00%)  |
| occurrences (all)                    | 1              | 0              | 0               |
| Haematocrit increased                |                |                |                 |
| subjects affected / exposed          | 1 / 67 (1.49%) | 0 / 31 (0.00%) | 0 / 18 (0.00%)  |
| occurrences (all)                    | 1              | 0              | 0               |
| Haemoglobin decreased                |                |                |                 |
| subjects affected / exposed          | 0 / 67 (0.00%) | 0 / 31 (0.00%) | 1 / 18 (5.56%)  |
| occurrences (all)                    | 0              | 0              | 5               |
| Lymphocyte count decreased           |                |                |                 |
| subjects affected / exposed          | 0 / 67 (0.00%) | 2 / 31 (6.45%) | 2 / 18 (11.11%) |
| occurrences (all)                    | 0              | 4              | 4               |
| Lymphocyte count increased           |                |                |                 |
| subjects affected / exposed          | 3 / 67 (4.48%) | 0 / 31 (0.00%) | 1 / 18 (5.56%)  |
| occurrences (all)                    | 4              | 0              | 1               |
| Monocyte percentage decreased        |                |                |                 |
| subjects affected / exposed          | 0 / 67 (0.00%) | 1 / 31 (3.23%) | 0 / 18 (0.00%)  |
| occurrences (all)                    | 0              | 1              | 0               |



|  |                      |                      |                       |
|--|----------------------|----------------------|-----------------------|
| Neutrophil count decreased<br>subjects affected / exposed<br>occurrences (all)           | 3 / 67 (4.48%)<br>36 | 3 / 31 (9.68%)<br>4  | 5 / 18 (27.78%)<br>13 |
| Neutrophil percentage decreased<br>subjects affected / exposed<br>occurrences (all)      | 0 / 67 (0.00%)<br>0  | 1 / 31 (3.23%)<br>1  | 0 / 18 (0.00%)<br>0   |
| Platelet count decreased<br>subjects affected / exposed<br>occurrences (all)             | 5 / 67 (7.46%)<br>11 | 2 / 31 (6.45%)<br>3  | 2 / 18 (11.11%)<br>5  |
| Prostatic specific antigen increased<br>subjects affected / exposed<br>occurrences (all) | 1 / 67 (1.49%)<br>1  | 0 / 31 (0.00%)<br>0  | 0 / 18 (0.00%)<br>0   |
| SARS-CoV-2 test positive<br>subjects affected / exposed<br>occurrences (all)             | 1 / 67 (1.49%)<br>1  | 0 / 31 (0.00%)<br>0  | 0 / 18 (0.00%)<br>0   |
| Urine output decreased<br>subjects affected / exposed<br>occurrences (all)               | 0 / 67 (0.00%)<br>0  | 1 / 31 (3.23%)<br>1  | 0 / 18 (0.00%)<br>0   |
| Weight decreased<br>subjects affected / exposed<br>occurrences (all)                     | 6 / 67 (8.96%)<br>7  | 4 / 31 (12.90%)<br>7 | 2 / 18 (11.11%)<br>2  |
| Weight increased<br>subjects affected / exposed<br>occurrences (all)                     | 1 / 67 (1.49%)<br>1  | 0 / 31 (0.00%)<br>0  | 0 / 18 (0.00%)<br>0   |
| White blood cell count decreased<br>subjects affected / exposed<br>occurrences (all)     | 3 / 67 (4.48%)<br>3  | 2 / 31 (6.45%)<br>6  | 2 / 18 (11.11%)<br>5  |
| White blood cell count increased<br>subjects affected / exposed<br>occurrences (all)     | 1 / 67 (1.49%)<br>1  | 0 / 31 (0.00%)<br>0  | 1 / 18 (5.56%)<br>1   |
| Injury, poisoning and procedural complications   |                      |                      |                       |
| Contusion<br>subjects affected / exposed<br>occurrences (all)                            | 6 / 67 (8.96%)<br>6  | 2 / 31 (6.45%)<br>3  | 1 / 18 (5.56%)<br>2   |
| Fall   |                      |                      |                       |

|                             |                  |                 |                 |
|-----------------------------|------------------|-----------------|-----------------|
| subjects affected / exposed | 4 / 67 (5.97%)   | 1 / 31 (3.23%)  | 0 / 18 (0.00%)  |
| occurrences (all)           | 7                | 1               | 0               |
| Fracture                    |                  |                 |                 |
| subjects affected / exposed | 1 / 67 (1.49%)   | 0 / 31 (0.00%)  | 0 / 18 (0.00%)  |
| occurrences (all)           | 1                | 0               | 0               |
| Incision site pain          |                  |                 |                 |
| subjects affected / exposed | 0 / 67 (0.00%)   | 0 / 31 (0.00%)  | 1 / 18 (5.56%)  |
| occurrences (all)           | 0                | 0               | 1               |
| Infusion related reaction   |                  |                 |                 |
| subjects affected / exposed | 15 / 67 (22.39%) | 5 / 31 (16.13%) | 9 / 18 (50.00%) |
| occurrences (all)           | 21               | 7               | 10              |
| Limb injury                 |                  |                 |                 |
| subjects affected / exposed | 1 / 67 (1.49%)   | 0 / 31 (0.00%)  | 0 / 18 (0.00%)  |
| occurrences (all)           | 2                | 0               | 0               |
| Muscle strain               |                  |                 |                 |
| subjects affected / exposed | 0 / 67 (0.00%)   | 1 / 31 (3.23%)  | 0 / 18 (0.00%)  |
| occurrences (all)           | 0                | 1               | 0               |
| Overdose                    |                  |                 |                 |
| subjects affected / exposed | 0 / 67 (0.00%)   | 1 / 31 (3.23%)  | 0 / 18 (0.00%)  |
| occurrences (all)           | 0                | 1               | 0               |
| Post procedural haemorrhage |                  |                 |                 |
| subjects affected / exposed | 1 / 67 (1.49%)   | 0 / 31 (0.00%)  | 0 / 18 (0.00%)  |
| occurrences (all)           | 1                | 0               | 0               |
| Skin abrasion               |                  |                 |                 |
| subjects affected / exposed | 0 / 67 (0.00%)   | 1 / 31 (3.23%)  | 0 / 18 (0.00%)  |
| occurrences (all)           | 0                | 1               | 0               |
| Skin laceration             |                  |                 |                 |
| subjects affected / exposed | 3 / 67 (4.48%)   | 1 / 31 (3.23%)  | 0 / 18 (0.00%)  |
| occurrences (all)           | 3                | 1               | 0               |
| Skin wound                  |                  |                 |                 |
| subjects affected / exposed | 1 / 67 (1.49%)   | 0 / 31 (0.00%)  | 0 / 18 (0.00%)  |
| occurrences (all)           | 1                | 0               | 0               |
| Spinal compression fracture |                  |                 |                 |
| subjects affected / exposed | 1 / 67 (1.49%)   | 1 / 31 (3.23%)  | 0 / 18 (0.00%)  |
| occurrences (all)           | 1                | 1               | 0               |
| Upper limb fracture         |                  |                 |                 |

|  |                |                |                |
|--|----------------|----------------|----------------|
| subjects affected / exposed                | 1 / 67 (1.49%) | 0 / 31 (0.00%) | 0 / 18 (0.00%) |
| occurrences (all)                          | 1              | 0              | 0              |
| Vaccination complication                   |                |                |                |
| subjects affected / exposed                | 1 / 67 (1.49%) | 0 / 31 (0.00%) | 0 / 18 (0.00%) |
| occurrences (all)                          | 1              | 0              | 0              |
| Wound                                      |                |                |                |
| subjects affected / exposed                | 1 / 67 (1.49%) | 0 / 31 (0.00%) | 0 / 18 (0.00%) |
| occurrences (all)                          | 1              | 0              | 0              |
| Wrist fracture                             |                |                |                |
| subjects affected / exposed                | 1 / 67 (1.49%) | 0 / 31 (0.00%) | 0 / 18 (0.00%) |
| occurrences (all)                          | 1              | 0              | 0              |
| Congenital, familial and genetic disorders |                |                |                |
| Hydrocele                                  |                |                |                |
| subjects affected / exposed                | 1 / 67 (1.49%) | 0 / 31 (0.00%) | 0 / 18 (0.00%) |
| occurrences (all)                          | 1              | 0              | 0              |
| Cardiac disorders                          |                |                |                |
| Angina pectoris                            |                |                |                |
| subjects affected / exposed                | 0 / 67 (0.00%) | 0 / 31 (0.00%) | 1 / 18 (5.56%) |
| occurrences (all)                          | 0              | 0              | 1              |
| Atrial fibrillation                        |                |                |                |
| subjects affected / exposed                | 2 / 67 (2.99%) | 1 / 31 (3.23%) | 0 / 18 (0.00%) |
| occurrences (all)                          | 3              | 1              | 0              |
| Atrial flutter                             |                |                |                |
| subjects affected / exposed                | 1 / 67 (1.49%) | 0 / 31 (0.00%) | 0 / 18 (0.00%) |
| occurrences (all)                          | 2              | 0              | 0              |
| Bradycardia                                |                |                |                |
| subjects affected / exposed                | 0 / 67 (0.00%) | 0 / 31 (0.00%) | 1 / 18 (5.56%) |
| occurrences (all)                          | 0              | 0              | 1              |
| Cardiac failure chronic                    |                |                |                |
| subjects affected / exposed                | 1 / 67 (1.49%) | 0 / 31 (0.00%) | 0 / 18 (0.00%) |
| occurrences (all)                          | 1              | 0              | 0              |
| Myocardial infarction                      |                |                |                |
| subjects affected / exposed                | 1 / 67 (1.49%) | 0 / 31 (0.00%) | 0 / 18 (0.00%) |
| occurrences (all)                          | 1              | 0              | 0              |
| Palpitations                               |                |                |                |

|                             |                  |                |                |
|-----------------------------|------------------|----------------|----------------|
| subjects affected / exposed | 0 / 67 (0.00%)   | 0 / 31 (0.00%) | 1 / 18 (5.56%) |
| occurrences (all)           | 0                | 0              | 1              |
| Pericardial effusion        |                  |                |                |
| subjects affected / exposed | 1 / 67 (1.49%)   | 0 / 31 (0.00%) | 0 / 18 (0.00%) |
| occurrences (all)           | 1                | 0              | 0              |
| Tachyarrhythmia             |                  |                |                |
| subjects affected / exposed | 0 / 67 (0.00%)   | 1 / 31 (3.23%) | 0 / 18 (0.00%) |
| occurrences (all)           | 0                | 1              | 0              |
| Tachycardia                 |                  |                |                |
| subjects affected / exposed | 1 / 67 (1.49%)   | 2 / 31 (6.45%) | 0 / 18 (0.00%) |
| occurrences (all)           | 1                | 3              | 0              |
| Nervous system disorders    |                  |                |                |
| Ataxia                      |                  |                |                |
| subjects affected / exposed | 1 / 67 (1.49%)   | 0 / 31 (0.00%) | 0 / 18 (0.00%) |
| occurrences (all)           | 1                | 0              | 0              |
| Carpal tunnel syndrome      |                  |                |                |
| subjects affected / exposed | 0 / 67 (0.00%)   | 1 / 31 (3.23%) | 0 / 18 (0.00%) |
| occurrences (all)           | 0                | 1              | 0              |
| Cognitive disorder          |                  |                |                |
| subjects affected / exposed | 0 / 67 (0.00%)   | 1 / 31 (3.23%) | 0 / 18 (0.00%) |
| occurrences (all)           | 0                | 1              | 0              |
| Dementia                    |                  |                |                |
| subjects affected / exposed | 2 / 67 (2.99%)   | 0 / 31 (0.00%) | 0 / 18 (0.00%) |
| occurrences (all)           | 2                | 0              | 0              |
| Disturbance in attention    |                  |                |                |
| subjects affected / exposed | 0 / 67 (0.00%)   | 1 / 31 (3.23%) | 0 / 18 (0.00%) |
| occurrences (all)           | 0                | 1              | 0              |
| Dizziness                   |                  |                |                |
| subjects affected / exposed | 12 / 67 (17.91%) | 2 / 31 (6.45%) | 1 / 18 (5.56%) |
| occurrences (all)           | 18               | 3              | 1              |
| Drooling                    |                  |                |                |
| subjects affected / exposed | 1 / 67 (1.49%)   | 0 / 31 (0.00%) | 0 / 18 (0.00%) |
| occurrences (all)           | 1                | 0              | 0              |
| Dysaesthesia                |                  |                |                |
| subjects affected / exposed | 1 / 67 (1.49%)   | 0 / 31 (0.00%) | 0 / 18 (0.00%) |
| occurrences (all)           | 1                | 0              | 0              |

|                               |                  |                 |                 |
|-------------------------------|------------------|-----------------|-----------------|
| Dysgeusia                     |                  |                 |                 |
| subjects affected / exposed   | 3 / 67 (4.48%)   | 4 / 31 (12.90%) | 0 / 18 (0.00%)  |
| occurrences (all)             | 3                | 7               | 0               |
| Encephalopathy                |                  |                 |                 |
| subjects affected / exposed   | 0 / 67 (0.00%)   | 0 / 31 (0.00%)  | 1 / 18 (5.56%)  |
| occurrences (all)             | 0                | 0               | 1               |
| Essential tremor              |                  |                 |                 |
| subjects affected / exposed   | 1 / 67 (1.49%)   | 0 / 31 (0.00%)  | 0 / 18 (0.00%)  |
| occurrences (all)             | 2                | 0               | 0               |
| Head discomfort               |                  |                 |                 |
| subjects affected / exposed   | 0 / 67 (0.00%)   | 0 / 31 (0.00%)  | 1 / 18 (5.56%)  |
| occurrences (all)             | 0                | 0               | 1               |
| Headache                      |                  |                 |                 |
| subjects affected / exposed   | 10 / 67 (14.93%) | 2 / 31 (6.45%)  | 1 / 18 (5.56%)  |
| occurrences (all)             | 16               | 2               | 1               |
| Hyperaesthesia                |                  |                 |                 |
| subjects affected / exposed   | 1 / 67 (1.49%)   | 0 / 31 (0.00%)  | 0 / 18 (0.00%)  |
| occurrences (all)             | 1                | 0               | 0               |
| Hypoaesthesia                 |                  |                 |                 |
| subjects affected / exposed   | 3 / 67 (4.48%)   | 1 / 31 (3.23%)  | 2 / 18 (11.11%) |
| occurrences (all)             | 5                | 1               | 3               |
| Memory impairment             |                  |                 |                 |
| subjects affected / exposed   | 2 / 67 (2.99%)   | 1 / 31 (3.23%)  | 0 / 18 (0.00%)  |
| occurrences (all)             | 2                | 1               | 0               |
| Myoclonus                     |                  |                 |                 |
| subjects affected / exposed   | 1 / 67 (1.49%)   | 0 / 31 (0.00%)  | 0 / 18 (0.00%)  |
| occurrences (all)             | 1                | 0               | 0               |
| Nervous system disorder       |                  |                 |                 |
| subjects affected / exposed   | 1 / 67 (1.49%)   | 0 / 31 (0.00%)  | 0 / 18 (0.00%)  |
| occurrences (all)             | 1                | 0               | 0               |
| Neuropathy peripheral         |                  |                 |                 |
| subjects affected / exposed   | 1 / 67 (1.49%)   | 0 / 31 (0.00%)  | 0 / 18 (0.00%)  |
| occurrences (all)             | 1                | 0               | 0               |
| Peripheral sensory neuropathy |                  |                 |                 |
| subjects affected / exposed   | 0 / 67 (0.00%)   | 0 / 31 (0.00%)  | 1 / 18 (5.56%)  |
| occurrences (all)             | 0                | 0               | 1               |

|                                      |                 |                |                |
|--------------------------------------|-----------------|----------------|----------------|
| Restless legs syndrome               |                 |                |                |
| subjects affected / exposed          | 1 / 67 (1.49%)  | 0 / 31 (0.00%) | 0 / 18 (0.00%) |
| occurrences (all)                    | 1               | 0              | 0              |
| Sciatica                             |                 |                |                |
| subjects affected / exposed          | 2 / 67 (2.99%)  | 0 / 31 (0.00%) | 0 / 18 (0.00%) |
| occurrences (all)                    | 3               | 0              | 0              |
| Seizure                              |                 |                |                |
| subjects affected / exposed          | 1 / 67 (1.49%)  | 0 / 31 (0.00%) | 0 / 18 (0.00%) |
| occurrences (all)                    | 3               | 0              | 0              |
| Slow speech                          |                 |                |                |
| subjects affected / exposed          | 0 / 67 (0.00%)  | 0 / 31 (0.00%) | 1 / 18 (5.56%) |
| occurrences (all)                    | 0               | 0              | 1              |
| Somnolence                           |                 |                |                |
| subjects affected / exposed          | 3 / 67 (4.48%)  | 0 / 31 (0.00%) | 0 / 18 (0.00%) |
| occurrences (all)                    | 3               | 0              | 0              |
| Syncope                              |                 |                |                |
| subjects affected / exposed          | 1 / 67 (1.49%)  | 0 / 31 (0.00%) | 0 / 18 (0.00%) |
| occurrences (all)                    | 1               | 0              | 0              |
| Tremor                               |                 |                |                |
| subjects affected / exposed          | 8 / 67 (11.94%) | 1 / 31 (3.23%) | 0 / 18 (0.00%) |
| occurrences (all)                    | 9               | 1              | 0              |
| Blood and lymphatic system disorders |                 |                |                |
| Anaemia                              |                 |                |                |
| subjects affected / exposed          | 8 / 67 (11.94%) | 3 / 31 (9.68%) | 1 / 18 (5.56%) |
| occurrences (all)                    | 18              | 3              | 3              |
| Febrile neutropenia                  |                 |                |                |
| subjects affected / exposed          | 1 / 67 (1.49%)  | 0 / 31 (0.00%) | 0 / 18 (0.00%) |
| occurrences (all)                    | 1               | 0              | 0              |
| Increased tendency to bruise         |                 |                |                |
| subjects affected / exposed          | 1 / 67 (1.49%)  | 0 / 31 (0.00%) | 0 / 18 (0.00%) |
| occurrences (all)                    | 1               | 0              | 0              |
| Iron deficiency anaemia              |                 |                |                |
| subjects affected / exposed          | 2 / 67 (2.99%)  | 1 / 31 (3.23%) | 0 / 18 (0.00%) |
| occurrences (all)                    | 7               | 1              | 0              |
| Leukocytosis                         |                 |                |                |

|                             |                  |                 |                 |
|-----------------------------|------------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 67 (1.49%)   | 0 / 31 (0.00%)  | 0 / 18 (0.00%)  |
| occurrences (all)           | 2                | 0               | 0               |
| Lymphocytosis               |                  |                 |                 |
| subjects affected / exposed | 0 / 67 (0.00%)   | 1 / 31 (3.23%)  | 0 / 18 (0.00%)  |
| occurrences (all)           | 0                | 1               | 0               |
| Neutropenia                 |                  |                 |                 |
| subjects affected / exposed | 17 / 67 (25.37%) | 6 / 31 (19.35%) | 6 / 18 (33.33%) |
| occurrences (all)           | 55               | 10              | 10              |
| Thrombocytopenia            |                  |                 |                 |
| subjects affected / exposed | 4 / 67 (5.97%)   | 0 / 31 (0.00%)  | 2 / 18 (11.11%) |
| occurrences (all)           | 5                | 0               | 3               |
| Ear and labyrinth disorders |                  |                 |                 |
| Deafness                    |                  |                 |                 |
| subjects affected / exposed | 1 / 67 (1.49%)   | 0 / 31 (0.00%)  | 0 / 18 (0.00%)  |
| occurrences (all)           | 1                | 0               | 0               |
| Deafness bilateral          |                  |                 |                 |
| subjects affected / exposed | 0 / 67 (0.00%)   | 1 / 31 (3.23%)  | 0 / 18 (0.00%)  |
| occurrences (all)           | 0                | 2               | 0               |
| Deafness unilateral         |                  |                 |                 |
| subjects affected / exposed | 1 / 67 (1.49%)   | 0 / 31 (0.00%)  | 0 / 18 (0.00%)  |
| occurrences (all)           | 3                | 0               | 0               |
| Ear pain                    |                  |                 |                 |
| subjects affected / exposed | 1 / 67 (1.49%)   | 1 / 31 (3.23%)  | 0 / 18 (0.00%)  |
| occurrences (all)           | 1                | 1               | 0               |
| Hyperacusis                 |                  |                 |                 |
| subjects affected / exposed | 1 / 67 (1.49%)   | 0 / 31 (0.00%)  | 0 / 18 (0.00%)  |
| occurrences (all)           | 1                | 0               | 0               |
| Hypoacusis                  |                  |                 |                 |
| subjects affected / exposed | 0 / 67 (0.00%)   | 0 / 31 (0.00%)  | 1 / 18 (5.56%)  |
| occurrences (all)           | 0                | 0               | 1               |
| Inner ear inflammation      |                  |                 |                 |
| subjects affected / exposed | 0 / 67 (0.00%)   | 1 / 31 (3.23%)  | 0 / 18 (0.00%)  |
| occurrences (all)           | 0                | 1               | 0               |
| Meniere's disease           |                  |                 |                 |
| subjects affected / exposed | 1 / 67 (1.49%)   | 0 / 31 (0.00%)  | 0 / 18 (0.00%)  |
| occurrences (all)           | 1                | 0               | 0               |

|  |                     |                     |                     |
|--|---------------------|---------------------|---------------------|
| Middle ear inflammation<br>subjects affected / exposed<br>occurrences (all)          | 1 / 67 (1.49%)<br>1 | 0 / 31 (0.00%)<br>0 | 0 / 18 (0.00%)<br>0 |
| Tinnitus<br>subjects affected / exposed<br>occurrences (all)                         | 3 / 67 (4.48%)<br>3 | 0 / 31 (0.00%)<br>0 | 1 / 18 (5.56%)<br>1 |
| Vertigo<br>subjects affected / exposed<br>occurrences (all)                          | 0 / 67 (0.00%)<br>0 | 2 / 31 (6.45%)<br>2 | 0 / 18 (0.00%)<br>0 |
| Vertigo positional<br>subjects affected / exposed<br>occurrences (all)               | 1 / 67 (1.49%)<br>1 | 0 / 31 (0.00%)<br>0 | 0 / 18 (0.00%)<br>0 |
| Eye disorders  |                     |                     |                     |
| Age-related macular degeneration<br>subjects affected / exposed<br>occurrences (all) | 1 / 67 (1.49%)<br>1 | 0 / 31 (0.00%)<br>0 | 0 / 18 (0.00%)<br>0 |
| Blepharitis<br>subjects affected / exposed<br>occurrences (all)                      | 0 / 67 (0.00%)<br>0 | 0 / 31 (0.00%)<br>0 | 1 / 18 (5.56%)<br>1 |
| Chalazion<br>subjects affected / exposed<br>occurrences (all)                        | 1 / 67 (1.49%)<br>1 | 0 / 31 (0.00%)<br>0 | 0 / 18 (0.00%)<br>0 |
| Conjunctival haemorrhage<br>subjects affected / exposed<br>occurrences (all)         | 1 / 67 (1.49%)<br>1 | 1 / 31 (3.23%)<br>2 | 0 / 18 (0.00%)<br>0 |
| Dry eye<br>subjects affected / exposed<br>occurrences (all)                          | 3 / 67 (4.48%)<br>4 | 0 / 31 (0.00%)<br>0 | 0 / 18 (0.00%)<br>0 |
| Eye irritation<br>subjects affected / exposed<br>occurrences (all)                   | 1 / 67 (1.49%)<br>1 | 0 / 31 (0.00%)<br>0 | 0 / 18 (0.00%)<br>0 |
| Eye swelling<br>subjects affected / exposed<br>occurrences (all)                     | 1 / 67 (1.49%)<br>1 | 0 / 31 (0.00%)<br>0 | 0 / 18 (0.00%)<br>0 |
| Lacrimation increased  |                     |                     |                     |



|                             |                  |                 |                 |
|-----------------------------|------------------|-----------------|-----------------|
| subjects affected / exposed | 2 / 67 (2.99%)   | 1 / 31 (3.23%)  | 0 / 18 (0.00%)  |
| occurrences (all)           | 2                | 1               | 0               |
| Ocular hyperaemia           |                  |                 |                 |
| subjects affected / exposed | 1 / 67 (1.49%)   | 0 / 31 (0.00%)  | 0 / 18 (0.00%)  |
| occurrences (all)           | 1                | 0               | 0               |
| Vision blurred              |                  |                 |                 |
| subjects affected / exposed | 3 / 67 (4.48%)   | 1 / 31 (3.23%)  | 0 / 18 (0.00%)  |
| occurrences (all)           | 3                | 1               | 0               |
| Visual brightness           |                  |                 |                 |
| subjects affected / exposed | 1 / 67 (1.49%)   | 0 / 31 (0.00%)  | 0 / 18 (0.00%)  |
| occurrences (all)           | 1                | 0               | 0               |
| Gastrointestinal disorders  |                  |                 |                 |
| Abdominal discomfort        |                  |                 |                 |
| subjects affected / exposed | 0 / 67 (0.00%)   | 0 / 31 (0.00%)  | 1 / 18 (5.56%)  |
| occurrences (all)           | 0                | 0               | 1               |
| Abdominal distension        |                  |                 |                 |
| subjects affected / exposed | 5 / 67 (7.46%)   | 2 / 31 (6.45%)  | 0 / 18 (0.00%)  |
| occurrences (all)           | 5                | 3               | 0               |
| Abdominal pain              |                  |                 |                 |
| subjects affected / exposed | 5 / 67 (7.46%)   | 5 / 31 (16.13%) | 0 / 18 (0.00%)  |
| occurrences (all)           | 5                | 7               | 0               |
| Abdominal pain lower        |                  |                 |                 |
| subjects affected / exposed | 1 / 67 (1.49%)   | 1 / 31 (3.23%)  | 0 / 18 (0.00%)  |
| occurrences (all)           | 1                | 1               | 0               |
| Abdominal pain upper        |                  |                 |                 |
| subjects affected / exposed | 4 / 67 (5.97%)   | 4 / 31 (12.90%) | 1 / 18 (5.56%)  |
| occurrences (all)           | 4                | 6               | 1               |
| Abdominal tenderness        |                  |                 |                 |
| subjects affected / exposed | 1 / 67 (1.49%)   | 0 / 31 (0.00%)  | 0 / 18 (0.00%)  |
| occurrences (all)           | 1                | 0               | 0               |
| Colitis                     |                  |                 |                 |
| subjects affected / exposed | 2 / 67 (2.99%)   | 2 / 31 (6.45%)  | 0 / 18 (0.00%)  |
| occurrences (all)           | 3                | 3               | 0               |
| Constipation                |                  |                 |                 |
| subjects affected / exposed | 11 / 67 (16.42%) | 4 / 31 (12.90%) | 2 / 18 (11.11%) |
| occurrences (all)           | 13               | 6               | 3               |

|                             |                  |                  |                 |
|-----------------------------|------------------|------------------|-----------------|
| Dental caries               |                  |                  |                 |
| subjects affected / exposed | 0 / 67 (0.00%)   | 1 / 31 (3.23%)   | 0 / 18 (0.00%)  |
| occurrences (all)           | 0                | 1                | 0               |
| Diarrhoea                   |                  |                  |                 |
| subjects affected / exposed | 35 / 67 (52.24%) | 11 / 31 (35.48%) | 6 / 18 (33.33%) |
| occurrences (all)           | 114              | 28               | 10              |
| Diverticulum intestinal     |                  |                  |                 |
| subjects affected / exposed | 1 / 67 (1.49%)   | 0 / 31 (0.00%)   | 0 / 18 (0.00%)  |
| occurrences (all)           | 1                | 0                | 0               |
| Dry mouth                   |                  |                  |                 |
| subjects affected / exposed | 2 / 67 (2.99%)   | 0 / 31 (0.00%)   | 0 / 18 (0.00%)  |
| occurrences (all)           | 2                | 0                | 0               |
| Dyspepsia                   |                  |                  |                 |
| subjects affected / exposed | 9 / 67 (13.43%)  | 2 / 31 (6.45%)   | 2 / 18 (11.11%) |
| occurrences (all)           | 12               | 2                | 2               |
| Dysphagia                   |                  |                  |                 |
| subjects affected / exposed | 1 / 67 (1.49%)   | 0 / 31 (0.00%)   | 0 / 18 (0.00%)  |
| occurrences (all)           | 1                | 0                | 0               |
| Enterocolitis               |                  |                  |                 |
| subjects affected / exposed | 0 / 67 (0.00%)   | 1 / 31 (3.23%)   | 0 / 18 (0.00%)  |
| occurrences (all)           | 0                | 1                | 0               |
| Enterovesical fistula       |                  |                  |                 |
| subjects affected / exposed | 0 / 67 (0.00%)   | 1 / 31 (3.23%)   | 0 / 18 (0.00%)  |
| occurrences (all)           | 0                | 1                | 0               |
| Eructation                  |                  |                  |                 |
| subjects affected / exposed | 1 / 67 (1.49%)   | 0 / 31 (0.00%)   | 0 / 18 (0.00%)  |
| occurrences (all)           | 1                | 0                | 0               |
| Faeces soft                 |                  |                  |                 |
| subjects affected / exposed | 1 / 67 (1.49%)   | 0 / 31 (0.00%)   | 0 / 18 (0.00%)  |
| occurrences (all)           | 1                | 0                | 0               |
| Flatulence                  |                  |                  |                 |
| subjects affected / exposed | 4 / 67 (5.97%)   | 2 / 31 (6.45%)   | 1 / 18 (5.56%)  |
| occurrences (all)           | 4                | 2                | 1               |
| Gastric dilatation          |                  |                  |                 |
| subjects affected / exposed | 1 / 67 (1.49%)   | 0 / 31 (0.00%)   | 0 / 18 (0.00%)  |
| occurrences (all)           | 1                | 0                | 0               |

|                                 |                  |                  |                 |
|---------------------------------|------------------|------------------|-----------------|
| Gastric polyps                  |                  |                  |                 |
| subjects affected / exposed     | 1 / 67 (1.49%)   | 0 / 31 (0.00%)   | 0 / 18 (0.00%)  |
| occurrences (all)               | 1                | 0                | 0               |
| Gastritis                       |                  |                  |                 |
| subjects affected / exposed     | 3 / 67 (4.48%)   | 0 / 31 (0.00%)   | 0 / 18 (0.00%)  |
| occurrences (all)               | 4                | 0                | 0               |
| Gastroesophageal reflux disease |                  |                  |                 |
| subjects affected / exposed     | 3 / 67 (4.48%)   | 3 / 31 (9.68%)   | 0 / 18 (0.00%)  |
| occurrences (all)               | 3                | 3                | 0               |
| Haematochezia                   |                  |                  |                 |
| subjects affected / exposed     | 1 / 67 (1.49%)   | 0 / 31 (0.00%)   | 0 / 18 (0.00%)  |
| occurrences (all)               | 1                | 0                | 0               |
| Haemoperitoneum                 |                  |                  |                 |
| subjects affected / exposed     | 0 / 67 (0.00%)   | 1 / 31 (3.23%)   | 0 / 18 (0.00%)  |
| occurrences (all)               | 0                | 1                | 0               |
| Haemorrhoidal haemorrhage       |                  |                  |                 |
| subjects affected / exposed     | 1 / 67 (1.49%)   | 0 / 31 (0.00%)   | 1 / 18 (5.56%)  |
| occurrences (all)               | 2                | 0                | 1               |
| Haemorrhoids                    |                  |                  |                 |
| subjects affected / exposed     | 1 / 67 (1.49%)   | 0 / 31 (0.00%)   | 0 / 18 (0.00%)  |
| occurrences (all)               | 1                | 0                | 0               |
| Hiatus hernia                   |                  |                  |                 |
| subjects affected / exposed     | 1 / 67 (1.49%)   | 0 / 31 (0.00%)   | 0 / 18 (0.00%)  |
| occurrences (all)               | 1                | 0                | 0               |
| Inguinal hernia                 |                  |                  |                 |
| subjects affected / exposed     | 1 / 67 (1.49%)   | 0 / 31 (0.00%)   | 0 / 18 (0.00%)  |
| occurrences (all)               | 1                | 0                | 0               |
| Large intestine polyp           |                  |                  |                 |
| subjects affected / exposed     | 0 / 67 (0.00%)   | 0 / 31 (0.00%)   | 1 / 18 (5.56%)  |
| occurrences (all)               | 0                | 0                | 1               |
| Nausea                          |                  |                  |                 |
| subjects affected / exposed     | 29 / 67 (43.28%) | 10 / 31 (32.26%) | 5 / 18 (27.78%) |
| occurrences (all)               | 47               | 15               | 8               |
| Oral pain                       |                  |                  |                 |
| subjects affected / exposed     | 1 / 67 (1.49%)   | 0 / 31 (0.00%)   | 0 / 18 (0.00%)  |
| occurrences (all)               | 1                | 0                | 0               |

|   |                        |                     |                     |
|---|------------------------|---------------------|---------------------|
| Paraesthesia oral<br>subjects affected / exposed<br>occurrences (all)         | 0 / 67 (0.00%)<br>0    | 0 / 31 (0.00%)<br>0 | 1 / 18 (5.56%)<br>1 |
| Rectal haemorrhage<br>subjects affected / exposed<br>occurrences (all)        | 1 / 67 (1.49%)<br>1    | 0 / 31 (0.00%)<br>0 | 0 / 18 (0.00%)<br>0 |
| Stomatitis<br>subjects affected / exposed<br>occurrences (all)                | 3 / 67 (4.48%)<br>3    | 0 / 31 (0.00%)<br>0 | 0 / 18 (0.00%)<br>0 |
| Tongue discomfort<br>subjects affected / exposed<br>occurrences (all)         | 1 / 67 (1.49%)<br>1    | 0 / 31 (0.00%)<br>0 | 0 / 18 (0.00%)<br>0 |
| Tongue ulceration<br>subjects affected / exposed<br>occurrences (all)         | 1 / 67 (1.49%)<br>1    | 0 / 31 (0.00%)<br>0 | 0 / 18 (0.00%)<br>0 |
| Vomiting<br>subjects affected / exposed<br>occurrences (all)                  | 11 / 67 (16.42%)<br>16 | 3 / 31 (9.68%)<br>3 | 1 / 18 (5.56%)<br>1 |
| Hepatobiliary disorders   |                        |                     |                     |
| Cholecystitis<br>subjects affected / exposed<br>occurrences (all)             | 1 / 67 (1.49%)<br>1    | 0 / 31 (0.00%)<br>0 | 0 / 18 (0.00%)<br>0 |
| Cholelithiasis<br>subjects affected / exposed<br>occurrences (all)            | 2 / 67 (2.99%)<br>2    | 0 / 31 (0.00%)<br>0 | 0 / 18 (0.00%)<br>0 |
| Drug-induced liver injury<br>subjects affected / exposed<br>occurrences (all) | 0 / 67 (0.00%)<br>0    | 1 / 31 (3.23%)<br>1 | 0 / 18 (0.00%)<br>0 |
| Hepatic failure<br>subjects affected / exposed<br>occurrences (all)           | 0 / 67 (0.00%)<br>0    | 1 / 31 (3.23%)<br>1 | 0 / 18 (0.00%)<br>0 |
| Hypertransaminasaemia<br>subjects affected / exposed<br>occurrences (all)     | 1 / 67 (1.49%)<br>2    | 0 / 31 (0.00%)<br>0 | 0 / 18 (0.00%)<br>0 |
| Skin and subcutaneous tissue disorders  |                        |                     |                     |

|                             |                |                |                |
|-----------------------------|----------------|----------------|----------------|
| Actinic keratosis           |                |                |                |
| subjects affected / exposed | 0 / 67 (0.00%) | 0 / 31 (0.00%) | 1 / 18 (5.56%) |
| occurrences (all)           | 0              | 0              | 2              |
| Alopecia                    |                |                |                |
| subjects affected / exposed | 2 / 67 (2.99%) | 0 / 31 (0.00%) | 0 / 18 (0.00%) |
| occurrences (all)           | 2              | 0              | 0              |
| Alopecia areata             |                |                |                |
| subjects affected / exposed | 1 / 67 (1.49%) | 0 / 31 (0.00%) | 0 / 18 (0.00%) |
| occurrences (all)           | 1              | 0              | 0              |
| Decubitus ulcer             |                |                |                |
| subjects affected / exposed | 0 / 67 (0.00%) | 0 / 31 (0.00%) | 1 / 18 (5.56%) |
| occurrences (all)           | 0              | 0              | 1              |
| Dermal cyst                 |                |                |                |
| subjects affected / exposed | 0 / 67 (0.00%) | 1 / 31 (3.23%) | 0 / 18 (0.00%) |
| occurrences (all)           | 0              | 1              | 0              |
| Dermatitis                  |                |                |                |
| subjects affected / exposed | 1 / 67 (1.49%) | 0 / 31 (0.00%) | 0 / 18 (0.00%) |
| occurrences (all)           | 1              | 0              | 0              |
| Dermatitis acneiform        |                |                |                |
| subjects affected / exposed | 0 / 67 (0.00%) | 1 / 31 (3.23%) | 0 / 18 (0.00%) |
| occurrences (all)           | 0              | 1              | 0              |
| Dermatitis allergic         |                |                |                |
| subjects affected / exposed | 0 / 67 (0.00%) | 0 / 31 (0.00%) | 1 / 18 (5.56%) |
| occurrences (all)           | 0              | 0              | 1              |
| Dry skin                    |                |                |                |
| subjects affected / exposed | 2 / 67 (2.99%) | 2 / 31 (6.45%) | 1 / 18 (5.56%) |
| occurrences (all)           | 3              | 7              | 1              |
| Ecchymosis                  |                |                |                |
| subjects affected / exposed | 0 / 67 (0.00%) | 1 / 31 (3.23%) | 0 / 18 (0.00%) |
| occurrences (all)           | 0              | 1              | 0              |
| Erythema                    |                |                |                |
| subjects affected / exposed | 2 / 67 (2.99%) | 1 / 31 (3.23%) | 1 / 18 (5.56%) |
| occurrences (all)           | 2              | 1              | 1              |
| Hyperhidrosis               |                |                |                |
| subjects affected / exposed | 0 / 67 (0.00%) | 2 / 31 (6.45%) | 0 / 18 (0.00%) |
| occurrences (all)           | 0              | 2              | 0              |

|  |                 |                 |                |
|--|-----------------|-----------------|----------------|
| Ingrowing nail                             |                 |                 |                |
| subjects affected / exposed                | 1 / 67 (1.49%)  | 0 / 31 (0.00%)  | 0 / 18 (0.00%) |
| occurrences (all)                          | 1               | 0               | 0              |
| Miliaria                                   |                 |                 |                |
| subjects affected / exposed                | 2 / 67 (2.99%)  | 0 / 31 (0.00%)  | 0 / 18 (0.00%) |
| occurrences (all)                          | 3               | 0               | 0              |
| Night sweats                               |                 |                 |                |
| subjects affected / exposed                | 7 / 67 (10.45%) | 2 / 31 (6.45%)  | 1 / 18 (5.56%) |
| occurrences (all)                          | 8               | 2               | 1              |
| Onychoclasia                               |                 |                 |                |
| subjects affected / exposed                | 1 / 67 (1.49%)  | 0 / 31 (0.00%)  | 0 / 18 (0.00%) |
| occurrences (all)                          | 1               | 0               | 0              |
| Pain of skin                               |                 |                 |                |
| subjects affected / exposed                | 0 / 67 (0.00%)  | 1 / 31 (3.23%)  | 0 / 18 (0.00%) |
| occurrences (all)                          | 0               | 1               | 0              |
| Palmar-plantar erythrodysesthesia syndrome |                 |                 |                |
| subjects affected / exposed                | 0 / 67 (0.00%)  | 1 / 31 (3.23%)  | 1 / 18 (5.56%) |
| occurrences (all)                          | 0               | 1               | 1              |
| Photosensitivity reaction                  |                 |                 |                |
| subjects affected / exposed                | 0 / 67 (0.00%)  | 1 / 31 (3.23%)  | 0 / 18 (0.00%) |
| occurrences (all)                          | 0               | 1               | 0              |
| Precancerous skin lesion                   |                 |                 |                |
| subjects affected / exposed                | 1 / 67 (1.49%)  | 0 / 31 (0.00%)  | 0 / 18 (0.00%) |
| occurrences (all)                          | 1               | 0               | 0              |
| Pruritus                                   |                 |                 |                |
| subjects affected / exposed                | 7 / 67 (10.45%) | 4 / 31 (12.90%) | 0 / 18 (0.00%) |
| occurrences (all)                          | 8               | 4               | 0              |
| Psoriasis                                  |                 |                 |                |
| subjects affected / exposed                | 0 / 67 (0.00%)  | 1 / 31 (3.23%)  | 0 / 18 (0.00%) |
| occurrences (all)                          | 0               | 1               | 0              |
| Rash                                       |                 |                 |                |
| subjects affected / exposed                | 6 / 67 (8.96%)  | 2 / 31 (6.45%)  | 1 / 18 (5.56%) |
| occurrences (all)                          | 11              | 2               | 1              |
| Rash maculo-papular                        |                 |                 |                |

|                             |                |                |                |
|-----------------------------|----------------|----------------|----------------|
| subjects affected / exposed | 3 / 67 (4.48%) | 3 / 31 (9.68%) | 0 / 18 (0.00%) |
| occurrences (all)           | 3              | 7              | 0              |
| Rash pruritic               |                |                |                |
| subjects affected / exposed | 1 / 67 (1.49%) | 0 / 31 (0.00%) | 0 / 18 (0.00%) |
| occurrences (all)           | 1              | 0              | 0              |
| Skin erosion                |                |                |                |
| subjects affected / exposed | 1 / 67 (1.49%) | 0 / 31 (0.00%) | 0 / 18 (0.00%) |
| occurrences (all)           | 1              | 0              | 0              |
| Skin hyperpigmentation      |                |                |                |
| subjects affected / exposed | 1 / 67 (1.49%) | 0 / 31 (0.00%) | 0 / 18 (0.00%) |
| occurrences (all)           | 1              | 0              | 0              |
| Skin irritation             |                |                |                |
| subjects affected / exposed | 1 / 67 (1.49%) | 0 / 31 (0.00%) | 0 / 18 (0.00%) |
| occurrences (all)           | 1              | 0              | 0              |
| Urticaria                   |                |                |                |
| subjects affected / exposed | 0 / 67 (0.00%) | 1 / 31 (3.23%) | 0 / 18 (0.00%) |
| occurrences (all)           | 0              | 2              | 0              |
| Renal and urinary disorders |                |                |                |
| Acute kidney injury         |                |                |                |
| subjects affected / exposed | 3 / 67 (4.48%) | 1 / 31 (3.23%) | 0 / 18 (0.00%) |
| occurrences (all)           | 4              | 2              | 0              |
| Chromaturia                 |                |                |                |
| subjects affected / exposed | 1 / 67 (1.49%) | 0 / 31 (0.00%) | 0 / 18 (0.00%) |
| occurrences (all)           | 1              | 0              | 0              |
| Chronic kidney disease      |                |                |                |
| subjects affected / exposed | 2 / 67 (2.99%) | 0 / 31 (0.00%) | 0 / 18 (0.00%) |
| occurrences (all)           | 2              | 0              | 0              |
| Dysuria                     |                |                |                |
| subjects affected / exposed | 1 / 67 (1.49%) | 0 / 31 (0.00%) | 0 / 18 (0.00%) |
| occurrences (all)           | 1              | 0              | 0              |
| Haematuria                  |                |                |                |
| subjects affected / exposed | 4 / 67 (5.97%) | 0 / 31 (0.00%) | 0 / 18 (0.00%) |
| occurrences (all)           | 4              | 0              | 0              |
| Micturition urgency         |                |                |                |
| subjects affected / exposed | 1 / 67 (1.49%) | 1 / 31 (3.23%) | 0 / 18 (0.00%) |
| occurrences (all)           | 1              | 1              | 0              |

|   |                  |                 |                 |
|---|------------------|-----------------|-----------------|
| Nocturia  |                  |                 |                 |
| subjects affected / exposed                     | 3 / 67 (4.48%)   | 0 / 31 (0.00%)  | 1 / 18 (5.56%)  |
| occurrences (all)                               | 3                | 0               | 1               |
| Pollakiuria                                     |                  |                 |                 |
| subjects affected / exposed                     | 3 / 67 (4.48%)   | 2 / 31 (6.45%)  | 0 / 18 (0.00%)  |
| occurrences (all)                               | 3                | 2               | 0               |
| Polyuria  |                  |                 |                 |
| subjects affected / exposed                     | 1 / 67 (1.49%)   | 0 / 31 (0.00%)  | 0 / 18 (0.00%)  |
| occurrences (all)                               | 1                | 0               | 0               |
| Renal colic                                     |                  |                 |                 |
| subjects affected / exposed                     | 1 / 67 (1.49%)   | 0 / 31 (0.00%)  | 0 / 18 (0.00%)  |
| occurrences (all)                               | 1                | 0               | 0               |
| Renal cyst                                      |                  |                 |                 |
| subjects affected / exposed                     | 1 / 67 (1.49%)   | 0 / 31 (0.00%)  | 0 / 18 (0.00%)  |
| occurrences (all)                               | 1                | 0               | 0               |
| Renal failure                                   |                  |                 |                 |
| subjects affected / exposed                     | 1 / 67 (1.49%)   | 0 / 31 (0.00%)  | 0 / 18 (0.00%)  |
| occurrences (all)                               | 1                | 0               | 0               |
| Urinary incontinence                            |                  |                 |                 |
| subjects affected / exposed                     | 2 / 67 (2.99%)   | 0 / 31 (0.00%)  | 0 / 18 (0.00%)  |
| occurrences (all)                               | 2                | 0               | 0               |
| Urinary retention                               |                  |                 |                 |
| subjects affected / exposed                     | 2 / 67 (2.99%)   | 1 / 31 (3.23%)  | 0 / 18 (0.00%)  |
| occurrences (all)                               | 2                | 2               | 0               |
| Urinary tract pain                              |                  |                 |                 |
| subjects affected / exposed                     | 1 / 67 (1.49%)   | 1 / 31 (3.23%)  | 0 / 18 (0.00%)  |
| occurrences (all)                               | 1                | 1               | 0               |
| Endocrine disorders                             |                  |                 |                 |
| Adrenal insufficiency                           |                  |                 |                 |
| subjects affected / exposed                     | 1 / 67 (1.49%)   | 0 / 31 (0.00%)  | 0 / 18 (0.00%)  |
| occurrences (all)                               | 1                | 0               | 0               |
| Musculoskeletal and connective tissue disorders |                  |                 |                 |
| Arthralgia                                      |                  |                 |                 |
| subjects affected / exposed                     | 12 / 67 (17.91%) | 4 / 31 (12.90%) | 2 / 18 (11.11%) |
| occurrences (all)                               | 20               | 11              | 2               |
| Arthritis                                       |                  |                 |                 |



|                                 |                  |                |                |
|---------------------------------|------------------|----------------|----------------|
| subjects affected / exposed     | 1 / 67 (1.49%)   | 0 / 31 (0.00%) | 1 / 18 (5.56%) |
| occurrences (all)               | 1                | 0              | 3              |
| Back pain                       |                  |                |                |
| subjects affected / exposed     | 12 / 67 (17.91%) | 2 / 31 (6.45%) | 1 / 18 (5.56%) |
| occurrences (all)               | 13               | 5              | 2              |
| Bone pain                       |                  |                |                |
| subjects affected / exposed     | 2 / 67 (2.99%)   | 0 / 31 (0.00%) | 1 / 18 (5.56%) |
| occurrences (all)               | 2                | 0              | 1              |
| Costochondritis                 |                  |                |                |
| subjects affected / exposed     | 0 / 67 (0.00%)   | 0 / 31 (0.00%) | 1 / 18 (5.56%) |
| occurrences (all)               | 0                | 0              | 1              |
| Flank pain                      |                  |                |                |
| subjects affected / exposed     | 3 / 67 (4.48%)   | 1 / 31 (3.23%) | 1 / 18 (5.56%) |
| occurrences (all)               | 4                | 1              | 1              |
| Gouty arthritis                 |                  |                |                |
| subjects affected / exposed     | 1 / 67 (1.49%)   | 0 / 31 (0.00%) | 0 / 18 (0.00%) |
| occurrences (all)               | 2                | 0              | 0              |
| Groin pain                      |                  |                |                |
| subjects affected / exposed     | 1 / 67 (1.49%)   | 0 / 31 (0.00%) | 0 / 18 (0.00%) |
| occurrences (all)               | 1                | 0              | 0              |
| Joint effusion                  |                  |                |                |
| subjects affected / exposed     | 1 / 67 (1.49%)   | 0 / 31 (0.00%) | 0 / 18 (0.00%) |
| occurrences (all)               | 1                | 0              | 0              |
| Joint range of motion decreased |                  |                |                |
| subjects affected / exposed     | 1 / 67 (1.49%)   | 0 / 31 (0.00%) | 0 / 18 (0.00%) |
| occurrences (all)               | 1                | 0              | 0              |
| Muscle spasms                   |                  |                |                |
| subjects affected / exposed     | 6 / 67 (8.96%)   | 3 / 31 (9.68%) | 0 / 18 (0.00%) |
| occurrences (all)               | 12               | 3              | 0              |
| Muscle tightness                |                  |                |                |
| subjects affected / exposed     | 1 / 67 (1.49%)   | 0 / 31 (0.00%) | 0 / 18 (0.00%) |
| occurrences (all)               | 1                | 0              | 0              |
| Muscle twitching                |                  |                |                |
| subjects affected / exposed     | 1 / 67 (1.49%)   | 0 / 31 (0.00%) | 0 / 18 (0.00%) |
| occurrences (all)               | 1                | 0              | 0              |
| Muscular weakness               |                  |                |                |

|                             |                |                 |                 |
|-----------------------------|----------------|-----------------|-----------------|
| subjects affected / exposed | 3 / 67 (4.48%) | 1 / 31 (3.23%)  | 2 / 18 (11.11%) |
| occurrences (all)           | 5              | 1               | 3               |
| Musculoskeletal chest pain  |                |                 |                 |
| subjects affected / exposed | 5 / 67 (7.46%) | 1 / 31 (3.23%)  | 1 / 18 (5.56%)  |
| occurrences (all)           | 5              | 1               | 1               |
| Musculoskeletal pain        |                |                 |                 |
| subjects affected / exposed | 6 / 67 (8.96%) | 0 / 31 (0.00%)  | 1 / 18 (5.56%)  |
| occurrences (all)           | 6              | 0               | 3               |
| Musculoskeletal stiffness   |                |                 |                 |
| subjects affected / exposed | 1 / 67 (1.49%) | 0 / 31 (0.00%)  | 0 / 18 (0.00%)  |
| occurrences (all)           | 1              | 0               | 0               |
| Myalgia                     |                |                 |                 |
| subjects affected / exposed | 4 / 67 (5.97%) | 4 / 31 (12.90%) | 1 / 18 (5.56%)  |
| occurrences (all)           | 7              | 4               | 1               |
| Neck pain                   |                |                 |                 |
| subjects affected / exposed | 4 / 67 (5.97%) | 1 / 31 (3.23%)  | 0 / 18 (0.00%)  |
| occurrences (all)           | 5              | 1               | 0               |
| Osteoarthritis              |                |                 |                 |
| subjects affected / exposed | 1 / 67 (1.49%) | 0 / 31 (0.00%)  | 0 / 18 (0.00%)  |
| occurrences (all)           | 1              | 0               | 0               |
| Osteopenia                  |                |                 |                 |
| subjects affected / exposed | 1 / 67 (1.49%) | 0 / 31 (0.00%)  | 0 / 18 (0.00%)  |
| occurrences (all)           | 1              | 0               | 0               |
| Osteoporosis                |                |                 |                 |
| subjects affected / exposed | 2 / 67 (2.99%) | 1 / 31 (3.23%)  | 0 / 18 (0.00%)  |
| occurrences (all)           | 2              | 1               | 0               |
| Pain in extremity           |                |                 |                 |
| subjects affected / exposed | 6 / 67 (8.96%) | 1 / 31 (3.23%)  | 3 / 18 (16.67%) |
| occurrences (all)           | 6              | 1               | 3               |
| Pain in jaw                 |                |                 |                 |
| subjects affected / exposed | 1 / 67 (1.49%) | 0 / 31 (0.00%)  | 0 / 18 (0.00%)  |
| occurrences (all)           | 1              | 0               | 0               |
| Spinal osteoarthritis       |                |                 |                 |
| subjects affected / exposed | 1 / 67 (1.49%) | 0 / 31 (0.00%)  | 0 / 18 (0.00%)  |
| occurrences (all)           | 1              | 0               | 0               |
| Infections and infestations |                |                 |                 |

|  |                |                |                 |
|--|----------------|----------------|-----------------|
| Babesiosis                             |                |                |                 |
| subjects affected / exposed            | 1 / 67 (1.49%) | 0 / 31 (0.00%) | 0 / 18 (0.00%)  |
| occurrences (all)                      | 1              | 0              | 0               |
| Body tinea                             |                |                |                 |
| subjects affected / exposed            | 0 / 67 (0.00%) | 1 / 31 (3.23%) | 0 / 18 (0.00%)  |
| occurrences (all)                      | 0              | 1              | 0               |
| Bronchitis                             |                |                |                 |
| subjects affected / exposed            | 4 / 67 (5.97%) | 3 / 31 (9.68%) | 0 / 18 (0.00%)  |
| occurrences (all)                      | 5              | 4              | 0               |
| COVID-19                               |                |                |                 |
| subjects affected / exposed            | 5 / 67 (7.46%) | 0 / 31 (0.00%) | 1 / 18 (5.56%)  |
| occurrences (all)                      | 6              | 0              | 1               |
| Campylobacter infection                |                |                |                 |
| subjects affected / exposed            | 1 / 67 (1.49%) | 0 / 31 (0.00%) | 0 / 18 (0.00%)  |
| occurrences (all)                      | 1              | 0              | 0               |
| Candida infection                      |                |                |                 |
| subjects affected / exposed            | 2 / 67 (2.99%) | 0 / 31 (0.00%) | 0 / 18 (0.00%)  |
| occurrences (all)                      | 3              | 0              | 0               |
| Chronic sinusitis                      |                |                |                 |
| subjects affected / exposed            | 2 / 67 (2.99%) | 0 / 31 (0.00%) | 1 / 18 (5.56%)  |
| occurrences (all)                      | 2              | 0              | 1               |
| Clostridium difficile colitis          |                |                |                 |
| subjects affected / exposed            | 1 / 67 (1.49%) | 0 / 31 (0.00%) | 0 / 18 (0.00%)  |
| occurrences (all)                      | 2              | 0              | 0               |
| Conjunctivitis                         |                |                |                 |
| subjects affected / exposed            | 1 / 67 (1.49%) | 0 / 31 (0.00%) | 0 / 18 (0.00%)  |
| occurrences (all)                      | 2              | 0              | 0               |
| Cystitis                               |                |                |                 |
| subjects affected / exposed            | 1 / 67 (1.49%) | 0 / 31 (0.00%) | 0 / 18 (0.00%)  |
| occurrences (all)                      | 1              | 0              | 0               |
| Cytomegalovirus infection              |                |                |                 |
| subjects affected / exposed            | 2 / 67 (2.99%) | 1 / 31 (3.23%) | 2 / 18 (11.11%) |
| occurrences (all)                      | 3              | 1              | 2               |
| Cytomegalovirus infection reactivation |                |                |                 |

|                             |                |                |                |
|-----------------------------|----------------|----------------|----------------|
| subjects affected / exposed | 1 / 67 (1.49%) | 0 / 31 (0.00%) | 0 / 18 (0.00%) |
| occurrences (all)           | 1              | 0              | 0              |
| Diverticulitis              |                |                |                |
| subjects affected / exposed | 1 / 67 (1.49%) | 0 / 31 (0.00%) | 0 / 18 (0.00%) |
| occurrences (all)           | 1              | 0              | 0              |
| Ear infection               |                |                |                |
| subjects affected / exposed | 2 / 67 (2.99%) | 1 / 31 (3.23%) | 1 / 18 (5.56%) |
| occurrences (all)           | 2              | 1              | 1              |
| Epididymitis                |                |                |                |
| subjects affected / exposed | 1 / 67 (1.49%) | 0 / 31 (0.00%) | 0 / 18 (0.00%) |
| occurrences (all)           | 1              | 0              | 0              |
| Folliculitis                |                |                |                |
| subjects affected / exposed | 1 / 67 (1.49%) | 0 / 31 (0.00%) | 0 / 18 (0.00%) |
| occurrences (all)           | 1              | 0              | 0              |
| Fungal oesophagitis         |                |                |                |
| subjects affected / exposed | 1 / 67 (1.49%) | 0 / 31 (0.00%) | 0 / 18 (0.00%) |
| occurrences (all)           | 1              | 0              | 0              |
| Fungal skin infection       |                |                |                |
| subjects affected / exposed | 1 / 67 (1.49%) | 1 / 31 (3.23%) | 0 / 18 (0.00%) |
| occurrences (all)           | 1              | 2              | 0              |
| Gastroenteritis             |                |                |                |
| subjects affected / exposed | 0 / 67 (0.00%) | 0 / 31 (0.00%) | 1 / 18 (5.56%) |
| occurrences (all)           | 0              | 0              | 1              |
| Gingivitis                  |                |                |                |
| subjects affected / exposed | 0 / 67 (0.00%) | 1 / 31 (3.23%) | 0 / 18 (0.00%) |
| occurrences (all)           | 0              | 1              | 0              |
| Herpes zoster               |                |                |                |
| subjects affected / exposed | 3 / 67 (4.48%) | 1 / 31 (3.23%) | 0 / 18 (0.00%) |
| occurrences (all)           | 3              | 2              | 0              |
| Hordeolum                   |                |                |                |
| subjects affected / exposed | 1 / 67 (1.49%) | 0 / 31 (0.00%) | 0 / 18 (0.00%) |
| occurrences (all)           | 1              | 0              | 0              |
| Influenza                   |                |                |                |
| subjects affected / exposed | 4 / 67 (5.97%) | 0 / 31 (0.00%) | 0 / 18 (0.00%) |
| occurrences (all)           | 4              | 0              | 0              |
| Laryngitis                  |                |                |                |

|                                       |                  |                |                 |
|---------------------------------------|------------------|----------------|-----------------|
| subjects affected / exposed           | 0 / 67 (0.00%)   | 0 / 31 (0.00%) | 1 / 18 (5.56%)  |
| occurrences (all)                     | 0                | 0              | 1               |
| Lower respiratory tract infection     |                  |                |                 |
| subjects affected / exposed           | 1 / 67 (1.49%)   | 0 / 31 (0.00%) | 0 / 18 (0.00%)  |
| occurrences (all)                     | 1                | 0              | 0               |
| Mastoiditis                           |                  |                |                 |
| subjects affected / exposed           | 0 / 67 (0.00%)   | 1 / 31 (3.23%) | 0 / 18 (0.00%)  |
| occurrences (all)                     | 0                | 1              | 0               |
| Mycobacterium avium complex infection |                  |                |                 |
| subjects affected / exposed           | 1 / 67 (1.49%)   | 0 / 31 (0.00%) | 0 / 18 (0.00%)  |
| occurrences (all)                     | 1                | 0              | 0               |
| Nasopharyngitis                       |                  |                |                 |
| subjects affected / exposed           | 1 / 67 (1.49%)   | 2 / 31 (6.45%) | 0 / 18 (0.00%)  |
| occurrences (all)                     | 2                | 2              | 0               |
| Oral candidiasis                      |                  |                |                 |
| subjects affected / exposed           | 0 / 67 (0.00%)   | 0 / 31 (0.00%) | 1 / 18 (5.56%)  |
| occurrences (all)                     | 0                | 0              | 1               |
| Oral herpes                           |                  |                |                 |
| subjects affected / exposed           | 2 / 67 (2.99%)   | 0 / 31 (0.00%) | 0 / 18 (0.00%)  |
| occurrences (all)                     | 2                | 0              | 0               |
| Otitis media                          |                  |                |                 |
| subjects affected / exposed           | 1 / 67 (1.49%)   | 0 / 31 (0.00%) | 0 / 18 (0.00%)  |
| occurrences (all)                     | 1                | 0              | 0               |
| Pharyngitis streptococcal             |                  |                |                 |
| subjects affected / exposed           | 1 / 67 (1.49%)   | 0 / 31 (0.00%) | 0 / 18 (0.00%)  |
| occurrences (all)                     | 1                | 0              | 0               |
| Pneumonia                             |                  |                |                 |
| subjects affected / exposed           | 12 / 67 (17.91%) | 1 / 31 (3.23%) | 4 / 18 (22.22%) |
| occurrences (all)                     | 13               | 1              | 4               |
| Pseudomonas infection                 |                  |                |                 |
| subjects affected / exposed           | 0 / 67 (0.00%)   | 0 / 31 (0.00%) | 1 / 18 (5.56%)  |
| occurrences (all)                     | 0                | 0              | 1               |
| Respiratory tract infection           |                  |                |                 |
| subjects affected / exposed           | 3 / 67 (4.48%)   | 0 / 31 (0.00%) | 1 / 18 (5.56%)  |
| occurrences (all)                     | 5                | 0              | 1               |

|   |                  |                 |                 |
|---|------------------|-----------------|-----------------|
| Rhinitis                                |                  |                 |                 |
| subjects affected / exposed             | 2 / 67 (2.99%)   | 0 / 31 (0.00%)  | 0 / 18 (0.00%)  |
| occurrences (all)                       | 2                | 0               | 0               |
| Rhinovirus infection                    |                  |                 |                 |
| subjects affected / exposed             | 1 / 67 (1.49%)   | 0 / 31 (0.00%)  | 1 / 18 (5.56%)  |
| occurrences (all)                       | 1                | 0               | 1               |
| Sepsis                                  |                  |                 |                 |
| subjects affected / exposed             | 1 / 67 (1.49%)   | 0 / 31 (0.00%)  | 1 / 18 (5.56%)  |
| occurrences (all)                       | 1                | 0               | 1               |
| Sinusitis                               |                  |                 |                 |
| subjects affected / exposed             | 3 / 67 (4.48%)   | 1 / 31 (3.23%)  | 1 / 18 (5.56%)  |
| occurrences (all)                       | 5                | 1               | 1               |
| Skin infection                          |                  |                 |                 |
| subjects affected / exposed             | 1 / 67 (1.49%)   | 0 / 31 (0.00%)  | 0 / 18 (0.00%)  |
| occurrences (all)                       | 2                | 0               | 0               |
| Tooth abscess                           |                  |                 |                 |
| subjects affected / exposed             | 0 / 67 (0.00%)   | 1 / 31 (3.23%)  | 0 / 18 (0.00%)  |
| occurrences (all)                       | 0                | 1               | 0               |
| Tooth infection                         |                  |                 |                 |
| subjects affected / exposed             | 2 / 67 (2.99%)   | 0 / 31 (0.00%)  | 0 / 18 (0.00%)  |
| occurrences (all)                       | 2                | 0               | 0               |
| Upper respiratory tract infection       |                  |                 |                 |
| subjects affected / exposed             | 14 / 67 (20.90%) | 9 / 31 (29.03%) | 4 / 18 (22.22%) |
| occurrences (all)                       | 21               | 10              | 5               |
| Urinary tract infection                 |                  |                 |                 |
| subjects affected / exposed             | 5 / 67 (7.46%)   | 2 / 31 (6.45%)  | 0 / 18 (0.00%)  |
| occurrences (all)                       | 10               | 2               | 0               |
| Viral upper respiratory tract infection |                  |                 |                 |
| subjects affected / exposed             | 1 / 67 (1.49%)   | 0 / 31 (0.00%)  | 1 / 18 (5.56%)  |
| occurrences (all)                       | 2                | 0               | 1               |
| Metabolism and nutrition disorders      |                  |                 |                 |
| Decreased appetite                      |                  |                 |                 |
| subjects affected / exposed             | 10 / 67 (14.93%) | 1 / 31 (3.23%)  | 3 / 18 (16.67%) |
| occurrences (all)                       | 13               | 4               | 3               |
| Dehydration                             |                  |                 |                 |

|                             |                 |                 |                 |
|-----------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed | 3 / 67 (4.48%)  | 2 / 31 (6.45%)  | 0 / 18 (0.00%)  |
| occurrences (all)           | 5               | 3               | 0               |
| Food intolerance            |                 |                 |                 |
| subjects affected / exposed | 1 / 67 (1.49%)  | 0 / 31 (0.00%)  | 0 / 18 (0.00%)  |
| occurrences (all)           | 1               | 0               | 0               |
| Hypercalcaemia              |                 |                 |                 |
| subjects affected / exposed | 0 / 67 (0.00%)  | 0 / 31 (0.00%)  | 1 / 18 (5.56%)  |
| occurrences (all)           | 0               | 0               | 1               |
| Hyperglycaemia              |                 |                 |                 |
| subjects affected / exposed | 4 / 67 (5.97%)  | 0 / 31 (0.00%)  | 2 / 18 (11.11%) |
| occurrences (all)           | 4               | 0               | 6               |
| Hyperkalaemia               |                 |                 |                 |
| subjects affected / exposed | 1 / 67 (1.49%)  | 0 / 31 (0.00%)  | 0 / 18 (0.00%)  |
| occurrences (all)           | 24              | 0               | 0               |
| Hypertriglyceridaemia       |                 |                 |                 |
| subjects affected / exposed | 1 / 67 (1.49%)  | 0 / 31 (0.00%)  | 0 / 18 (0.00%)  |
| occurrences (all)           | 1               | 0               | 0               |
| Hyperuricaemia              |                 |                 |                 |
| subjects affected / exposed | 4 / 67 (5.97%)  | 0 / 31 (0.00%)  | 1 / 18 (5.56%)  |
| occurrences (all)           | 4               | 0               | 1               |
| Hypoalbuminaemia            |                 |                 |                 |
| subjects affected / exposed | 0 / 67 (0.00%)  | 0 / 31 (0.00%)  | 1 / 18 (5.56%)  |
| occurrences (all)           | 0               | 0               | 1               |
| Hypocalcaemia               |                 |                 |                 |
| subjects affected / exposed | 5 / 67 (7.46%)  | 3 / 31 (9.68%)  | 0 / 18 (0.00%)  |
| occurrences (all)           | 5               | 5               | 0               |
| Hypoglycaemia               |                 |                 |                 |
| subjects affected / exposed | 1 / 67 (1.49%)  | 0 / 31 (0.00%)  | 2 / 18 (11.11%) |
| occurrences (all)           | 1               | 0               | 3               |
| Hypokalaemia                |                 |                 |                 |
| subjects affected / exposed | 9 / 67 (13.43%) | 4 / 31 (12.90%) | 1 / 18 (5.56%)  |
| occurrences (all)           | 20              | 4               | 1               |
| Hypomagnesaemia             |                 |                 |                 |
| subjects affected / exposed | 1 / 67 (1.49%)  | 1 / 31 (3.23%)  | 0 / 18 (0.00%)  |
| occurrences (all)           | 2               | 2               | 0               |
| Hyponatraemia               |                 |                 |                 |

|                             |                |                |                 |
|-----------------------------|----------------|----------------|-----------------|
| subjects affected / exposed | 3 / 67 (4.48%) | 1 / 31 (3.23%) | 0 / 18 (0.00%)  |
| occurrences (all)           | 6              | 1              | 0               |
| Hypophosphataemia           |                |                |                 |
| subjects affected / exposed | 4 / 67 (5.97%) | 2 / 31 (6.45%) | 2 / 18 (11.11%) |
| occurrences (all)           | 5              | 4              | 3               |
| Iron deficiency             |                |                |                 |
| subjects affected / exposed | 1 / 67 (1.49%) | 0 / 31 (0.00%) | 0 / 18 (0.00%)  |
| occurrences (all)           | 2              | 0              | 0               |
| Obesity                     |                |                |                 |
| subjects affected / exposed | 0 / 67 (0.00%) | 0 / 31 (0.00%) | 1 / 18 (5.56%)  |
| occurrences (all)           | 0              | 0              | 3               |



## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date            | Amendment   |
|-----------------|---|
| 24 August 2016  | As per amendment 1: 1. All subjects were required to start prophylaxis treatment with pneumocystis jiroveci pneumonia (PCP) and antiviral therapy (previously at investigator discretion). 2. The phrasing of response assessment intervals was revised for clarity from "at Weeks 12, 24, 36, 48, and every 12 weeks thereafter" to "following the completions of cycles 3, 6, 9 12, 15, and 18 and every 3 cycles thereafter". 3. Urine pregnancy test schedule and wording for tumor evaluation were updated in the schedule of assessments and treatment schedule. 4. The shelf life of ublituximab was increased to 36 months from 24 months when stored between +2 C / +8 C to reflect newly available stability data on ublituximab drug product. 5. Included the most recent adverse event information related to ublituximab and umbralisib corresponding to the latest Investigator Brochures.  |
| 07 March 2017   | As per amendment 2: 1. Inclusion criteria was updated to provide a minimum time on a study arm of 2 cycles and included units (per microlitre) in regard to absolute neutrophil count (ANC) and platelet count. 2. Exclusion criteria was updated to clarify prophylaxis as "anti-pneumocystis pneumonia prophylaxis" and excluded subjects with prior live virus vaccines. 3. Appendix of the protocol (Contraceptive Guidelines and Pregnancy) was updated to delete the word "highly effective" and included follow-up recommendations for subjects entering the study from treatment arm B (obinutuzumab alone) in Study UTX-TGR-304. 4. Frequency of computed tomography (CT) scans for efficacy evaluation was revised to allow scans at every 3 or 6 cycles after Cycle 9 at the discretion of the investigator, to limit exposure to radiation. 5. The 21-day timeframe for signing informed consent was removed. 6. Informed consent was removed from the table of study assessment of the protocol as it was not a 21-day screening procedure.  |
| 29 March 2017   | As per amendment 3, definition of SAE was updated.  |
| 20 October 2017 | As per amendment 4: 1. Inclusion Criteria was updated to include: There is no required timeframe to begin treatment on the protocol, however, if other therapies to treat the disease are implemented in the interim, the subject was not eligible to enroll in the study. 2. Exclusion Criteria was updated to clarify the use of anti-pneumocystis pneumonia prophylaxis. 3. Treatment schedule was updated to increase the screening period from 21 to 28 days, included MRD testing for subjects who had a PR and increased the window for scans from +/- 7 days to +/- 14 days. 4. Specified the treatment schema for subjects crossing over from each of the 4 arms in the UTX-TGR-304 protocol 5. Included information regarding a new vial size for ublituximab. 6. Updated with the latest dose delay/modification guidance for ublituximab and umbralisib, included guidance for diarrhea and colitis events 7. Updated to include process of transferring drug from the UTX-TGR-304 protocol, if applicable. 8. Updated to include the most recent adverse event information related to ublituximab and umbralisib corresponding to the latest Investigator Brochures. 9. Removed text: At follow-up time points, the LDs for individual lesions and the SPD of all nodal target lesions will be considered. Because nodal target lesions that have one or both diameters >0 cm and <1.0 cm cannot be reliably measured, a default value of 1.0 cm will be assigned for each diameter that meets these criteria and the resulting perpendicular diameters (PPD) will be used in SPD calculations. Based on this convention, a CR may be achieved even if an SPD value is >0 cm <sup>2</sup> (i.e., if all lymph nodes measure <1.0 cm <sup>2</sup> )" to allow for more accurate measurements of nodal target lesions. 10. Updates were made throughout to include umbralisib as the generic name of TGR-1202. |

|                 |  |
|-----------------|--|
| 22 January 2019 | As per amendment 5: 1. Inclusion Criteria was updated to clarify that subjects with specified ANC and platelet count can be included unless cytopenias were related to bone marrow involvement and allowed subjects with Gilbert's Disease and Autoimmune Hemolytic Anemia. 2. Inclusion Criteria was updated to include the usage of the modified Cockcroft Gault utilizing ideal body mass. 3. Exclusion Criteria added: Evidence of chronic active Hepatitis B (HBV, not including subjects with prior hepatitis B vaccination; or positive serum Hepatitis B antibody) or chronic active Hepatitis C infection (HCV), cytomegalovirus (CMV), or known history of HIV. If HBc antibody, HCV antibody or CMV IgM is positive the subject must be evaluated for the presence of HBV, HCV, or CMV by polymerase chain reaction (PCR). 4. Tumor Evaluations updated as: Evaluations are to be obtained during cycles 3, 6 & 12. Following cycle 12, evaluations should occur at least every 12 cycles; Serum Virology was added to include HBsAG, HBc antibody, HCV antibody, and CMV IgG and IgM at screening and CMV surveillance while subjects were receiving umbralisib in study assessments and treatment schedule. 5. Follow up assessments schedule was added to clarify follow up assessments if a subject comes off study treatment. 6. Treatment plan was updated to clarify pneumocystis jiroveci pneumonia (PJP) and anti-viral prophylaxis language and provided more clear guidelines for timing of pre-medications for ublituximab. 7. Removed requirement for subjects to discontinue study drugs if held for more than 28 days. |
|-----------------|--|

Notes:

## Interruptions (globally)

Were there any global interruptions to the trial? No

## Limitations and caveats

None reported