



Clinical trial results:

High-dose chemotherapy and autologous stem cell transplant or consolidating conventional chemotherapy in primary CNS lymphoma - randomized phase III trial

Summary

| | |
|--------------------------|------------------|
| EudraCT number | 2012-000620-17 |
| Trial protocol | DE DK NO IT |
| Global end of trial date | 25 February 2022 |

Results information

| | |
|--------------------------------|------------------|
| Result version number | v1 |
| This version publication date | 22 February 2024 |
| First version publication date | 22 February 2024 |

Trial information

Trial identification

| | |
|-----------------------|--------------|
| Sponsor protocol code | DRKS00005503 |
|-----------------------|--------------|

Additional study identifiers

| | |
|------------------------------------|----------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT02531841 |
| WHO universal trial number (UTN) | - |
| Other trial identifiers | DRKS: 00005503 |

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | Klinikum Der Landeshauptstadt Stuttgart gKAöR |
| Sponsor organisation address | Kriegsbergstrasse 60, Stuttgart, Germany, 70174 |
| Public contact | PD Dr. med. Elisabeth Schorb, Medical Center - University of Freiburg, Germany, +49 761 270 35361, elisabeth.schorb@uniklinik-freiburg.de |
| Scientific contact | PD Dr. med. Elisabeth Schorb, Medical Center - University of Freiburg, Germany, +49 761 270 35361, elisabeth.schorb@uniklinik-freiburg.de |

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 | 18 September 2023 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 09 February 2022 |
| Global end of trial reached? | Yes |
| Global end of trial date | 25 February 2022 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

To demonstrate the efficacy measured as progression-free survival (PFS) of intensive chemotherapy followed by autologous stem-cell transplantation compared to conventional chemotherapy

Protection of trial subjects:

Interim analyses regarding safety issues were performed regularly in order to inform the Data Monitoring Committee (DMC). The underlying principles for the DMC are the patients' ethical and safety aspects. It is the task of the DMC to examine whether the study's conduct is still ethically justifiable, whether security of the patients is ensured and whether the study's conduct is acceptable. Data on the patient's vital signs were taken at screening and all subsequent visits. The patient was free to withdraw from the study for any reason and at any time without giving reason for doing so and without penalty or prejudice.

Background therapy: -

Evidence for comparator: -

| | |
|---|--------------|
| Actual start date of recruitment | 16 July 2014 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|----------------|
| Country: Number of subjects enrolled | Norway: 4 |
| Country: Number of subjects enrolled | Denmark: 11 |
| Country: Number of subjects enrolled | Germany: 284 |
| Country: Number of subjects enrolled | Italy: 46 |
| Country: Number of subjects enrolled | Switzerland: 1 |
| Worldwide total number of subjects | 346 |
| EEA total number of subjects | 345 |

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) | 262 |
| From 65 to 84 years | 84 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details: -

Pre-assignment period milestones

| | |
|----------------------------|-----|
| Number of subjects started | 346 |
|----------------------------|-----|

| | |
|------------------------------|-----|
| Number of subjects completed | 346 |
|------------------------------|-----|

Period 1

| | |
|----------------|---------------------|
| Period 1 title | Induction treatment |
|----------------|---------------------|

| | |
|------------------------------|-----|
| Is this the baseline period? | Yes |
|------------------------------|-----|

| | |
|-------------------|----------------|
| Allocation method | Not applicable |
|-------------------|----------------|

| | |
|---------------|-------------|
| Blinding used | Not blinded |
|---------------|-------------|

Blinding implementation details:

Single arm treatment period

Arms

| | |
|-----------|---------------------|
| Arm title | Induction treatment |
|-----------|---------------------|

Arm description:

4 cycles (every 3 weeks), stem-cell harvest after 2nd cycle:

- Rituximab 375 mg/m²/d i.v. (days 0, 5)
- MTX 3.5 g/m² i.v. (day 1)
- Ara-C 2 x 2 g/m²/d i.v. (days 2-3)
- Thiotepa 30 mg/m² i.v. (day 4)

| | |
|----------|---------------------|
| Arm type | Induction treatment |
|----------|---------------------|

| | |
|--|-----------|
| Investigational medicinal product name | Rituximab |
|--|-----------|

| | |
|--|--|
| Investigational medicinal product code | |
|--|--|

| | |
|------------|-----------|
| Other name | MabThera® |
|------------|-----------|

| | |
|----------------------|---------------------------------------|
| Pharmaceutical forms | Concentrate for solution for infusion |
|----------------------|---------------------------------------|

| | |
|--------------------------|---------------------------------------|
| Routes of administration | Concentrate for solution for infusion |
|--------------------------|---------------------------------------|

Dosage and administration details:

Strength: 10 mg/mL (referred to concentrate)

Dose: 3000 mg/m² (total), for induction treatment and consolidation treatment

For induction treatment: 375 mg/m²/d i.v. (day 0, 5)

| | |
|--|----------|
| Investigational medicinal product name | Thiotepa |
|--|----------|

| | |
|--|--|
| Investigational medicinal product code | |
|--|--|

| | |
|------------|------------------|
| Other name | TEPADINA® 100 mg |
|------------|------------------|

| | |
|----------------------|--|
| Pharmaceutical forms | Powder for concentrate for solution for infusion |
|----------------------|--|

| | |
|--------------------------|-----------------------|
| Routes of administration | Solution for infusion |
|--------------------------|-----------------------|

Dosage and administration details:

Strength: 10 mg/mL (refers to concentrate)

Dose: 30 mg/kg (total),

For induction treatment: 30 mg/m² i.v. (day 4)

| | |
|--|------------|
| Investigational medicinal product name | Cytarabine |
|--|------------|

| | |
|--|--|
| Investigational medicinal product code | |
|--|--|

| | |
|------------|-----------------------------------|
| Other name | ARA-cell® 4000 mg Infusionslösung |
|------------|-----------------------------------|

| | |
|----------------------|-----------------------|
| Pharmaceutical forms | Solution for infusion |
|----------------------|-----------------------|

| | |
|--|---------------------------------------|
| Routes of administration | Solution for infusion |
| Dosage and administration details: | |
| Strength: 50 mg/mL | |
| Dose: 32 g/m ² (total) | |
| For induction treatment: 2 x 2 g/m ² /d i.v. (days 2-3) | |
| Investigational medicinal product name | Methotrexate |
| Investigational medicinal product code | |
| Other name | Methotrexat HC 1000 mg Lösung Medac |
| Pharmaceutical forms | Concentrate for solution for infusion |
| Routes of administration | Concentrate for solution for infusion |
| Dosage and administration details: | |
| Strength: 100 mg/mL MTX (referred to concentrate) | |
| Dose: 14 g/m ² (total), for induction treatment | |
| For induction treatment: 3.5 g/m ² i.v. (day 1) | |

| Number of subjects in period 1 | Induction treatment |
|---|---------------------|
| Started | 346 |
| Completed | 230 |
| Not completed | 116 |
| incl. insufficient bone marrow recovery | 15 |
| Toxicity, AE/SAE | 56 |
| Wish of patient | 5 |
| Protocol deviation | 40 |

| | |
|---|-------------------------|
| Period 2 | |
| Period 2 title | Consolidation treatment |
| Is this the baseline period? | No |
| Allocation method | Randomised - controlled |
| Blinding used | Not blinded |
| Arms | |
| Are arms mutually exclusive? | Yes |
| Arm title | R-DeVIC |
| Arm description: | |
| 2 cycles of R-DeVIC (every 3 weeks): | |
| - Rituximab 375 mg/m ² /d i.v. (d 0) | |
| - Dexamethasone 40 mg/d i.v. (d 1-3) | |
| - Etoposide 100 mg/m ² /d i.v. (d 1-3) | |
| - Ifosfamide 1500 mg/m ² /d i.v. (d 1-3) | |
| - Carboplatin 300 mg/m ² i.v. (d 1) | |
| Arm type | Active comparator |

| | |
|--|---------------------------------------|
| Investigational medicinal product name | Rituximab |
| Investigational medicinal product code | |
| Other name | MabThera® |
| Pharmaceutical forms | Concentrate for solution for infusion |
| Routes of administration | Concentrate for solution for infusion |

Dosage and administration details:

Strength: 10 mg/mL (referred to concentrate)

Dose: 3000 mg/m² (total), for induction treatment and consolidation treatment

For consolidation treatment: 375 mg/m² i.v. (day 0)

| | |
|--|--|
| Investigational medicinal product name | Thiotepa |
| Investigational medicinal product code | |
| Other name | TEPADINA® 100 mg |
| Pharmaceutical forms | Powder for concentrate for solution for infusion |
| Routes of administration | Solution for infusion |

Dosage and administration details:

Strength: 10 mg/mL (refers to concentrate)

Dose: 30 mg/kg (total), for induction treatment, 20 mg/kg (total), for high-dose consolidation

| | |
|--|-----------------------------------|
| Investigational medicinal product name | Cytarabine |
| Investigational medicinal product code | |
| Other name | ARA-cell® 4000 mg Infusionslösung |
| Pharmaceutical forms | Solution for infusion |
| Routes of administration | Solution for infusion |

Dosage and administration details:

Strength: 50 mg/mL

Dose: 32 g/m² (total), for induction treatment

| | |
|--|---------------------------------------|
| Investigational medicinal product name | Methotrexate |
| Investigational medicinal product code | |
| Other name | Methotrexat HC 1000 mg Lösung Medac |
| Pharmaceutical forms | Concentrate for solution for infusion |
| Routes of administration | Concentrate for solution for infusion |

Dosage and administration details:

Strength: 100 mg/mL MTX (referred to concentrate)

Dose: 14 g/m² (total), for induction treatment

| | |
|--|---------------------------------------|
| Investigational medicinal product name | Ifosfamide |
| Investigational medicinal product code | |
| Other name | IFO-cell® 5 g |
| Pharmaceutical forms | Concentrate for solution for infusion |
| Routes of administration | Concentrate for solution for infusion |

Dosage and administration details:

Strength: 200 mg/mL

Dose: 9000 mg/m² (total), for consolidation Arm A

| | |
|--|----------------------------------|
| Investigational medicinal product name | Etoposide/VP-16 |
| Investigational medicinal product code | |
| Other name | ETOPOPHOS® 1000 mg |
| Pharmaceutical forms | Powder for solution for infusion |
| Routes of administration | Solution for infusion |

Dosage and administration details:

Strength: 11,4 mg/mL Etoposide phosphate (= 10 mg/mL Etoposide, referred to concentrate)

Dose: 600 mg/m² (total), for consolidation Arm A

| | |
|--|---------------------------|
| Investigational medicinal product name | Dexamethasone |
| Investigational medicinal product code | |
| Other name | Fortecortin® Inject 40 mg |
| Pharmaceutical forms | Solution for injection |

| | |
|---|---------------------------------------|
| Routes of administration | Solution for injection |
| Dosage and administration details: | |
| Strength: 8,744 mg/ml Dexamethason-21-dihydrogen phosphate disodium (= 8 mg/ml dexamethasone) | |
| Dose: 240 mg (total), for consolidation Arm A | |
| Investigational medicinal product name | Busulfan |
| Investigational medicinal product code | |
| Other name | Busilvex® |
| Pharmaceutical forms | Concentrate for solution for infusion |
| Routes of administration | Concentrate for solution for infusion |

Dosage and administration details:

Strength: 6 mg/mL (refers to concentrate)

Dose: 6.4 mg/ml (total)

| | |
|--|---------------------------------------|
| Investigational medicinal product name | Carboplatin |
| Investigational medicinal product code | |
| Other name | CARBO-cell® 10 mg/mL Infusionslösung |
| Pharmaceutical forms | Concentrate for solution for infusion |
| Routes of administration | Concentrate for solution for infusion |

Dosage and administration details:

Strength: 10 mg/mL

Dose: 600 mg/m² (total), for consolidation Arm A

| | |
|--|--|
| Investigational medicinal product name | Carmustine/BCNU |
| Investigational medicinal product code | |
| Other name | CARMUBRIS® |
| Pharmaceutical forms | Powder and solvent for solution for infusion |
| Routes of administration | Solution for infusion |

Dosage and administration details:

Strength: 3.3 mg/mL (refers to concentrate)

Dose: 400 mg/m² (total), for consolidation in experimental intervention

| | |
|------------------|----------|
| Arm title | HDT-ASCT |
|------------------|----------|

Arm description:

High-dose chemotherapy (HDT):

- BCNU* 400 mg/m² i.v. (d -6)
- Thiotepa 2 x 5 mg/kg/d i.v. (d -5-(-4))
- ASCT (d 0)

* if not available at study site, Busulfan could have been administered: Busulfan 3.2 mg/kg/d i.v. (d -8-(-7))

| | |
|--|--|
| Arm type | Experimental |
| Investigational medicinal product name | Carmustine/BCNU |
| Investigational medicinal product code | |
| Other name | CARMUBRIS® |
| Pharmaceutical forms | Powder and solvent for solution for infusion |
| Routes of administration | Solution for infusion |

Dosage and administration details:

Strength: 3.3 mg/mL (refers to concentrate)

Dose: 400 mg/m² (total).

For consolidation treatment: BCNU 400 mg/m² i.v. (d -6). If not available at study site, Busulfan could have been administered:

Busulfan 3.2 mg/kg/d i.v. (d -8-(-7))

| | |
|--|--|
| Investigational medicinal product name | Thiotepa |
| Investigational medicinal product code | |
| Other name | TEPADINA® 100 mg |
| Pharmaceutical forms | Powder for concentrate for solution for infusion |
| Routes of administration | Solution for infusion |

Dosage and administration details:

Strength: 10 mg/mL (refers to concentrate)

Dose: 30 mg/kg (total),
For consolidation treatment: 2 x 5 mg/kg/d i.v. (d -5-(-4))

| Number of subjects in period 2 | R-DeVIC | HDT-ASCT |
|---------------------------------------|---------|----------|
| Started | 115 | 115 |
| Completed | 115 | 114 |
| Not completed | 0 | 1 |
| Major I/E violation | - | 1 |

Baseline characteristics

Reporting groups

| | |
|-----------------------|---------------------|
| Reporting group title | Induction treatment |
|-----------------------|---------------------|

Reporting group description: -

| Reporting group values | Induction treatment | Total | |
|---|---------------------|-------|--|
| Number of subjects | 346 | 346 | |
| Age categorical | | | |
| Units: Subjects | | | |
| In utero | 0 | 0 | |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | |
| Newborns (0-27 days) | 0 | 0 | |
| Infants and toddlers (28 days-23 months) | 0 | 0 | |
| Children (2-11 years) | 0 | 0 | |
| Adolescents (12-17 years) | 0 | 0 | |
| Adults (18-64 years) | 262 | 262 | |
| From 65-84 years | 84 | 84 | |
| 85 years and over | 0 | 0 | |
| Age continuous | | | |
| Units: years | | | |
| arithmetic mean | 57.8 | | |
| standard deviation | ± 9.5 | - | |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 150 | 150 | |
| Male | 196 | 196 | |

End points

End points reporting groups

| Reporting group title | Induction treatment |
|---|---------------------|
| Reporting group description: 4 cycles (every 3 weeks), stem-cell harvest after 2nd cycle: - Rituximab 375 mg/m ² /d i.v. (days 0, 5) - MTX 3.5 g/m ² i.v. (day 1) - Ara-C 2 x 2 g/m ² /d i.v. (days 2-3) - Thiotepa 30 mg/m ² i.v. (day 4) | |
| Reporting group title | R-DeVIC |
| Reporting group description: 2 cycles of R-DeVIC (every 3 weeks): - Rituximab 375 mg/m ² /d i.v. (d 0) - Dexamethasone 40 mg/d i.v. (d 1-3) - Etoposide 100 mg/m ² /d i.v. (d 1-3) - Ifosfamide 1500 mg/m ² /d i.v. (d 1-3) - Carboplatin 300 mg/m ² i.v. (d 1) | |
| Reporting group title | HDT-ASCT |
| Reporting group description: High-dose chemotherapy (HDT): - BCNU* 400 mg/m ² i.v. (d -6) - Thiotepa 2 x 5 mg/kg/d i.v. (d -5-(-4)) - ASCT (d 0) * if not available at study site, Busulfan could have been administered: Busulfan 3.2 mg/kg/d i.v. (d -8-(-7)) | |

Primary: Progression-free survival (FAS)

| End point title | Progression-free survival (FAS) |
|--|---------------------------------|
| End point description: | |
| End point type | Primary |
| End point timeframe: Time from randomization until disease progression), disease relapse after achieving complete response (CR), or death from any cause. | |

| End point values | R-DeVIC | HDT-ASCT | | |
|----------------------------------|---------------------|---------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 115 | 114 | | |
| Units: Rate | | | | |
| number (confidence interval 95%) | | | | |
| 6 months | 0.83 (0.74 to 0.88) | 0.83 (0.75 to 0.89) | | |
| 12 months | 0.71 (0.62 to 0.78) | 0.83 (0.74 to 0.88) | | |
| 24 months | 0.61 (0.51 to 0.69) | 0.79 (0.70 to 0.85) | | |
| 36 months | 0.51 (0.41 to 0.60) | 0.78 (0.69 to 0.85) | | |
| 48 months | 0.50 (0.40 to 0.59) | 0.77 (0.67 to 0.83) | | |

| | | | | |
|-----------|---------------------|---------------------|--|--|
| 60 months | 0.46 (0.35 to 0.56) | 0.74 (0.62 to 0.82) | | |
|-----------|---------------------|---------------------|--|--|

Statistical analyses

| | |
|---|-------------------------|
| Statistical analysis title | Cox regression analysis |
| Statistical analysis description: | |
| The primary endpoint PFS was analyzed with a Cox proportional hazards model, containing the randomized treatment as hypothesis variable and the stratification variable response status as a covariate. | |
| Comparison groups | R-DeVIC v HDT-ASCT |
| Number of subjects included in analysis | 229 |
| Analysis specification | Pre-specified |
| Analysis type | equivalence |
| P-value | = 0.0003 |
| Method | Regression, Cox |
| Parameter estimate | Cox proportional hazard |
| Point estimate | 0.43 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.27 |
| upper limit | 0.68 |

Secondary: Overall survival (FAS)

| | |
|---|------------------------|
| End point title | Overall survival (FAS) |
| End point description: | |
| End point type | Secondary |
| End point timeframe: | |
| Time from randomization until death from any cause. | |

| End point values | R-DeVIC | HDT-ASCT | | |
|----------------------------------|---------------------|---------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 115 | 114 | | |
| Units: Rate | | | | |
| number (confidence interval 95%) | | | | |
| 6 months | 0.96 (0.90 to 0.98) | 0.93 (0.86 to 0.96) | | |
| 12 months | 0.89 (0.81 to 0.93) | 0.91 (0.84 to 0.95) | | |
| 24 months | 0.80 (0.72 to 0.87) | 0.87 (0.79 to 0.92) | | |

| | | | | |
|-----------|---------------------|---------------------|--|--|
| 36 months | 0.71 (0.61 to 0.78) | 0.86 (0.78 to 0.91) | | |
| 48 months | 0.68 (0.58 to 0.76) | 0.84 (0.76 to 0.90) | | |
| 60 months | 0.63 (0.52 to 0.73) | 0.84 (0.76 to 0.90) | | |

Statistical analyses

| Statistical analysis title | Hazard Ratio |
|---|--------------------|
| Comparison groups | R-DeVIC v HDT-ASCT |
| Number of subjects included in analysis | 229 |
| Analysis specification | Pre-specified |
| Analysis type | equivalence |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.46 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.26 |
| upper limit | 0.81 |

Secondary: Relapse rate

| | |
|-------------------------|--------------|
| End point title | Relapse rate |
| End point description: | |
| End point type | Secondary |
| End point timeframe: | |
| Time from randomization | |

| End point values | R-DeVIC | HDT-ASCT | | |
|----------------------------------|---------------------------|---------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 115 | 114 | | |
| Units: Rate | | | | |
| number (confidence interval 95%) | | | | |
| 6 months | 0.1667 (0.1048 to 0.2409) | 0.1316 (0.0772 to 0.2008) | | |
| 12 months | 0.2725 (0.1940 to 0.3567) | 0.1404 (0.0839 to 0.2109) | | |
| 24 months | 0.3736 (0.2842 to 0.4629) | 0.1770 (0.1129 to 0.2530) | | |
| 36 months | 0.4494 (0.3519 to 0.5419) | 0.1864 (0.1204 to 0.2636) | | |

| | | | | |
|-----------|---------------------------|---------------------------|--|--|
| 48 months | 0.4636 (0.3640 to 0.5572) | 0.1994 (0.1300 to 0.2796) | | |
| 60 months | 0.4820 (0.3784 to 0.5782) | 0.2300 (0.1433 to 0.3289) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Non Relapse Mortality (FAS)

| | |
|-----------------|-----------------------------|
| End point title | Non Relapse Mortality (FAS) |
|-----------------|-----------------------------|

End point description:

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Time from randomization to death without prior relapse / disease progression

| End point values | R-DeVIC | HDT-ASCT | | |
|----------------------------------|---------------------------|---------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 115 | 114 | | |
| Units: Rate | | | | |
| number (confidence interval 95%) | | | | |
| 6 months | 0.0088 (0.0008 to 0.0437) | 0.0351 (0.0114 to 0.0813) | | |
| 12 months | 0.0175 (0.0034 to 0.0565) | 0.0351 (0.0114 to 0.0813) | | |
| 24 months | 0.0175 (0.0034 to 0.0565) | 0.0351 (0.0114 to 0.0813) | | |
| 36 months | 0.0386 (0.0124 to 0.0896) | 0.0351 (0.0114 to 0.0813) | | |
| 48 months | 0.0386 (0.0124 to 0.0896) | 0.0351 (0.0114 to 0.0813) | | |
| 60 months | 0.0626 (0.0200 to 0.1404) | 0.0351 (0.0114 to 0.0813) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Quality of life EORTC QLQ-C30: 1 year follow-up

| | |
|------------------------|---|
| End point title | Quality of life EORTC QLQ-C30: 1 year follow-up |
| End point description: | |
| End point type | Secondary |
| End point timeframe: | |
| 1 year follow up | |

| End point values | R-DeVIC | HDT-ASCT | | |
|--------------------------------------|--------------------|--------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 115 | 114 | | |
| Units: Points | | | | |
| arithmetic mean (standard deviation) | | | | |
| 1 year follow-up | 63.6 (\pm 20.1) | 64.9 (\pm 20.8) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Quality of life EORTC QLQ-C30: EOT change from screening

| | |
|---|--|
| End point title | Quality of life EORTC QLQ-C30: EOT change from screening |
| End point description: | |
| Only patients with paired values before and after therapy were considered | |
| End point type | Secondary |
| End point timeframe: | |
| From screening to end of treatment | |

| End point values | R-DeVIC | HDT-ASCT | | |
|---|-------------------|-------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 115 | 114 | | |
| Units: Points | | | | |
| arithmetic mean (standard deviation) | | | | |
| Change from screening to end of treatment | 6.9 (\pm 31.4) | 8.3 (\pm 29.7) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Quality of life EORTC QLQ-C30: 1 year follow-up: change from screening

| | |
|-----------------|--|
| End point title | Quality of life EORTC QLQ-C30: 1 year follow-up: change from screening |
|-----------------|--|

End point description:

Only patients with paired values before and after therapy were considered.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

From screening to 1 year follow up

| End point values | R-DeVIC | HDT-ASCT | | |
|---|--------------------|--------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 115 | 114 | | |
| Units: Points | | | | |
| arithmetic mean (standard deviation) | | | | |
| 1 year follow-up: change from screening | 11.0 (\pm 30.1) | 14.8 (\pm 27.5) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Quality of life EORTC QLQ-C30: Screening

| | |
|-----------------|--|
| End point title | Quality of life EORTC QLQ-C30: Screening |
|-----------------|--|

End point description:

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

at screening

| End point values | R-DeVIC | HDT-ASCT | | |
|--------------------------------------|--------------------|--------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 115 | 114 | | |
| Units: Points | | | | |
| arithmetic mean (standard deviation) | | | | |
| Screening | 49.8 (\pm 26.1) | 47.1 (\pm 27.2) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Quality of life EORTC QLQ-C30: Response assessment II

| | |
|-----------------|---|
| End point title | Quality of life EORTC QLQ-C30: Response assessment II |
|-----------------|---|

End point description:

| | |
|------------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Response assessment II | |

| End point values | R-DeVIC | HDT-ASCT | | |
|--------------------------------------|--------------------|--------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 115 | 114 | | |
| Units: Points | | | | |
| arithmetic mean (standard deviation) | | | | |
| Response assessment II | 55.0 (\pm 21.6) | 57.5 (\pm 19.5) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Quality of life EORTC QLQ-C30: EOT

| | |
|------------------------|------------------------------------|
| End point title | Quality of life EORTC QLQ-C30: EOT |
| End point description: | |
| End point type | Secondary |
| End point timeframe: | |
| End of treatment | |

| End point values | R-DeVIC | HDT-ASCT | | |
|--------------------------------------|--------------------|--------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 115 | 114 | | |
| Units: Points | | | | |
| arithmetic mean (standard deviation) | | | | |
| End of treatment | 57.7 (\pm 20.9) | 53.1 (\pm 51.0) | | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Complete study

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

Dictionary used

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

| | |
|--------------------|----|
| Dictionary version | 22 |
|--------------------|----|

Reporting groups

| | |
|-----------------------|-----------------|
| Reporting group title | Arm A (R-DeVic) |
|-----------------------|-----------------|

Reporting group description: -

| | |
|-----------------------|-------------------|
| Reporting group title | Induction therapy |
|-----------------------|-------------------|

Reporting group description: -

| | |
|-----------------------|------------------|
| Reporting group title | Arm B (HDT-ASCT) |
|-----------------------|------------------|

Reporting group description: -

| Serious adverse events | Arm A (R-DeVic) | Induction therapy | Arm B (HDT-ASCT) |
|---|-------------------|--------------------|-------------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 25 / 108 (23.15%) | 200 / 346 (57.80%) | 29 / 111 (26.13%) |
| number of deaths (all causes) | 36 | 63 | 17 |
| number of deaths resulting from adverse events | 3 | 25 | 5 |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Acute myeloid leukaemia | | | |
| subjects affected / exposed | 2 / 108 (1.85%) | 0 / 346 (0.00%) | 0 / 111 (0.00%) |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 2 / 2 | 0 / 0 | 0 / 0 |
| Myelodysplastic syndrome | | | |
| subjects affected / exposed | 1 / 108 (0.93%) | 0 / 346 (0.00%) | 0 / 111 (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 |
| Vascular disorders | | | |
| Deep vein thrombosis | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 0 / 346 (0.00%) | 1 / 111 (0.90%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypotension | | | |

| | | | |
|--|-----------------|------------------|-----------------|
| subjects affected / exposed | 0 / 108 (0.00%) | 1 / 346 (0.29%) | 0 / 111 (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 |
| Jugular vein thrombosis | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 1 / 346 (0.29%) | 0 / 111 (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 |
| Thrombosis | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 1 / 346 (0.29%) | 0 / 111 (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 |
| General disorders and administration site conditions | | | |
| Asthenia | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 1 / 346 (0.29%) | 0 / 111 (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 |
| Mucosal inflammation | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 2 / 346 (0.58%) | 1 / 111 (0.90%) |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 2 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pain | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 1 / 346 (0.29%) | 0 / 111 (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 |
| Pyrexia | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 11 / 346 (3.18%) | 2 / 111 (1.80%) |
| occurrences causally related to treatment / all | 0 / 0 | 6 / 11 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Acute respiratory distress syndrome | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 1 / 346 (0.29%) | 0 / 111 (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 |

| | | | |
|---|-----------------|-----------------|-----------------|
| Acute respiratory failure | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 1 / 346 (0.29%) | 0 / 111 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Epistaxis | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 2 / 346 (0.58%) | 0 / 111 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 3 / 3 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Haemothorax | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 1 / 346 (0.29%) | 0 / 111 (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 |
| Hypercapnia | | | |
| subjects affected / exposed | 1 / 108 (0.93%) | 0 / 346 (0.00%) | 0 / 111 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lung infiltration | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 1 / 346 (0.29%) | 0 / 111 (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 |
| Interstitial lung disease | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 1 / 346 (0.29%) | 0 / 111 (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 |
| Pulmonary embolism | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 1 / 346 (0.29%) | 1 / 111 (0.90%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Pneumothorax | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 2 / 346 (0.58%) | 0 / 111 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonitis | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 108 (0.00%) | 1 / 346 (0.29%) | 0 / 111 (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 |
| Respiratory failure | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 1 / 346 (0.29%) | 0 / 111 (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 |
| Respiratory arrest | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 1 / 346 (0.29%) | 0 / 111 (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 |
| Psychiatric disorders | | | |
| Acute psychosis | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 1 / 346 (0.29%) | 0 / 111 (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 |
| Confusional state | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 1 / 346 (0.29%) | 0 / 111 (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 |
| Depression | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 0 / 346 (0.00%) | 1 / 111 (0.90%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Self-injurious ideation | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 1 / 346 (0.29%) | 0 / 111 (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 |
| Suicide attempt | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 1 / 346 (0.29%) | 0 / 111 (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 |
| Investigations | | | |

| | | | |
|--|-----------------|-----------------|-----------------|
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 1 / 346 (0.29%) | 0 / 111 (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 |
| Blood creatinine increased | | | |
| subjects affected / exposed | 1 / 108 (0.93%) | 1 / 346 (0.29%) | 0 / 111 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| C-reactive protein increased | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 2 / 346 (0.58%) | 0 / 111 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Chemotherapeutic drug level increased | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 1 / 346 (0.29%) | 0 / 111 (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 |
| Eastern Cooperative Oncology Group performance status worsened | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 1 / 346 (0.29%) | 0 / 111 (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 |
| Haemoglobin decreased | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 1 / 346 (0.29%) | 0 / 111 (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 |
| Hepatic enzyme increased | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 1 / 346 (0.29%) | 0 / 111 (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 |
| Neutrophil count decreased | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 1 / 346 (0.29%) | 0 / 111 (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 |
| Platelet count decreased | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 2 / 108 (1.85%) | 3 / 346 (0.87%) | 0 / 111 (0.00%) |
| occurrences causally related to treatment / all | 2 / 2 | 3 / 3 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Transaminases increased | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 1 / 346 (0.29%) | 0 / 111 (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 |
| Injury, poisoning and procedural complications | | | |
| Brain herniation | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 1 / 346 (0.29%) | 0 / 111 (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 |
| Haemolytic transfusion reaction | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 1 / 346 (0.29%) | 0 / 111 (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 |
| Seroma | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 1 / 346 (0.29%) | 0 / 111 (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 |
| Transplant failure | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 0 / 346 (0.00%) | 1 / 111 (0.90%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Wound dehiscence | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 2 / 346 (0.58%) | 0 / 111 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac disorders | | | |
| Acute myocardial infarction | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 2 / 346 (0.58%) | 0 / 111 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|-----------------|-----------------|-----------------|
| Atrial fibrillation | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 2 / 346 (0.58%) | 0 / 111 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac failure | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 1 / 346 (0.29%) | 0 / 111 (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 |
| Cardiac arrest | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 1 / 346 (0.29%) | 0 / 111 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nervous system disorders | | | |
| Brain oedema | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 1 / 346 (0.29%) | 0 / 111 (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 |
| Cerebellar syndrome | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 1 / 346 (0.29%) | 0 / 111 (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 |
| Cerebral haemorrhage | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 1 / 346 (0.29%) | 0 / 111 (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 |
| Cerebral infarction | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 1 / 346 (0.29%) | 0 / 111 (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 |
| Cerebrovascular accident | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 1 / 346 (0.29%) | 0 / 111 (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 |
| Dysarthria | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 108 (0.00%) | 1 / 346 (0.29%) | 0 / 111 (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 |
| Epilepsy | | | |
| subjects affected / exposed | 1 / 108 (0.93%) | 1 / 346 (0.29%) | 0 / 111 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Haemorrhage intracranial | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 1 / 346 (0.29%) | 0 / 111 (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 |
| Hydrocephalus | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 1 / 346 (0.29%) | 0 / 111 (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 |
| Hypoaesthesia | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 1 / 346 (0.29%) | 0 / 111 (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 |
| IIIrd nerve paralysis | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 1 / 346 (0.29%) | 0 / 111 (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 |
| Meningism | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 1 / 346 (0.29%) | 0 / 111 (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 |
| Neurotoxicity | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 1 / 346 (0.29%) | 0 / 111 (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 |
| Seizure | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 108 (0.93%) | 2 / 346 (0.58%) | 0 / 111 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Syncope | | | |
| subjects affected / exposed | 1 / 108 (0.93%) | 0 / 346 (0.00%) | 0 / 111 (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 |
| Subdural hygroma | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 1 / 346 (0.29%) | 0 / 111 (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 |
| Transient ischaemic attack | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 1 / 346 (0.29%) | 0 / 111 (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 |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 3 / 108 (2.78%) | 8 / 346 (2.31%) | 1 / 111 (0.90%) |
| occurrences causally related to treatment / all | 3 / 3 | 7 / 8 | 2 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bicytopenia | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 1 / 346 (0.29%) | 0 / 111 (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 |
| Cytopenia | | | |
| subjects affected / exposed | 1 / 108 (0.93%) | 0 / 346 (0.00%) | 0 / 111 (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 |
| Febrile bone marrow aplasia | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 2 / 346 (0.58%) | 0 / 111 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Febrile neutropenia | | | |

| | | | |
|---|-----------------|-------------------|-----------------|
| subjects affected / exposed | 3 / 108 (2.78%) | 45 / 346 (13.01%) | 1 / 111 (0.90%) |
| occurrences causally related to treatment / all | 3 / 3 | 55 / 57 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Leukopenia | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 3 / 346 (0.87%) | 0 / 111 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 3 / 3 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Neutropenia | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 5 / 346 (1.45%) | 0 / 111 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 4 / 5 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pancytopenia | | | |
| subjects affected / exposed | 2 / 108 (1.85%) | 11 / 346 (3.18%) | 3 / 111 (2.70%) |
| occurrences causally related to treatment / all | 2 / 2 | 17 / 17 | 3 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Thrombocytopenia | | | |
| subjects affected / exposed | 4 / 108 (3.70%) | 13 / 346 (3.76%) | 2 / 111 (1.80%) |
| occurrences causally related to treatment / all | 4 / 4 | 13 / 14 | 1 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Ear and labyrinth disorders | | | |
| Vertigo | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 1 / 346 (0.29%) | 0 / 111 (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 |
| Gastrointestinal disorders | | | |
| Colitis ischaemic | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 1 / 346 (0.29%) | 0 / 111 (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 |
| Duodenal ulcer | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 1 / 346 (0.29%) | 0 / 111 (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 |
| Diverticular perforation | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 108 (0.00%) | 1 / 346 (0.29%) | 0 / 111 (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 |
| Mechanical ileus | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 1 / 346 (0.29%) | 0 / 111 (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 |
| Lower gastrointestinal haemorrhage | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 1 / 346 (0.29%) | 0 / 111 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Large intestine perforation | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 1 / 346 (0.29%) | 0 / 111 (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 |
| Intestinal perforation | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 1 / 346 (0.29%) | 0 / 111 (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 |
| Pancreatitis | | | |
| subjects affected / exposed | 1 / 108 (0.93%) | 0 / 346 (0.00%) | 0 / 111 (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 |
| Proctitis ulcerative | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 1 / 346 (0.29%) | 0 / 111 (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 |
| Stomatitis | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 3 / 346 (0.87%) | 1 / 111 (0.90%) |
| occurrences causally related to treatment / all | 0 / 0 | 3 / 3 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Upper gastrointestinal haemorrhage | | | |

| | | | |
|---|-----------------|------------------|-----------------|
| subjects affected / exposed | 0 / 108 (0.00%) | 1 / 346 (0.29%) | 0 / 111 (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 |
| Vomiting | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 1 / 346 (0.29%) | 0 / 111 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatobiliary disorders | | | |
| Gallbladder rupture | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 0 / 346 (0.00%) | 1 / 111 (0.90%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatotoxicity | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 1 / 346 (0.29%) | 1 / 111 (0.90%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Skin and subcutaneous tissue disorders | | | |
| Hyperhidrosis | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 1 / 346 (0.29%) | 0 / 111 (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 |
| Renal and urinary disorders | | | |
| Acute kidney injury | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 12 / 346 (3.47%) | 4 / 111 (3.60%) |
| occurrences causally related to treatment / all | 0 / 0 | 11 / 12 | 2 / 4 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal failure | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 4 / 346 (1.16%) | 0 / 111 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 3 / 4 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal tubular disorder | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 1 / 346 (0.29%) | 0 / 111 (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 |

| | | | |
|---|-----------------|-----------------|-----------------|
| Endocrine disorders | | | |
| Diabetes insipidus | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 0 / 346 (0.00%) | 1 / 111 (0.90%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Musculoskeletal and connective tissue disorders | | | |
| Back pain | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 2 / 346 (0.58%) | 0 / 111 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 3 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bone pain | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 1 / 346 (0.29%) | 0 / 111 (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 |
| Muscle spasms | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 1 / 346 (0.29%) | 0 / 111 (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 |
| Infections and infestations | | | |
| Abscess jaw | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 1 / 346 (0.29%) | 0 / 111 (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 |
| Abscess | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 1 / 346 (0.29%) | 0 / 111 (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 |
| Arthritis bacterial | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 1 / 346 (0.29%) | 0 / 111 (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 |
| Atypical mycobacterial infection | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 108 (0.00%) | 1 / 346 (0.29%) | 0 / 111 (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 |
| Atypical pneumonia | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 1 / 346 (0.29%) | 1 / 111 (0.90%) |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 2 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bacterial sepsis | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 2 / 346 (0.58%) | 0 / 111 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Brain abscess | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 1 / 346 (0.29%) | 0 / 111 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bronchitis | | | |
| subjects affected / exposed | 1 / 108 (0.93%) | 1 / 346 (0.29%) | 0 / 111 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Candida sepsis | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 1 / 346 (0.29%) | 0 / 111 (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 |
| Cerebral candidiasis | | | |
| subjects affected / exposed | 1 / 108 (0.93%) | 0 / 346 (0.00%) | 0 / 111 (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 |
| Clostridium difficile colitis | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 2 / 346 (0.58%) | 0 / 111 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Clostridium difficile infection | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 108 (0.00%) | 1 / 346 (0.29%) | 0 / 111 (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 |
| Cytomegalovirus infection | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 2 / 346 (0.58%) | 0 / 111 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cytomegalovirus infection reactivation | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 0 / 346 (0.00%) | 1 / 111 (0.90%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Device related infection | | | |
| subjects affected / exposed | 1 / 108 (0.93%) | 5 / 346 (1.45%) | 0 / 111 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 5 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Device related sepsis | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 2 / 346 (0.58%) | 1 / 111 (0.90%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Diverticulitis | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 3 / 346 (0.87%) | 0 / 111 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 3 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Empyema | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 1 / 346 (0.29%) | 0 / 111 (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 |
| Endocarditis staphylococcal | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 1 / 346 (0.29%) | 0 / 111 (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 |
| Escherichia bacteraemia | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 108 (0.93%) | 0 / 346 (0.00%) | 0 / 111 (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 |
| Escherichia infection | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 1 / 346 (0.29%) | 0 / 111 (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 |
| Escherichia sepsis | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 4 / 346 (1.16%) | 0 / 111 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 4 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Febrile infection | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 1 / 346 (0.29%) | 0 / 111 (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 |
| Gastroenteritis Escherichia coli | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 1 / 346 (0.29%) | 0 / 111 (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 |
| H1N1 influenza | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 1 / 346 (0.29%) | 0 / 111 (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 |
| Herpes zoster infection neurological | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 1 / 346 (0.29%) | 0 / 111 (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 |
| Infection | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 7 / 346 (2.02%) | 2 / 111 (1.80%) |
| occurrences causally related to treatment / all | 0 / 0 | 5 / 8 | 2 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Influenza | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 108 (0.00%) | 1 / 346 (0.29%) | 0 / 111 (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 |
| Medical device site infection | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 2 / 346 (0.58%) | 0 / 111 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Klebsiella infection | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 1 / 346 (0.29%) | 0 / 111 (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 |
| Neutropenic sepsis | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 5 / 346 (1.45%) | 3 / 111 (2.70%) |
| occurrences causally related to treatment / all | 0 / 0 | 5 / 5 | 3 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 1 / 1 | 1 / 1 |
| Neutropenic infection | | | |
| subjects affected / exposed | 1 / 108 (0.93%) | 8 / 346 (2.31%) | 0 / 111 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 7 / 8 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Osteomyelitis | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 1 / 346 (0.29%) | 0 / 111 (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 |
| Necrotising soft tissue infection | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 1 / 346 (0.29%) | 0 / 111 (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 |
| Mucormycosis | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 1 / 346 (0.29%) | 0 / 111 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonia escherichia | | | |

| | | | |
|---|-----------------|------------------|-----------------|
| subjects affected / exposed | 0 / 108 (0.00%) | 1 / 346 (0.29%) | 0 / 111 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonia cytomegaloviral | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 1 / 346 (0.29%) | 0 / 111 (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 |
| Pneumonia bacterial | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 1 / 346 (0.29%) | 0 / 111 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonia | | | |
| subjects affected / exposed | 2 / 108 (1.85%) | 24 / 346 (6.94%) | 4 / 111 (3.60%) |
| occurrences causally related to treatment / all | 1 / 2 | 20 / 26 | 3 / 4 |
| deaths causally related to treatment / all | 0 / 0 | 4 / 4 | 2 / 2 |
| Parainfluenzae virus infection | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 1 / 346 (0.29%) | 0 / 111 (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 |
| Osteomyelitis bacterial | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 1 / 346 (0.29%) | 0 / 111 (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 |
| Peritonitis | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 1 / 346 (0.29%) | 0 / 111 (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 |
| Pseudomonal sepsis | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 1 / 346 (0.29%) | 0 / 111 (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 |
| Pseudomembranous colitis | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 108 (0.00%) | 1 / 346 (0.29%) | 0 / 111 (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 |
| Post procedural infection | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 2 / 346 (0.58%) | 0 / 111 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonia necrotising | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 0 / 346 (0.00%) | 1 / 111 (0.90%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonia klebsiella | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 1 / 346 (0.29%) | 0 / 111 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonia influenzal | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 2 / 346 (0.58%) | 0 / 111 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pulmonary sepsis | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 3 / 346 (0.87%) | 0 / 111 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 3 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| Pneumonia fungal | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 2 / 346 (0.58%) | 1 / 111 (0.90%) |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 2 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| Rectal abscess | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 1 / 346 (0.29%) | 0 / 111 (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 |
| Pyelonephritis | | | |

| | | | |
|---|-----------------|------------------|-----------------|
| subjects affected / exposed | 0 / 108 (0.00%) | 1 / 346 (0.29%) | 0 / 111 (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 |
| Puncture site abscess | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 1 / 346 (0.29%) | 0 / 111 (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 |
| Sepsis | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 18 / 346 (5.20%) | 2 / 111 (1.80%) |
| occurrences causally related to treatment / all | 0 / 0 | 12 / 19 | 2 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 3 / 3 | 1 / 1 |
| Respiratory tract infection viral | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 1 / 346 (0.29%) | 0 / 111 (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 |
| Septic shock | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 8 / 346 (2.31%) | 3 / 111 (2.70%) |
| occurrences causally related to treatment / all | 0 / 0 | 7 / 9 | 3 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 3 / 3 | 0 / 0 |
| Skin infection | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 2 / 346 (0.58%) | 0 / 111 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Staphylococcal sepsis | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 1 / 346 (0.29%) | 0 / 111 (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 |
| Tooth abscess | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 1 / 346 (0.29%) | 0 / 111 (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 |
| Urinary tract infection | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 108 (0.00%) | 2 / 346 (0.58%) | 1 / 111 (0.90%) |
| occurrences causally related to treatment / all | 0 / 0 | 3 / 3 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Wound abscess | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 1 / 346 (0.29%) | 0 / 111 (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 |
| Viral infection | | | |
| subjects affected / exposed | 1 / 108 (0.93%) | 0 / 346 (0.00%) | 0 / 111 (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 |
| Urosepsis | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 1 / 346 (0.29%) | 0 / 111 (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 |
| Wound infection | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 1 / 346 (0.29%) | 0 / 111 (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 |
| Metabolism and nutrition disorders | | | |
| Decreased appetite | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 1 / 346 (0.29%) | 0 / 111 (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 |
| Gout | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 1 / 346 (0.29%) | 0 / 111 (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 |
| Hyperkalaemia | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 1 / 346 (0.29%) | 0 / 111 (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 |
| Hypernatraemia | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 108 (0.00%) | 0 / 346 (0.00%) | 1 / 111 (0.90%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypoglycaemia | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 0 / 346 (0.00%) | 1 / 111 (0.90%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypokalaemia | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 0 / 346 (0.00%) | 2 / 111 (1.80%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

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

| Non-serious adverse events | Arm A (R-DeVic) | Induction therapy | Arm B (HDT-ASCT) |
|---|---------------------|--------------------|---------------------|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 108 / 108 (100.00%) | 344 / 346 (99.42%) | 111 / 111 (100.00%) |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Plasma cell myeloma | | | |
| subjects affected / exposed | 1 / 108 (0.93%) | 0 / 346 (0.00%) | 0 / 111 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Prostate cancer | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 1 / 346 (0.29%) | 0 / 111 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Vascular disorders | | | |
| Deep vein thrombosis | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 3 / 346 (0.87%) | 0 / 111 (0.00%) |
| occurrences (all) | 0 | 3 | 0 |
| Embolism | | | |
| subjects affected / exposed | 3 / 108 (2.78%) | 31 / 346 (8.96%) | 2 / 111 (1.80%) |
| occurrences (all) | 3 | 31 | 2 |
| Flushing | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 1 / 346 (0.29%) | 1 / 111 (0.90%) |
| occurrences (all) | 0 | 1 | 1 |

| | | | |
|--|-------------------|-------------------|-------------------|
| Haematoma | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 5 / 346 (1.45%) | 0 / 111 (0.00%) |
| occurrences (all) | 0 | 5 | 0 |
| Hypertension | | | |
| subjects affected / exposed | 17 / 108 (15.74%) | 94 / 346 (27.17%) | 28 / 111 (25.23%) |
| occurrences (all) | 17 | 94 | 28 |
| Hypotension | | | |
| subjects affected / exposed | 7 / 108 (6.48%) | 48 / 346 (13.87%) | 15 / 111 (13.51%) |
| occurrences (all) | 7 | 50 | 15 |
| Jugular vein thrombosis | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 0 / 346 (0.00%) | 1 / 111 (0.90%) |
| occurrences (all) | 0 | 0 | 1 |
| Phlebitis | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 10 / 346 (2.89%) | 2 / 111 (1.80%) |
| occurrences (all) | 0 | 10 | 2 |
| Subclavian vein thrombosis | | | |
| subjects affected / exposed | 1 / 108 (0.93%) | 1 / 346 (0.29%) | 0 / 111 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Superficial vein thrombosis | | | |
| subjects affected / exposed | 1 / 108 (0.93%) | 0 / 346 (0.00%) | 0 / 111 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Thrombosis | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 1 / 346 (0.29%) | 0 / 111 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Thrombophlebitis superficial | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 1 / 346 (0.29%) | 0 / 111 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Surgical and medical procedures | | | |
| Lung lobectomy | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 1 / 346 (0.29%) | 0 / 111 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Tooth extraction | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 1 / 346 (0.29%) | 0 / 111 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| General disorders and administration site conditions | | | |

| | | | |
|-----------------------------|-------------------|--------------------|-------------------|
| Asthenia | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 0 / 346 (0.00%) | 1 / 111 (0.90%) |
| occurrences (all) | 0 | 0 | 1 |
| Chest pain | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 1 / 346 (0.29%) | 0 / 111 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Chills | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 1 / 346 (0.29%) | 0 / 111 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Device related thrombosis | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 1 / 346 (0.29%) | 0 / 111 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Face oedema | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 3 / 346 (0.87%) | 0 / 111 (0.00%) |
| occurrences (all) | 0 | 3 | 0 |
| Gait disturbance | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 1 / 346 (0.29%) | 0 / 111 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Fatigue | | | |
| subjects affected / exposed | 25 / 108 (23.15%) | 110 / 346 (31.79%) | 37 / 111 (33.33%) |
| occurrences (all) | 25 | 112 | 37 |
| Impaired healing | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 1 / 346 (0.29%) | 0 / 111 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Influenza like illness | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 1 / 346 (0.29%) | 0 / 111 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Infusion site extravasation | | | |
| subjects affected / exposed | 2 / 108 (1.85%) | 1 / 346 (0.29%) | 0 / 111 (0.00%) |
| occurrences (all) | 2 | 1 | 0 |
| Injection site haematoma | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 0 / 346 (0.00%) | 1 / 111 (0.90%) |
| occurrences (all) | 0 | 0 | 1 |
| Injection site haemorrhage | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 1 / 346 (0.29%) | 0 / 111 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |

| | | | |
|---|-------------------------|---------------------------|-------------------------|
| Localised oedema subjects affected / exposed occurrences (all) | 0 / 108 (0.00%) 0 | 1 / 346 (0.29%) 1 | 0 / 111 (0.00%) 0 |
| Mucosal inflammation subjects affected / exposed occurrences (all) | 1 / 108 (0.93%) 1 | 1 / 346 (0.29%) 1 | 1 / 111 (0.90%) 1 |
| Multiple organ dysfunction syndrome subjects affected / exposed occurrences (all) | 0 / 108 (0.00%) 0 | 2 / 346 (0.58%) 2 | 0 / 111 (0.00%) 0 |
| Oedema peripheral subjects affected / exposed occurrences (all) | 19 / 108 (17.59%) 19 | 106 / 346 (30.64%) 108 | 21 / 111 (18.92%) 21 |
| Pain subjects affected / exposed occurrences (all) | 14 / 108 (12.96%) 14 | 119 / 346 (34.39%) 120 | 25 / 111 (22.52%) 25 |
| Oedema subjects affected / exposed occurrences (all) | 0 / 108 (0.00%) 0 | 0 / 346 (0.00%) 0 | 1 / 111 (0.90%) 1 |
| Pyrexia subjects affected / exposed occurrences (all) | 10 / 108 (9.26%) 10 | 164 / 346 (47.40%) 169 | 49 / 111 (44.14%) 49 |
| Swelling face subjects affected / exposed occurrences (all) | 0 / 108 (0.00%) 0 | 1 / 346 (0.29%) 1 | 0 / 111 (0.00%) 0 |
| Immune system disorders Hypersensitivity subjects affected / exposed occurrences (all) | 1 / 108 (0.93%) 1 | 32 / 346 (9.25%) 32 | 11 / 111 (9.91%) 11 |
| Reproductive system and breast disorders Penis disorder subjects affected / exposed occurrences (all) | 0 / 108 (0.00%) 0 | 1 / 346 (0.29%) 1 | 0 / 111 (0.00%) 0 |
| Respiratory, thoracic and mediastinal disorders Aspiration subjects affected / exposed occurrences (all) | 0 / 108 (0.00%) 0 | 1 / 346 (0.29%) 1 | 1 / 111 (0.90%) 1 |

| | | | |
|-----------------------------|-----------------|-------------------|------------------|
| Asthma | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 1 / 346 (0.29%) | 0 / 111 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Atelectasis | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 0 / 346 (0.00%) | 1 / 111 (0.90%) |
| occurrences (all) | 0 | 0 | 1 |
| Cough | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 7 / 346 (2.02%) | 3 / 111 (2.70%) |
| occurrences (all) | 0 | 7 | 3 |
| Dyspnoea | | | |
| subjects affected / exposed | 4 / 108 (3.70%) | 55 / 346 (15.90%) | 8 / 111 (7.21%) |
| occurrences (all) | 4 | 55 | 8 |
| Epistaxis | | | |
| subjects affected / exposed | 6 / 108 (5.56%) | 67 / 346 (19.36%) | 10 / 111 (9.01%) |
| occurrences (all) | 6 | 68 | 10 |
| Hiccups | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 2 / 346 (0.58%) | 2 / 111 (1.80%) |
| occurrences (all) | 0 | 2 | 2 |
| Hypoxia | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 11 / 346 (3.18%) | 1 / 111 (0.90%) |
| occurrences (all) | 0 | 11 | 1 |
| Lung diffusion disorder | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 0 / 346 (0.00%) | 1 / 111 (0.90%) |
| occurrences (all) | 0 | 0 | 1 |
| Oropharyngeal pain | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 4 / 346 (1.16%) | 2 / 111 (1.80%) |
| occurrences (all) | 0 | 4 | 2 |
| Pleural effusion | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 0 / 346 (0.00%) | 1 / 111 (0.90%) |
| occurrences (all) | 0 | 0 | 1 |
| Pleuritic pain | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 2 / 346 (0.58%) | 2 / 111 (1.80%) |
| occurrences (all) | 0 | 2 | 2 |
| Pneumothorax | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 1 / 346 (0.29%) | 0 / 111 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |

| | | | |
|---|-------------------------|-------------------------|-------------------------|
| Pulmonary haemorrhage subjects affected / exposed occurrences (all) | 0 / 108 (0.00%) 0 | 3 / 346 (0.87%) 3 | 0 / 111 (0.00%) 0 |
| Respiratory failure subjects affected / exposed occurrences (all) | 0 / 108 (0.00%) 0 | 1 / 346 (0.29%) 1 | 0 / 111 (0.00%) 0 |
| Psychiatric disorders | | | |
| Agitation subjects affected / exposed occurrences (all) | 0 / 108 (0.00%) 0 | 3 / 346 (0.87%) 5 | 1 / 111 (0.90%) 1 |
| Anxiety subjects affected / exposed occurrences (all) | 0 / 108 (0.00%) 0 | 3 / 346 (0.87%) 4 | 0 / 111 (0.00%) 0 |
| Depressed mood subjects affected / exposed occurrences (all) | 0 / 108 (0.00%) 0 | 1 / 346 (0.29%) 1 | 0 / 111 (0.00%) 0 |
| Confusional state subjects affected / exposed occurrences (all) | 9 / 108 (8.33%) 9 | 83 / 346 (23.99%) 83 | 17 / 111 (15.32%) 17 |
| Depression subjects affected / exposed occurrences (all) | 13 / 108 (12.04%) 13 | 45 / 346 (13.01%) 45 | 10 / 111 (9.01%) 10 |
| Hallucination subjects affected / exposed occurrences (all) | 1 / 108 (0.93%) 1 | 11 / 346 (3.18%) 11 | 6 / 111 (5.41%) 6 |
| Insomnia subjects affected / exposed occurrences (all) | 7 / 108 (6.48%) 8 | 31 / 346 (8.96%) 31 | 6 / 111 (5.41%) 6 |
| Mania subjects affected / exposed occurrences (all) | 0 / 108 (0.00%) 0 | 1 / 346 (0.29%) 1 | 0 / 111 (0.00%) 0 |
| Panic attack subjects affected / exposed occurrences (all) | 0 / 108 (0.00%) 0 | 1 / 346 (0.29%) 1 | 0 / 111 (0.00%) 0 |
| Suicidal ideation | | | |

| | | | |
|---------------------------------------|-------------------|--------------------|-------------------|
| subjects affected / exposed | 0 / 108 (0.00%) | 1 / 346 (0.29%) | 0 / 111 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Investigations | | | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 47 / 108 (43.52%) | 280 / 346 (80.92%) | 50 / 111 (45.05%) |
| occurrences (all) | 47 | 281 | 50 |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 26 / 108 (24.07%) | 230 / 346 (66.47%) | 48 / 111 (43.24%) |
| occurrences (all) | 26 | 232 | 48 |
| Blood alkaline phosphatase increased | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 2 / 346 (0.58%) | 0 / 111 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Blood alkaline phosphatase abnormal | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 1 / 346 (0.29%) | 0 / 111 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Blood bilirubin increased | | | |
| subjects affected / exposed | 8 / 108 (7.41%) | 119 / 346 (34.39%) | 18 / 111 (16.22%) |
| occurrences (all) | 8 | 119 | 18 |
| Blood culture positive | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 1 / 346 (0.29%) | 0 / 111 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Blood lactate dehydrogenase increased | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 1 / 346 (0.29%) | 0 / 111 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| C-reactive protein increased | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 3 / 346 (0.87%) | 0 / 111 (0.00%) |
| occurrences (all) | 0 | 4 | 0 |
| Blood creatinine increased | | | |
| subjects affected / exposed | 21 / 108 (19.44%) | 134 / 346 (38.73%) | 24 / 111 (21.62%) |
| occurrences (all) | 21 | 137 | 24 |
| Electrocardiogram QT prolonged | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 1 / 346 (0.29%) | 0 / 111 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Electrocardiogram T wave inversion | | | |

| | | | |
|--|-------------------|--------------------|-------------------|
| subjects affected / exposed | 0 / 108 (0.00%) | 1 / 346 (0.29%) | 0 / 111 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Forced expiratory volume decreased | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 3 / 346 (0.87%) | 2 / 111 (1.80%) |
| occurrences (all) | 0 | 3 | 2 |
| Gamma-glutamyltransferase increased | | | |
| subjects affected / exposed | 51 / 108 (47.22%) | 230 / 346 (66.47%) | 71 / 111 (63.96%) |
| occurrences (all) | 51 | 232 | 71 |
| Platelet count decreased | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 1 / 346 (0.29%) | 0 / 111 (0.00%) |
| occurrences (all) | 0 | 3 | 0 |
| Weight decreased | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 1 / 346 (0.29%) | 0 / 111 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Weight increased | | | |
| subjects affected / exposed | 2 / 108 (1.85%) | 2 / 346 (0.58%) | 0 / 111 (0.00%) |
| occurrences (all) | 2 | 2 | 0 |
| Injury, poisoning and procedural complications | | | |
| Contusion | | | |
| subjects affected / exposed | 1 / 108 (0.93%) | 1 / 346 (0.29%) | 0 / 111 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Fall | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 12 / 346 (3.47%) | 0 / 111 (0.00%) |
| occurrences (all) | 0 | 13 | 0 |
| Infusion related reaction | | | |
| subjects affected / exposed | 1 / 108 (0.93%) | 16 / 346 (4.62%) | 12 / 111 (10.81%) |
| occurrences (all) | 1 | 16 | 12 |
| Procedural pneumothorax | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 1 / 346 (0.29%) | 0 / 111 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Transfusion reaction | | | |
| subjects affected / exposed | 1 / 108 (0.93%) | 1 / 346 (0.29%) | 0 / 111 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Cardiac disorders | | | |

| | | | |
|---|----------------------|------------------------|----------------------|
| Acute coronary syndrome subjects affected / exposed occurrences (all) | 0 / 108 (0.00%) 0 | 3 / 346 (0.87%) 3 | 0 / 111 (0.00%) 0 |
| Atrial fibrillation subjects affected / exposed occurrences (all) | 2 / 108 (1.85%) 2 | 12 / 346 (3.47%) 13 | 5 / 111 (4.50%) 6 |
| Bradycardia subjects affected / exposed occurrences (all) | 0 / 108 (0.00%) 0 | 1 / 346 (0.29%) 1 | 0 / 111 (0.00%) 0 |
| Palpitations subjects affected / exposed occurrences (all) | 1 / 108 (0.93%) 1 | 9 / 346 (2.60%) 9 | 1 / 111 (0.90%) 1 |
| Sinus bradycardia subjects affected / exposed occurrences (all) | 0 / 108 (0.00%) 0 | 2 / 346 (0.58%) 2 | 1 / 111 (0.90%) 2 |
| Sinus node dysfunction subjects affected / exposed occurrences (all) | 0 / 108 (0.00%) 0 | 1 / 346 (0.29%) 1 | 0 / 111 (0.00%) 0 |
| Sinus tachycardia subjects affected / exposed occurrences (all) | 0 / 108 (0.00%) 0 | 0 / 346 (0.00%) 0 | 2 / 111 (1.80%) 2 |
| Tachycardia subjects affected / exposed occurrences (all) | 0 / 108 (0.00%) 0 | 2 / 346 (0.58%) 2 | 1 / 111 (0.90%) 1 |
| Ventricular arrhythmia subjects affected / exposed occurrences (all) | 0 / 108 (0.00%) 0 | 7 / 346 (2.02%) 7 | 2 / 111 (1.80%) 2 |
| Nervous system disorders | | | |
| Balance disorder subjects affected / exposed occurrences (all) | 0 / 108 (0.00%) 0 | 2 / 346 (0.58%) 2 | 0 / 111 (0.00%) 0 |
| Cognitive disorder subjects affected / exposed occurrences (all) | 0 / 108 (0.00%) 0 | 1 / 346 (0.29%) 1 | 0 / 111 (0.00%) 0 |
| Dizziness | | | |

| | | | |
|-----------------------------|-------------------|--------------------|-------------------|
| subjects affected / exposed | 0 / 108 (0.00%) | 11 / 346 (3.18%) | 3 / 111 (2.70%) |
| occurrences (all) | 0 | 13 | 3 |
| Dizziness postural | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 2 / 346 (0.58%) | 0 / 111 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Dysaesthesia | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 0 / 346 (0.00%) | 1 / 111 (0.90%) |
| occurrences (all) | 0 | 0 | 1 |
| Dysarthria | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 1 / 346 (0.29%) | 0 / 111 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Dysgeusia | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 1 / 346 (0.29%) | 0 / 111 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Encephalopathy | | | |
| subjects affected / exposed | 2 / 108 (1.85%) | 0 / 346 (0.00%) | 0 / 111 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Headache | | | |
| subjects affected / exposed | 14 / 108 (12.96%) | 100 / 346 (28.90%) | 14 / 111 (12.61%) |
| occurrences (all) | 14 | 100 | 14 |
| Hemiplegia | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 1 / 346 (0.29%) | 0 / 111 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Horner's syndrome | | | |
| subjects affected / exposed | 1 / 108 (0.93%) | 0 / 346 (0.00%) | 0 / 111 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Lethargy | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 1 / 346 (0.29%) | 0 / 111 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Leukoencephalopathy | | | |
| subjects affected / exposed | 1 / 108 (0.93%) | 3 / 346 (0.87%) | 2 / 111 (1.80%) |
| occurrences (all) | 1 | 3 | 2 |
| Loss of consciousness | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 2 / 346 (0.58%) | 0 / 111 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Memory impairment | | | |

| | | | |
|-------------------------------|-----------------|------------------|-----------------|
| subjects affected / exposed | 0 / 108 (0.00%) | 0 / 346 (0.00%) | 1 / 111 (0.90%) |
| occurrences (all) | 0 | 0 | 1 |
| Motor dysfunction | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 1 / 346 (0.29%) | 0 / 111 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Orthostatic intolerance | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 1 / 346 (0.29%) | 0 / 111 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Partial seizures | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 1 / 346 (0.29%) | 0 / 111 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Parkinsonism | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 1 / 346 (0.29%) | 0 / 111 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Paraesthesia | | | |
| subjects affected / exposed | 6 / 108 (5.56%) | 26 / 346 (7.51%) | 3 / 111 (2.70%) |
| occurrences (all) | 6 | 26 | 3 |
| Peripheral sensory neuropathy | | | |
| subjects affected / exposed | 7 / 108 (6.48%) | 17 / 346 (4.91%) | 1 / 111 (0.90%) |
| occurrences (all) | 7 | 17 | 1 |
| Peripheral motor neuropathy | | | |
| subjects affected / exposed | 3 / 108 (2.78%) | 15 / 346 (4.34%) | 1 / 111 (0.90%) |
| occurrences (all) | 3 | 15 | 1 |
| Quadriparesis | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 1 / 346 (0.29%) | 0 / 111 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Seizure | | | |
| subjects affected / exposed | 1 / 108 (0.93%) | 2 / 346 (0.58%) | 0 / 111 (0.00%) |
| occurrences (all) | 1 | 3 | 0 |
| Somnolence | | | |
| subjects affected / exposed | 5 / 108 (4.63%) | 19 / 346 (5.49%) | 5 / 111 (4.50%) |
| occurrences (all) | 5 | 19 | 5 |
| Syncope | | | |
| subjects affected / exposed | 3 / 108 (2.78%) | 17 / 346 (4.91%) | 3 / 111 (2.70%) |
| occurrences (all) | 4 | 17 | 3 |
| Tremor | | | |

| | | | |
|--|----------------------|----------------------|----------------------|
| subjects affected / exposed occurrences (all) | 1 / 108 (0.93%) 1 | 5 / 346 (1.45%) 5 | 1 / 111 (0.90%) 1 |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 102 / 108 (94.44%) | 330 / 346 (95.38%) | 103 / 111 (92.79%) |
| occurrences (all) | 102 | 336 | 103 |
| Febrile neutropenia | | | |
| subjects affected / exposed | 14 / 108 (12.96%) | 176 / 346 (50.87%) | 67 / 111 (60.36%) |
| occurrences (all) | 14 | 182 | 67 |
| Haemolysis | | | |
| subjects affected / exposed | 3 / 108 (2.78%) | 6 / 346 (1.73%) | 3 / 111 (2.70%) |
| occurrences (all) | 3 | 6 | 3 |
| Leukopenia | | | |
| subjects affected / exposed | 89 / 108 (82.41%) | 313 / 346 (90.46%) | 101 / 111 (90.99%) |
| occurrences (all) | 89 | 313 | 101 |
| Lymphadenopathy | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 1 / 346 (0.29%) | 0 / 111 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Lymphopenia | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 1 / 346 (0.29%) | 1 / 111 (0.90%) |
| occurrences (all) | 0 | 1 | 1 |
| Neutropenia | | | |
| subjects affected / exposed | 74 / 108 (68.52%) | 260 / 346 (75.14%) | 85 / 111 (76.58%) |
| occurrences (all) | 74 | 261 | 85 |
| Thrombocytosis | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 1 / 346 (0.29%) | 0 / 111 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Thrombocytopenia | | | |
| subjects affected / exposed | 101 / 108 (93.52%) | 330 / 346 (95.38%) | 108 / 111 (97.30%) |
| occurrences (all) | 102 | 334 | 109 |
| Ear and labyrinth disorders | | | |
| Ear pain | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 0 / 346 (0.00%) | 1 / 111 (0.90%) |
| occurrences (all) | 0 | 0 | 1 |
| Hypoacusis | | | |

| | | | |
|--|----------------------|----------------------|----------------------|
| subjects affected / exposed occurrences (all) | 0 / 108 (0.00%) 0 | 2 / 346 (0.58%) 2 | 0 / 111 (0.00%) 0 |
| Tinnitus subjects affected / exposed occurrences (all) | 0 / 108 (0.00%) 0 | 1 / 346 (0.29%) 1 | 0 / 111 (0.00%) 0 |
| Vertigo subjects affected / exposed occurrences (all) | 0 / 108 (0.00%) 0 | 5 / 346 (1.45%) 5 | 0 / 111 (0.00%) 0 |
| Eye disorders | | | |
| Conjunctival haemorrhage subjects affected / exposed occurrences (all) | 0 / 108 (0.00%) 0 | 2 / 346 (0.58%) 2 | 0 / 111 (0.00%) 0 |
| Diplopia subjects affected / exposed occurrences (all) | 1 / 108 (0.93%) 1 | 0 / 346 (0.00%) 0 | 0 / 111 (0.00%) 0 |
| Dry eye subjects affected / exposed occurrences (all) | 0 / 108 (0.00%) 0 | 3 / 346 (0.87%) 3 | 0 / 111 (0.00%) 0 |
| Eye haematoma subjects affected / exposed occurrences (all) | 0 / 108 (0.00%) 0 | 1 / 346 (0.29%) 1 | 0 / 111 (0.00%) 0 |
| Lacrimation increased subjects affected / exposed occurrences (all) | 0 / 108 (0.00%) 0 | 1 / 346 (0.29%) 1 | 0 / 111 (0.00%) 0 |
| Ocular hyperaemia subjects affected / exposed occurrences (all) | 0 / 108 (0.00%) 0 | 1 / 346 (0.29%) 1 | 0 / 111 (0.00%) 0 |
| Retinal haemorrhage subjects affected / exposed occurrences (all) | 0 / 108 (0.00%) 0 | 1 / 346 (0.29%) 1 | 0 / 111 (0.00%) 0 |
| Swelling of eyelid subjects affected / exposed occurrences (all) | 0 / 108 (0.00%) 0 | 1 / 346 (0.29%) 1 | 0 / 111 (0.00%) 0 |
| Vitreous haemorrhage subjects affected / exposed occurrences (all) | 1 / 108 (0.93%) 1 | 0 / 346 (0.00%) 0 | 0 / 111 (0.00%) 0 |

| | | | |
|---|-------------------------|-------------------------|-------------------------|
| Visual impairment subjects affected / exposed occurrences (all) | 0 / 108 (0.00%) 0 | 1 / 346 (0.29%) 1 | 0 / 111 (0.00%) 0 |
| Visual acuity reduced subjects affected / exposed occurrences (all) | 0 / 108 (0.00%) 0 | 1 / 346 (0.29%) 1 | 0 / 111 (0.00%) 0 |
| Vision blurred subjects affected / exposed occurrences (all) | 0 / 108 (0.00%) 0 | 3 / 346 (0.87%) 3 | 1 / 111 (0.90%) 1 |
| Visual field defect subjects affected / exposed occurrences (all) | 0 / 108 (0.00%) 0 | 2 / 346 (0.58%) 2 | 0 / 111 (0.00%) 0 |
| Gastrointestinal disorders | | | |
| Abdominal pain subjects affected / exposed occurrences (all) | 6 / 108 (5.56%) 6 | 56 / 346 (16.18%) 56 | 23 / 111 (20.72%) 23 |
| Anal ulcer subjects affected / exposed occurrences (all) | 0 / 108 (0.00%) 0 | 1 / 346 (0.29%) 1 | 0 / 111 (0.00%) 0 |
| Aphthous ulcer subjects affected / exposed occurrences (all) | 0 / 108 (0.00%) 0 | 1 / 346 (0.29%) 2 | 0 / 111 (0.00%) 0 |
| Anal fissure subjects affected / exposed occurrences (all) | 0 / 108 (0.00%) 0 | 1 / 346 (0.29%) 1 | 0 / 111 (0.00%) 0 |
| Ascites subjects affected / exposed occurrences (all) | 0 / 108 (0.00%) 0 | 3 / 346 (0.87%) 3 | 1 / 111 (0.90%) 1 |
| Colitis subjects affected / exposed occurrences (all) | 0 / 108 (0.00%) 0 | 2 / 346 (0.58%) 2 | 0 / 111 (0.00%) 0 |
| Constipation subjects affected / exposed occurrences (all) | 12 / 108 (11.11%) 13 | 74 / 346 (21.39%) 74 | 9 / 111 (8.11%) 9 |
| Dental caries | | | |

| | | | |
|----------------------------------|-------------------|--------------------|-------------------|
| subjects affected / exposed | 0 / 108 (0.00%) | 2 / 346 (0.58%) | 0 / 111 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Dyspepsia | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 1 / 346 (0.29%) | 2 / 111 (1.80%) |
| occurrences (all) | 0 | 1 | 2 |
| Dysphagia | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 1 / 346 (0.29%) | 1 / 111 (0.90%) |
| occurrences (all) | 0 | 1 | 1 |
| Diarrhoea | | | |
| subjects affected / exposed | 7 / 108 (6.48%) | 67 / 346 (19.36%) | 65 / 111 (58.56%) |
| occurrences (all) | 7 | 69 | 65 |
| Haemorrhoids | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 3 / 346 (0.87%) | 0 / 111 (0.00%) |
| occurrences (all) | 0 | 3 | 0 |
| Gastritis | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 0 / 346 (0.00%) | 2 / 111 (1.80%) |
| occurrences (all) | 0 | 0 | 2 |
| Gastrooesophageal reflux disease | | | |
| subjects affected / exposed | 2 / 108 (1.85%) | 14 / 346 (4.05%) | 3 / 111 (2.70%) |
| occurrences (all) | 2 | 14 | 3 |
| Haemorrhoidal haemorrhage | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 18 / 346 (5.20%) | 0 / 111 (0.00%) |
| occurrences (all) | 0 | 18 | 0 |
| Haemorrhoids thrombosed | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 1 / 346 (0.29%) | 0 / 111 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Ileus | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 1 / 346 (0.29%) | 0 / 111 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Nausea | | | |
| subjects affected / exposed | 23 / 108 (21.30%) | 113 / 346 (32.66%) | 63 / 111 (56.76%) |
| occurrences (all) | 23 | 114 | 63 |
| Oesophagitis | | | |
| subjects affected / exposed | 1 / 108 (0.93%) | 6 / 346 (1.73%) | 5 / 111 (4.50%) |
| occurrences (all) | 1 | 6 | 5 |
| Palatal disorder | | | |

| | | | |
|-----------------------------|------------------|--------------------|-------------------|
| subjects affected / exposed | 0 / 108 (0.00%) | 1 / 346 (0.29%) | 0 / 111 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Pancreatitis | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 1 / 346 (0.29%) | 0 / 111 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Rectal ulcer | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 1 / 346 (0.29%) | 0 / 111 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Proctalgia | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 2 / 346 (0.58%) | 0 / 111 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Salivary gland calculus | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 1 / 346 (0.29%) | 0 / 111 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Salivary hypersecretion | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 0 / 346 (0.00%) | 1 / 111 (0.90%) |
| occurrences (all) | 0 | 0 | 1 |
| Stomatitis | | | |
| subjects affected / exposed | 10 / 108 (9.26%) | 115 / 346 (33.24%) | 87 / 111 (78.38%) |
| occurrences (all) | 10 | 118 | 87 |
| Tongue haemorrhage | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 1 / 346 (0.29%) | 0 / 111 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Tooth disorder | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 1 / 346 (0.29%) | 0 / 111 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Toothache | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 2 / 346 (0.58%) | 0 / 111 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Vomiting | | | |
| subjects affected / exposed | 9 / 108 (8.33%) | 50 / 346 (14.45%) | 44 / 111 (39.64%) |
| occurrences (all) | 9 | 50 | 44 |
| Hepatobiliary disorders | | | |
| Cholelithiasis | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 1 / 346 (0.29%) | 0 / 111 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |

| | | | |
|--|-------------------|--------------------|-------------------|
| Hepatic failure | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 3 / 346 (0.87%) | 0 / 111 (0.00%) |
| occurrences (all) | 0 | 4 | 0 |
| Hepatic steatosis | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 2 / 346 (0.58%) | 0 / 111 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Skin and subcutaneous tissue disorders | | | |
| Acne | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 2 / 346 (0.58%) | 0 / 111 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Alopecia | | | |
| subjects affected / exposed | 38 / 108 (35.19%) | 144 / 346 (41.62%) | 49 / 111 (44.14%) |
| occurrences (all) | 38 | 144 | 49 |
| Decubitus ulcer | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 2 / 346 (0.58%) | 0 / 111 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Dermatitis | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 1 / 346 (0.29%) | 0 / 111 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Dermatitis contact | | | |
| subjects affected / exposed | 1 / 108 (0.93%) | 0 / 346 (0.00%) | 0 / 111 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Dermatitis bullous | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 1 / 346 (0.29%) | 0 / 111 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Dry skin | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 0 / 346 (0.00%) | 1 / 111 (0.90%) |
| occurrences (all) | 0 | 0 | 1 |
| Epidermolysis | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 0 / 346 (0.00%) | 1 / 111 (0.90%) |
| occurrences (all) | 0 | 0 | 1 |
| Erythema | | | |
| subjects affected / exposed | 1 / 108 (0.93%) | 0 / 346 (0.00%) | 1 / 111 (0.90%) |
| occurrences (all) | 1 | 0 | 1 |
| Hyperhidrosis | | | |

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|---|-----------------|------------------|-----------------|
| subjects affected / exposed | 0 / 108 (0.00%) | 1 / 346 (0.29%) | 0 / 111 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Palmar-plantar erythrodysaesthesia syndrome | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 0 / 346 (0.00%) | 1 / 111 (0.90%) |
| occurrences (all) | 0 | 0 | 1 |
| Night sweats | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 3 / 346 (0.87%) | 0 / 111 (0.00%) |
| occurrences (all) | 0 | 3 | 0 |
| Petechiae | | | |
| subjects affected / exposed | 1 / 108 (0.93%) | 5 / 346 (1.45%) | 0 / 111 (0.00%) |
| occurrences (all) | 1 | 5 | 0 |
| Pruritus | | | |
| subjects affected / exposed | 2 / 108 (1.85%) | 26 / 346 (7.51%) | 6 / 111 (5.41%) |
| occurrences (all) | 2 | 26 | 6 |
| Rash erythematous | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 1 / 346 (0.29%) | 0 / 111 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Rash | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 5 / 346 (1.45%) | 1 / 111 (0.90%) |
| occurrences (all) | 0 | 7 | 2 |
| Skin ulcer | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 0 / 346 (0.00%) | 1 / 111 (0.90%) |
| occurrences (all) | 0 | 0 | 1 |
| Solar lentigo | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 1 / 346 (0.29%) | 0 / 111 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Urticaria | | | |
| subjects affected / exposed | 2 / 108 (1.85%) | 27 / 346 (7.80%) | 5 / 111 (4.50%) |
| occurrences (all) | 2 | 27 | 5 |
| Renal and urinary disorders | | | |
| Acute kidney injury | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 5 / 346 (1.45%) | 1 / 111 (0.90%) |
| occurrences (all) | 0 | 5 | 1 |
| Chronic kidney disease | | | |

| | | | |
|---|-----------------|------------------|-----------------|
| subjects affected / exposed | 0 / 108 (0.00%) | 13 / 346 (3.76%) | 2 / 111 (1.80%) |
| occurrences (all) | 0 | 14 | 2 |
| Haematuria | | | |
| subjects affected / exposed | 2 / 108 (1.85%) | 12 / 346 (3.47%) | 4 / 111 (3.60%) |
| occurrences (all) | 2 | 12 | 4 |
| Nocturia | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 2 / 346 (0.58%) | 0 / 111 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Pollakiuria | | | |
| subjects affected / exposed | 1 / 108 (0.93%) | 4 / 346 (1.16%) | 0 / 111 (0.00%) |
| occurrences (all) | 1 | 5 | 0 |
| Urinary retention | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 1 / 346 (0.29%) | 0 / 111 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Urinary incontinence | | | |
| subjects affected / exposed | 1 / 108 (0.93%) | 1 / 346 (0.29%) | 0 / 111 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Urethral haemorrhage | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 1 / 346 (0.29%) | 0 / 111 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Endocrine disorders | | | |
| Cushingoid | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 4 / 346 (1.16%) | 0 / 111 (0.00%) |
| occurrences (all) | 0 | 4 | 0 |
| Hypothyroidism | | | |
| subjects affected / exposed | 3 / 108 (2.78%) | 17 / 346 (4.91%) | 0 / 111 (0.00%) |
| occurrences (all) | 3 | 17 | 0 |
| Hyperthyroidism | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 16 / 346 (4.62%) | 1 / 111 (0.90%) |
| occurrences (all) | 0 | 16 | 1 |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 5 / 346 (1.45%) | 0 / 111 (0.00%) |
| occurrences (all) | 0 | 6 | 0 |
| Arthritis | | | |

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|-----------------------------|-----------------|-------------------|-----------------|
| subjects affected / exposed | 0 / 108 (0.00%) | 1 / 346 (0.29%) | 0 / 111 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Back pain | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 1 / 346 (0.29%) | 0 / 111 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Bone pain | | | |
| subjects affected / exposed | 4 / 108 (3.70%) | 84 / 346 (24.28%) | 5 / 111 (4.50%) |
| occurrences (all) | 4 | 85 | 5 |
| Exostosis | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 1 / 346 (0.29%) | 0 / 111 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Joint ankylosis | | | |
| subjects affected / exposed | 1 / 108 (0.93%) | 0 / 346 (0.00%) | 0 / 111 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Joint swelling | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 1 / 346 (0.29%) | 0 / 111 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Muscle spasms | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 1 / 346 (0.29%) | 0 / 111 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Muscular weakness | | | |
| subjects affected / exposed | 5 / 108 (4.63%) | 25 / 346 (7.23%) | 4 / 111 (3.60%) |
| occurrences (all) | 5 | 25 | 4 |
| Musculoskeletal stiffness | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 1 / 346 (0.29%) | 0 / 111 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Myalgia | | | |
| subjects affected / exposed | 1 / 108 (0.93%) | 8 / 346 (2.31%) | 1 / 111 (0.90%) |
| occurrences (all) | 1 | 8 | 1 |
| Sjogren's syndrome | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 1 / 346 (0.29%) | 0 / 111 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Rhabdomyolysis | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 1 / 346 (0.29%) | 0 / 111 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Sacroiliitis | | | |

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|---------------------------------|-----------------|------------------|-----------------|
| subjects affected / exposed | 0 / 108 (0.00%) | 1 / 346 (0.29%) | 0 / 111 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Soft tissue necrosis | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 1 / 346 (0.29%) | 0 / 111 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Infections and infestations | | | |
| Abdominal infection | | | |
| subjects affected / exposed | 1 / 108 (0.93%) | 13 / 346 (3.76%) | 8 / 111 (7.21%) |
| occurrences (all) | 1 | 13 | 8 |
| Acarodermatitis | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 1 / 346 (0.29%) | 0 / 111 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Atypical pneumonia | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 1 / 346 (0.29%) | 0 / 111 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Bronchitis | | | |
| subjects affected / exposed | 6 / 108 (5.56%) | 30 / 346 (8.67%) | 4 / 111 (3.60%) |
| occurrences (all) | 6 | 30 | 4 |
| Cellulitis | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 1 / 346 (0.29%) | 0 / 111 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Clostridial infection | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 1 / 346 (0.29%) | 0 / 111 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Clostridium difficile infection | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 1 / 346 (0.29%) | 2 / 111 (1.80%) |
| occurrences (all) | 0 | 1 | 2 |
| Conjunctivitis | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 2 / 346 (0.58%) | 0 / 111 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Cutaneous mucormycosis | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 1 / 346 (0.29%) | 0 / 111 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Cytomegalovirus infection | | | |
| reactivation | | | |

| | | | |
|-------------------------------------|-----------------|-------------------|-------------------|
| subjects affected / exposed | 0 / 108 (0.00%) | 1 / 346 (0.29%) | 1 / 111 (0.90%) |
| occurrences (all) | 0 | 1 | 1 |
| Device related infection | | | |
| subjects affected / exposed | 3 / 108 (2.78%) | 53 / 346 (15.32%) | 23 / 111 (20.72%) |
| occurrences (all) | 3 | 55 | 23 |
| Encephalitis | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 1 / 346 (0.29%) | 0 / 111 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Enterobacter sepsis | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 1 / 346 (0.29%) | 0 / 111 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Enterococcal infection | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 1 / 346 (0.29%) | 0 / 111 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Erysipelas | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 1 / 346 (0.29%) | 0 / 111 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Escherichia bacteraemia | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 1 / 346 (0.29%) | 0 / 111 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Escherichia infection | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 3 / 346 (0.87%) | 0 / 111 (0.00%) |
| occurrences (all) | 0 | 3 | 0 |
| Escherichia sepsis | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 1 / 346 (0.29%) | 0 / 111 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Escherichia urinary tract infection | | | |
| subjects affected / exposed | 1 / 108 (0.93%) | 1 / 346 (0.29%) | 0 / 111 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Eye infection | | | |
| subjects affected / exposed | 3 / 108 (2.78%) | 7 / 346 (2.02%) | 0 / 111 (0.00%) |
| occurrences (all) | 3 | 8 | 0 |
| Folliculitis | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 3 / 346 (0.87%) | 0 / 111 (0.00%) |
| occurrences (all) | 0 | 3 | 0 |
| Fungal skin infection | | | |

| | | | |
|-------------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 108 (0.00%) | 1 / 346 (0.29%) | 0 / 111 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Hepatitis A | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 2 / 346 (0.58%) | 0 / 111 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Herpes simplex | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 1 / 346 (0.29%) | 0 / 111 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Herpes virus infection | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 1 / 346 (0.29%) | 0 / 111 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Human herpesvirus 6 infection | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 1 / 346 (0.29%) | 0 / 111 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Influenza | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 4 / 346 (1.16%) | 0 / 111 (0.00%) |
| occurrences (all) | 0 | 4 | 0 |
| Infection | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 6 / 346 (1.73%) | 1 / 111 (0.90%) |
| occurrences (all) | 0 | 6 | 1 |
| Klebsiella bacteraemia | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 1 / 346 (0.29%) | 0 / 111 (0.00%) |
| occurrences (all) | 0 | 3 | 0 |
| Klebsiella infection | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 1 / 346 (0.29%) | 0 / 111 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Labyrinthitis | | | |
| subjects affected / exposed | 1 / 108 (0.93%) | 0 / 346 (0.00%) | 0 / 111 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Laryngitis | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 0 / 346 (0.00%) | 1 / 111 (0.90%) |
| occurrences (all) | 0 | 0 | 1 |
| Meningitis viral | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 1 / 346 (0.29%) | 0 / 111 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Mucosal infection | | | |

| | | | |
|--------------------------------|-----------------|-------------------|-------------------|
| subjects affected / exposed | 2 / 108 (1.85%) | 42 / 346 (12.14%) | 23 / 111 (20.72%) |
| occurrences (all) | 2 | 42 | 23 |
| Nasopharyngitis | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 2 / 346 (0.58%) | 0 / 111 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Neutropenic sepsis | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 2 / 346 (0.58%) | 0 / 111 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Neutropenic infection | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 1 / 346 (0.29%) | 0 / 111 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Oesophageal candidiasis | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 0 / 346 (0.00%) | 1 / 111 (0.90%) |
| occurrences (all) | 0 | 0 | 1 |
| Oral candidiasis | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 1 / 346 (0.29%) | 0 / 111 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Oropharyngeal candidiasis | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 0 / 346 (0.00%) | 1 / 111 (0.90%) |
| occurrences (all) | 0 | 0 | 1 |
| Otitis media | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 1 / 346 (0.29%) | 0 / 111 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Parotitis | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 1 / 346 (0.29%) | 0 / 111 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Parainfluenzae virus infection | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 1 / 346 (0.29%) | 0 / 111 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Pharyngitis | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 1 / 346 (0.29%) | 0 / 111 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Proteus infection | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 1 / 346 (0.29%) | 0 / 111 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Rash pustular | | | |

| | | | |
|-----------------------------|-----------------|-------------------|-----------------|
| subjects affected / exposed | 0 / 108 (0.00%) | 1 / 346 (0.29%) | 0 / 111 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Pseudomonal sepsis | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 1 / 346 (0.29%) | 0 / 111 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Pseudomonal bacteraemia | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 1 / 346 (0.29%) | 0 / 111 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Pneumonia | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 36 / 346 (10.40%) | 5 / 111 (4.50%) |
| occurrences (all) | 0 | 37 | 5 |
| Sinusitis | | | |
| subjects affected / exposed | 2 / 108 (1.85%) | 2 / 346 (0.58%) | 0 / 111 (0.00%) |
| occurrences (all) | 2 | 2 | 0 |
| Skin infection | | | |
| subjects affected / exposed | 5 / 108 (4.63%) | 38 / 346 (10.98%) | 4 / 111 (3.60%) |
| occurrences (all) | 5 | 38 | 4 |
| Soft tissue infection | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 1 / 346 (0.29%) | 0 / 111 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Sepsis | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 0 / 346 (0.00%) | 1 / 111 (0.90%) |
| occurrences (all) | 0 | 0 | 1 |
| Staphylococcal sepsis | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 3 / 346 (0.87%) | 0 / 111 (0.00%) |
| occurrences (all) | 0 | 3 | 0 |
| Staphylococcal bacteraemia | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 1 / 346 (0.29%) | 0 / 111 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Streptococcal bacteraemia | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 0 / 346 (0.00%) | 1 / 111 (0.90%) |
| occurrences (all) | 0 | 0 | 1 |
| Subcutaneous abscess | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 1 / 346 (0.29%) | 0 / 111 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Systemic candida | | | |

| | | | |
|------------------------------------|-----------------|-------------------|-------------------|
| subjects affected / exposed | 0 / 108 (0.00%) | 1 / 346 (0.29%) | 0 / 111 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Staphylococcal infection | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 2 / 346 (0.58%) | 0 / 111 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Urinary tract infection bacterial | | | |
| subjects affected / exposed | 1 / 108 (0.93%) | 0 / 346 (0.00%) | 0 / 111 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Urinary tract infection | | | |
| subjects affected / exposed | 9 / 108 (8.33%) | 52 / 346 (15.03%) | 14 / 111 (12.61%) |
| occurrences (all) | 9 | 53 | 14 |
| Tooth infection | | | |
| subjects affected / exposed | 1 / 108 (0.93%) | 10 / 346 (2.89%) | 0 / 111 (0.00%) |
| occurrences (all) | 1 | 10 | 0 |
| Vulval abscess | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 1 / 346 (0.29%) | 0 / 111 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Vascular device infection | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 1 / 346 (0.29%) | 0 / 111 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Metabolism and nutrition disorders | | | |
| Decreased appetite | | | |
| subjects affected / exposed | 4 / 108 (3.70%) | 27 / 346 (7.80%) | 8 / 111 (7.21%) |
| occurrences (all) | 4 | 27 | 8 |
| Dehydration | | | |
| subjects affected / exposed | 2 / 108 (1.85%) | 8 / 346 (2.31%) | 0 / 111 (0.00%) |
| occurrences (all) | 2 | 8 | 0 |
| Diabetes mellitus | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 1 / 346 (0.29%) | 0 / 111 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Fluid overload | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 1 / 346 (0.29%) | 0 / 111 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Gout | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 3 / 346 (0.87%) | 1 / 111 (0.90%) |
| occurrences (all) | 0 | 4 | 1 |

| | | | |
|-----------------------------|-------------------|--------------------|-------------------|
| Hyperglycaemia | | | |
| subjects affected / exposed | 29 / 108 (26.85%) | 152 / 346 (43.93%) | 25 / 111 (22.52%) |
| occurrences (all) | 29 | 154 | 25 |
| Hyperkalaemia | | | |
| subjects affected / exposed | 11 / 108 (10.19%) | 71 / 346 (20.52%) | 10 / 111 (9.01%) |
| occurrences (all) | 11 | 71 | 10 |
| Hypernatraemia | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 3 / 346 (0.87%) | 0 / 111 (0.00%) |
| occurrences (all) | 0 | 3 | 0 |
| Hypoalbuminaemia | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 1 / 346 (0.29%) | 0 / 111 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Hypocalcaemia | | | |
| subjects affected / exposed | 2 / 108 (1.85%) | 3 / 346 (0.87%) | 0 / 111 (0.00%) |
| occurrences (all) | 2 | 3 | 0 |
| Hypokalaemia | | | |
| subjects affected / exposed | 3 / 108 (2.78%) | 19 / 346 (5.49%) | 5 / 111 (4.50%) |
| occurrences (all) | 4 | 24 | 5 |
| Hypomagnesaemia | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 1 / 346 (0.29%) | 0 / 111 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Hyponatraemia | | | |
| subjects affected / exposed | 20 / 108 (18.52%) | 121 / 346 (34.97%) | 29 / 111 (26.13%) |
| occurrences (all) | 20 | 121 | 29 |
| Hypophosphataemia | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 1 / 346 (0.29%) | 0 / 111 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|---------------|--|
| 20 April 2018 | <p>Administrative changes: Change of principal investigator in center Hannover, Closure of study center Berlin (no recruitment), Registration of trial in ClinicalTrials.gov (NCT02531841) Clarification with reference to in-/exclusion criteria:</p> <ul style="list-style-type: none">• Addition of randomization criterion no. 4: "Exclusion criterion no. 6 not applicable for re-check for randomization"• Additional wording in randomization criterion no. 1: "Sufficient stem cell harvest ($\geq 3 \times 10^6$ CD34+ cells/kg of body weight)"• Additional wording in exclusion criterion no. 6: "Only applicable for patient inclusion (registration) not applicable for re-check for randomization"• Correction of contents regarding the contraception time period of female and male patients on the basis of three SmPCs <p>Sample size calculation: Increase of</p> <ul style="list-style-type: none">• recruitment period due to increase of number of patients enrolled• number of patients, that need to be recruited to obtain the originally planned number of 220 patients, that were to be randomized <p>Adaption of figures and timelines:</p> <ul style="list-style-type: none">• Addition of specification "for evaluation of primary endpoint" regarding trial duration and time table <p>Adaption of involved number of sites and countries:</p> <ul style="list-style-type: none">• Number of sites increased and the participating countries changed <p>Adaption in flow chart:</p> <ul style="list-style-type: none">• Specification of response statement: "Whole brain MRI and response statement according to IPCG criteria"• More detailed timelines for RA III in case of postponement of consolidation therapy• Addition of more precise time period recommended for FU visits during year 3-5 and after year 5 <p>Addition of special treatment recommendations regarding the Induction treatment phase.</p> <p>A special "pregnancy form", which must be used replaced the former so called "SAE reporting form".</p> <p>Detailed explanation was added regarding storage and use of stem cells.</p> <p>Improved wording regarding documentation and reporting of AEs and SAEs.</p> <p>Explanation regarding the handling of biomaterial was added.</p> |
| 14 June 2018 | <p>Additional demand of ethics committee to substantial amendment 01: Change in wording in Patient Informed Consent (PIC), version V03, section 12 regarding the notification of health damages which could have occurred as a result of the clinical study. Furthermore, a change in wording regarding documentation and reporting of AEs (section 10.1.2): "AEs must be documented ... until day 60 after last administration of study medication randomization. If patient could not be randomized, AE documentation and reporting should be made until day 60 after last administration of study medication".</p> |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

<http://www.ncbi.nlm.nih.gov/pubmed/27098429>