

**Clinical trial results:****A Multicenter, Phase III, Open-Label, Randomized Study in Previously Untreated Patients With Advanced Indolent Non-Hodgkin's Lymphoma Evaluating the Benefit of GA101 (RO5072759) Plus Chemotherapy Compared with Rituximab Plus Chemotherapy Followed by GA101 or Rituximab Maintenance Therapy in Responders****Summary**

| | |
|--------------------------|-------------------------------|
| EudraCT number | 2010-024132-41 |
| Trial protocol | BE GB CZ SE DE HU FR ES IT FI |
| Global end of trial date | 30 July 2021 |

Results information

| | |
|--------------------------------|---------------|
| Result version number | v2 |
| This version publication date | 22 July 2022 |
| First version publication date | 16 March 2017 |
| Version creation reason | |

Trial information**Trial identification**

| | |
|-----------------------|---------|
| Sponsor protocol code | BO21223 |
|-----------------------|---------|

Additional study identifiers

| | |
|------------------------------------|---------------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT01332968 |
| WHO universal trial number (UTN) | - |
| Other trial identifiers | Study name: GALLIUM |

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | F. Hoffmann-La Roche AG |
| Sponsor organisation address | Grenzacherstrasse 124, Basel, Switzerland, CH-4070 |
| Public contact | F. Hoffmann-La Roche AG, F. Hoffmann-La Roche AG, +41 616878333, global.trial_information@roche.com |
| Scientific contact | F. Hoffmann-La Roche AG, F. Hoffmann-La Roche AG, +41 616878333, global.trial_information@roche.com |

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

| | |
|--|-----------------|
| Analysis stage | Final |
| Date of interim/final analysis | 30 July 2021 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 31 January 2016 |
| Global end of trial reached? | Yes |
| Global end of trial date | 30 July 2021 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

To assess the efficacy of obinutuzumab (RO5072759) in combination with chemotherapy compared to rituximab (MabThera/Rituxan) with chemotherapy followed by obinutuzumab or rituximab maintenance in subjects with previously untreated advanced follicular non-Hodgkin's lymphoma.

Protection of trial subjects:

All study subjects were required to read and sign an Informed Consent Form.

Background therapy: -

Evidence for comparator: -

| | |
|---|--------------|
| Actual start date of recruitment | 06 July 2011 |
| Long term follow-up planned | Yes |
| Long term follow-up rationale | Efficacy |
| Long term follow-up duration | 5 Years |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|------------------------|
| Country: Number of subjects enrolled | China: 58 |
| Country: Number of subjects enrolled | Japan: 129 |
| Country: Number of subjects enrolled | Taiwan: 4 |
| Country: Number of subjects enrolled | Czechia: 100 |
| Country: Number of subjects enrolled | Hungary: 71 |
| Country: Number of subjects enrolled | Russian Federation: 12 |
| Country: Number of subjects enrolled | Canada: 138 |
| Country: Number of subjects enrolled | United States: 31 |
| Country: Number of subjects enrolled | Australia: 135 |
| Country: Number of subjects enrolled | Israel: 6 |
| Country: Number of subjects enrolled | Belgium: 35 |
| Country: Number of subjects enrolled | Germany: 237 |
| Country: Number of subjects enrolled | Spain: 48 |
| Country: Number of subjects enrolled | Finland: 4 |
| Country: Number of subjects enrolled | France: 30 |
| Country: Number of subjects enrolled | United Kingdom: 294 |
| Country: Number of subjects enrolled | Italy: 59 |
| Country: Number of subjects enrolled | Sweden: 10 |

| | |
|------------------------------------|------|
| Worldwide total number of subjects | 1401 |
| EEA total number of subjects | 594 |

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) | 937 |
| From 65 to 84 years | 454 |
| 85 years and over | 10 |

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 177 centers in 18 countries.

Pre-assignment

Screening details:

Eleven patients withdrew from the study after randomization but prior to receiving study treatment.

Period 1

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

Arms

| | |
|------------------------------|----|
| Are arms mutually exclusive? | No |
|------------------------------|----|

| | |
|------------------|------------------------------------|
| Arm title | Rituximab+Chemotherapy – Induction |
|------------------|------------------------------------|

Arm description:

Subjects received either 8 cycles of rituximab along with 6 cycles of cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) (21-day cycle) or 8 cycles of rituximab along with 8 cycles of cyclophosphamide, vincristine, and prednisone (CVP) (21-day cycles) or 6 cycles of rituximab along with 6 cycles of bendamustine (28-day cycle) during induction period. The chemotherapy regimen (CHOP or CVP or bendamustine) for individual subject was chosen by the site prior to initiation of the study.

| | |
|--|-----------------------|
| Arm type | Active comparator |
| Investigational medicinal product name | Vincristine |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Vincristine 1.4 mg/m² (maximum 2 mg) IV will be administered on Day 1 of each cycle during induction period.

| | |
|--|----------------------------------|
| Investigational medicinal product name | Cyclophosphamide |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Powder for solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Cyclophosphamide 750 milligrams per square metre (mg/m²) will be administered intravenously (IV) on Day 1 of each cycle during induction period.

| | |
|--|----------------------------------|
| Investigational medicinal product name | Doxorubicin |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Powder for solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Doxorubicin 50 mg/m² IV will be administered on Day 1 of each cycle during induction period.

| | |
|--|----------------------------------|
| Investigational medicinal product name | Bendamustine |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Powder for solution for infusion |
| Routes of administration | Intravenous use |

| | |
|--|---------------------------------------|
| Dosage and administration details: | |
| Bendamustine 90 mg/m ² IV infusion will be administered on Days 1 and 2 of each cycle during induction period. | |
| Investigational medicinal product name | Rituximab |
| Investigational medicinal product code | |
| Other name | MabThera/Rituxan |
| Pharmaceutical forms | Concentrate for solution for infusion |
| Routes of administration | Intravenous use |
| Dosage and administration details: | |
| Rituximab 375 mg/m ² IV infusion will be administered on Day 1 of each cycle during induction period and rituximab 375 mg/m ² every 2 months during maintenance period. | |
| Investigational medicinal product name | Prednisone |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |
| Dosage and administration details: | |
| Prednisone 100 mg (or equivalent prednisolone or methylprednisolone) will be administered orally on Days 1-5 of each cycle during induction period | |
| Arm title | Obinutuzumab+Chemotherapy – Induction |
| Arm description: | |
| Subjects received either 8 cycles of obinutuzumab along with 6 cycles of CHOP (21-day cycle) or 8 cycles of obinutuzumab along with 8 cycles of CVP (21-day cycles) or 6 cycles of obinutuzumab along with 6 cycles of bendamustine (28-day cycle) during induction period. The chemotherapy regimen (CHOP or CVP or bendamustine) for individual subject was chosen by the site prior to initiation of the study. | |
| Arm type | Experimental |
| Investigational medicinal product name | Obinutuzumab |
| Investigational medicinal product code | |
| Other name | GA101; RO5072759 |
| Pharmaceutical forms | Concentrate for solution for infusion |
| Routes of administration | Intravenous use |
| Dosage and administration details: | |
| Obinutuzumab 1000 mg IV infusion will be administered on Day 1, 8, and 15 of Cycle 1 and then on Day 1 of each subsequent cycle during induction period and obinutuzumab 1000 mg IV infusion every 2 months during maintenance period. | |
| Investigational medicinal product name | Cyclophosphamide |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Powder for solution for infusion |
| Routes of administration | Intravenous use |
| Dosage and administration details: | |
| Cyclophosphamide 750 mg/m ² IV will be administered on Day 1 of each cycle during induction period. | |
| Investigational medicinal product name | Prednisone |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |
| Dosage and administration details: | |
| Prednisone 100 mg (or equivalent prednisolone or methylprednisolone) will be administered orally on Days 1-5 of each cycle during induction period | |
| Investigational medicinal product name | Vincristine |
| Investigational medicinal product code | |
| Other name | |

| | |
|--|---|
| Pharmaceutical forms | Solution for infusion |
| Routes of administration | Intravenous use |
| Dosage and administration details: Vincristine 1.4 mg/m ² (maximum 2 mg) IV will be administered on Day 1 of each cycle during induction period. | |
| Investigational medicinal product name | Bendamustine |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Powder for solution for infusion |
| Routes of administration | Intravenous use |
| Dosage and administration details: Bendamustine 90 mg/m ² IV infusion will be administered on Days 1 and 2 of each cycle during induction period. | |
| Investigational medicinal product name | Doxorubicin |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Powder for solution for infusion |
| Routes of administration | Intravenous use |
| Dosage and administration details: Doxorubicin 50 mg/m ² IV will be administered on Day 1 of each cycle during induction period. | |
| Arm title | Rituximab+Chemotherapy – Maintenance |
| Arm description: The induction period was followed by either a maintenance or observation period for responders or non-responders, respectively. Responders received rituximab monotherapy every 2 months for 2 years during the maintenance period. | |
| Arm type | Active comparator |
| Investigational medicinal product name | Rituximab |
| Investigational medicinal product code | |
| Other name | MabThera/Rituxan |
| Pharmaceutical forms | Concentrate for solution for infusion |
| Routes of administration | Intravenous use |
| Dosage and administration details: Rituximab 375 mg/m ² IV infusion will be administered on Day 1 of each cycle during induction period and rituximab 375 mg/m ² every 2 months during maintenance period. | |
| Arm title | Obinutuzumab+Chemotherapy – Maintenance |
| Arm description: The induction period was followed by either a maintenance or observation period for responders or non-responders, respectively. Responders received obinutuzumab monotherapy every 2 months for 2 years during the maintenance period. | |
| Arm type | Experimental |
| Investigational medicinal product name | Obinutuzumab |
| Investigational medicinal product code | |
| Other name | GA101; RO5072759 |
| Pharmaceutical forms | Concentrate for solution for infusion |
| Routes of administration | Intravenous use |
| Dosage and administration details: Obinutuzumab 1000 mg IV infusion will be administered on Day 1, 8, and 15 of Cycle 1 and then on Day 1 of each subsequent cycle during induction period and obinutuzumab 1000 mg IV infusion every 2 months during maintenance period. | |
| Arm title | Rituximab+Chemotherapy – Observation |
| Arm description: The induction period was followed by either a maintenance or observation period for responders or non-responders, respectively. Non-responders received no protocol specified treatment during the 2-year observation period. | |

| | |
|--|---------------------------------------|
| Arm type | Active comparator |
| Investigational medicinal product name | Rituximab |
| Investigational medicinal product code | |
| Other name | MabThera/Rituxan |
| Pharmaceutical forms | Concentrate for solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Rituximab 375 mg/m² IV infusion will be administered on Day 1 of each cycle during induction period and rituximab 375 mg/m² every 2 months during maintenance period.

| | |
|------------------|---|
| Arm title | Obinutuzumab+Chemotherapy – Observation |
|------------------|---|

Arm description:

The induction period was followed by either a maintenance or observation period for responders or non-responders, respectively. Non-responders received no protocol specified treatment during the 2-year observation period.

| | |
|--|---------------------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Obinutuzumab |
| Investigational medicinal product code | |
| Other name | GA101; RO5072759 |
| Pharmaceutical forms | Concentrate for solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Obinutuzumab 1000 mg IV infusion will be administered on Day 1, 8, and 15 of Cycle 1 and then on Day 1 of each subsequent cycle during induction period and obinutuzumab 1000 mg IV infusion every 2 months during maintenance period.

| | |
|------------------|------------------------------------|
| Arm title | Rituximab+Chemotherapy – Follow-up |
|------------------|------------------------------------|

Arm description:

Finally, subjects were followed during a 5-year follow-up period.

| | |
|--|---------------------------------------|
| Arm type | Active comparator |
| Investigational medicinal product name | Rituximab |
| Investigational medicinal product code | |
| Other name | MabThera/Rituxan |
| Pharmaceutical forms | Concentrate for solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Rituximab 375 mg/m² IV infusion will be administered on Day 1 of each cycle during induction period and rituximab 375 mg/m² every 2 months during maintenance period.

| | |
|------------------|---------------------------------------|
| Arm title | Obinutuzumab+Chemotherapy – Follow-up |
|------------------|---------------------------------------|

Arm description:

Finally, subjects were followed during a 5-year follow-up period.

| | |
|--|---------------------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Obinutuzumab |
| Investigational medicinal product code | |
| Other name | GA101; RO5072759 |
| Pharmaceutical forms | Concentrate for solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Obinutuzumab 1000 mg IV infusion will be administered on Day 1, 8, and 15 of Cycle 1 and then on Day 1 of each subsequent cycle during induction period and obinutuzumab 1000 mg IV infusion every 2 months during maintenance period.

| Number of subjects in period 1 | Rituximab+Chemotherapy – Induction | Obinutuzumab+Chemotherapy – Induction | Rituximab+Chemotherapy – Maintenance |
|--------------------------------|------------------------------------|---------------------------------------|--------------------------------------|
| | | | |
| Started | 699 | 702 | 612 |
| Completed | 641 | 646 | 451 |
| Not completed | 58 | 56 | 161 |
| Physician decision | 6 | 1 | 14 |
| Adverse Event | 23 | 26 | 53 |
| Death | 1 | 4 | 5 |
| Progressive Disease | 15 | 7 | 72 |
| Not Specified | 2 | 2 | 4 |
| Non-compliance | 1 | - | 4 |
| Randomised but not treated | 4 | 7 | - |
| Withdrawal by Subject | 3 | 5 | 7 |
| Lost to follow-up | - | - | 1 |
| Protocol deviation | 3 | 4 | 1 |
| No reason provided | - | - | - |

| Number of subjects in period 1 | Obinutuzumab+Chemotherapy – Maintenance | Rituximab+Chemotherapy – Observation | Obinutuzumab+Chemotherapy – Observation |
|--------------------------------|---|--------------------------------------|---|
| | | | |
| Started | 624 | 12 | 11 |
| Completed | 475 | 12 | 10 |
| Not completed | 149 | 0 | 1 |
| Physician decision | 19 | - | 1 |
| Adverse Event | 66 | - | - |
| Death | 6 | - | - |
| Progressive Disease | 40 | - | - |
| Not Specified | 7 | - | - |
| Non-compliance | 3 | - | - |
| Randomised but not treated | - | - | - |
| Withdrawal by Subject | 5 | - | - |
| Lost to follow-up | 2 | - | - |
| Protocol deviation | 1 | - | - |
| No reason provided | - | - | - |

| Number of subjects in period 1 | Rituximab+Chemotherapy – Follow-up | Obinutuzumab+Chemotherapy – Follow-up |
|--------------------------------|------------------------------------|---------------------------------------|
| | | |
| Started | 554 | 602 |
| Completed | 324 | 367 |
| Not completed | 230 | 235 |
| Physician decision | 12 | 15 |
| Adverse Event | - | 4 |

| | | |
|----------------------------|-----|-----|
| Death | 27 | 30 |
| Progressive Disease | 126 | 106 |
| Not Specified | 18 | 21 |
| Non-compliance | 4 | 9 |
| Randomised but not treated | - | - |
| Withdrawal by Subject | 29 | 32 |
| Lost to follow-up | 11 | 15 |
| Protocol deviation | 1 | - |
| No reason provided | 2 | 3 |

Baseline characteristics

Reporting groups

| | |
|--------------------------------|----------------|
| Reporting group title | Overall Period |
| Reporting group description: - | |

| Reporting group values | Overall Period | Total | |
|---|----------------|-------|--|
| Number of subjects | 1401 | 1401 | |
| Age Categorical | | | |
| Units: Subjects | | | |
| Adults (18-64 years) | 937 | 937 | |
| From 65-84 years | 454 | 454 | |
| 85 years and over | 10 | 10 | |
| Age Continuous | | | |
| Units: years | | | |
| arithmetic mean | 58.5 | | |
| standard deviation | ± 11.9 | - | |
| Gender Categorical | | | |
| Units: Subjects | | | |
| Female | 739 | 739 | |
| Male | 662 | 662 | |
| Age Continuous in Follicular Lymphoma Sub-Population | | | |
| Age continuous for subjects with follicular lymphoma, who encompassed the population for the primary endpoint (n=601 for each arm in the follicular lymphoma intent-to-treat population). | | | |
| Units: years | | | |
| arithmetic mean | 57.9 | | |
| standard deviation | ± 11.9 | - | |

Subject analysis sets

| | |
|----------------------------|------------------------|
| Subject analysis set title | Rituximab+Chemotherapy |
| Subject analysis set type | Intention-to-treat |

Subject analysis set description:

Subjects received either 8 cycles of rituximab along with 6 cycles of cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) (21-day cycle) or 8 cycles of rituximab along with 8 cycles of cyclophosphamide, vincristine, and prednisone (CVP) (21-day cycles) or 6 cycles of rituximab along with 6 cycles of bendamustine (28-day cycle) during the induction period. The induction period was followed by either a maintenance or observation period for responders or non-responders, respectively. Responders received rituximab monotherapy every 2 months for 2 years during the maintenance period. Non-responders received no protocol specified treatment during the 2-year observation period. Finally, subjects were followed during a 5-year follow-up period. The chemotherapy regimen (CHOP or CVP or bendamustine) for individual subject was chosen by the site prior to initiation of the study.

| | |
|----------------------------|---------------------------|
| Subject analysis set title | Obinutuzumab+Chemotherapy |
| Subject analysis set type | Intention-to-treat |

Subject analysis set description:

Subjects received either 8 cycles of obinutuzumab along with 6 cycles of CHOP (21-day cycle) or 8 cycles of obinutuzumab along with 8 cycles of CVP (21-day cycles) or 6 cycles of obinutuzumab along with 6 cycles of bendamustine (28-day cycle) during induction period. The induction period was followed by either a maintenance or observation period for responders or non-responders, respectively. Responders received obinutuzumab monotherapy every 2 months for 2 years during the maintenance period. Non-responders received no protocol specified treatment during the 2-year observation period. Finally, subjects were followed during a 5-year follow-up period. The chemotherapy regimen (CHOP or

| Reporting group values | Rituximab+Chemotherapy | Obinutuzumab+Chemotherapy | |
|---|------------------------|---------------------------|--|
| Number of subjects | 699 | 702 | |
| Age Categorical Units: Subjects | | | |
| Adults (18-64 years) | 473 | 464 | |
| From 65-84 years | 221 | 233 | |
| 85 years and over | 5 | 5 | |
| Age Continuous Units: years | | | |
| arithmetic mean | 58.1 | 58.9 | |
| standard deviation | ± 12.3 | ± 11.6 | |
| Gender Categorical Units: Subjects | | | |
| Female | 374 | 365 | |
| Male | 325 | 337 | |
| Age Continuous in Follicular Lymphoma Sub-Population | | | |
| Age continuous for subjects with follicular lymphoma, who encompassed the population for the primary endpoint (n=601 for each arm in the follicular lymphoma intent-to-treat population). | | | |
| Units: years | | | |
| arithmetic mean | 57.7 | 58.2 | |
| standard deviation | ± 12.2 | ± 11.5 | |

End points

End points reporting groups

| | |
|---|---|
| Reporting group title | Rituximab+Chemotherapy – Induction |
| Reporting group description: Subjects received either 8 cycles of rituximab along with 6 cycles of cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) (21-day cycle) or 8 cycles of rituximab along with 8 cycles of cyclophosphamide, vincristine, and prednisone (CVP) (21-day cycles) or 6 cycles of rituximab along with 6 cycles of bendamustine (28-day cycle) during induction period. The chemotherapy regimen (CHOP or CVP or bendamustine) for individual subject was chosen by the site prior to initiation of the study. | |
| Reporting group title | Obinutuzumab+Chemotherapy – Induction |
| Reporting group description: Subjects received either 8 cycles of obinutuzumab along with 6 cycles of CHOP (21-day cycle) or 8 cycles of obinutuzumab along with 8 cycles of CVP (21-day cycles) or 6 cycles of obinutuzumab along with 6 cycles of bendamustine (28-day cycle) during induction period. The chemotherapy regimen (CHOP or CVP or bendamustine) for individual subject was chosen by the site prior to initiation of the study. | |
| Reporting group title | Rituximab+Chemotherapy – Maintenance |
| Reporting group description: The induction period was followed by either a maintenance or observation period for responders or non-responders, respectively. Responders received rituximab monotherapy every 2 months for 2 years during the maintenance period. | |
| Reporting group title | Obinutuzumab+Chemotherapy – Maintenance |
| Reporting group description: The induction period was followed by either a maintenance or observation period for responders or non-responders, respectively. Responders received obinutuzumab monotherapy every 2 months for 2 years during the maintenance period. | |
| Reporting group title | Rituximab+Chemotherapy – Observation |
| Reporting group description: The induction period was followed by either a maintenance or observation period for responders or non-responders, respectively. Non-responders received no protocol specified treatment during the 2-year observation period. | |
| Reporting group title | Obinutuzumab+Chemotherapy – Observation |
| Reporting group description: The induction period was followed by either a maintenance or observation period for responders or non-responders, respectively. Non-responders received no protocol specified treatment during the 2-year observation period. | |
| Reporting group title | Rituximab+Chemotherapy – Follow-up |
| Reporting group description: Finally, subjects were followed during a 5-year follow-up period. | |
| Reporting group title | Obinutuzumab+Chemotherapy – Follow-up |
| Reporting group description: Finally, subjects were followed during a 5-year follow-up period. | |
| Subject analysis set title | Rituximab+Chemotherapy |
| Subject analysis set type | Intention-to-treat |
| Subject analysis set description: Subjects received either 8 cycles of rituximab along with 6 cycles of cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) (21-day cycle) or 8 cycles of rituximab along with 8 cycles of cyclophosphamide, vincristine, and prednisone (CVP) (21-day cycles) or 6 cycles of rituximab along with 6 cycles of bendamustine (28-day cycle) during the induction period. The induction period was followed by either a maintenance or observation period for responders or non-responders, respectively. Responders received rituximab monotherapy every 2 months for 2 years during the maintenance period. Non-responders received no protocol specified treatment during the 2-year observation period. Finally, subjects were followed during a 5-year follow-up period. The chemotherapy regimen (CHOP or CVP or bendamustine) for individual subject was chosen by the site prior to initiation of the study. | |
| Subject analysis set title | Obinutuzumab+Chemotherapy |
| Subject analysis set type | Intention-to-treat |

Subject analysis set description:

Subjects received either 8 cycles of obinutuzumab along with 6 cycles of CHOP (21-day cycle) or 8 cycles of obinutuzumab along with 8 cycles of CVP (21-day cycles) or 6 cycles of obinutuzumab along with 6 cycles of bendamustine (28-day cycle) during induction period. The induction period was followed by either a maintenance or observation period for responders or non-responders, respectively. Responders received obinutuzumab monotherapy every 2 months for 2 years during the maintenance period. Non-responders received no protocol specified treatment during the 2-year observation period. Finally, subjects were followed during a 5-year follow-up period. The chemotherapy regimen (CHOP or CVP or bendamustine) for individual subject was chosen by the site prior to initiation of the study.

Primary: Progression-Free Survival (PFS) in the Follicular Lymphoma Population, Investigator-Assessed

| | |
|-----------------|--|
| End point title | Progression-Free Survival (PFS) in the Follicular Lymphoma Population, Investigator-Assessed |
|-----------------|--|

End point description:

PFS in subjects with follicular lymphoma was defined as the time from randomisation until the first documented day of disease progression or death from any cause, whichever occurred first, on the basis of investigator assessments according to the Revised Response Criteria for Malignant Lymphoma. Progression was defined as at least 50% increase in nodal lesions or $\geq 50\%$ increase in any node > 1 centimetre (cm) or $\geq 50\%$ increase in other target measurable lesions and/or appearance of any new bone marrow involvement and/or appearance of any new lesion > 1.5 cm or $\geq 50\%$ increase in any previously involved node with a diameter ≤ 1 cm such that it is now > 1.5 cm. Tumour measurements were obtained by computed tomography (CT) or magnetic resonance imaging (MRI). The intent-to-treat follicular lymphoma population (FL ITT) was defined as all randomised subjects with follicular histology grouped according to treatment arm regardless of what treatments were actually received.

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

End point timeframe:

Baseline up to 10 years

| End point values | Rituximab+Chemotherapy | Obinutuzumab+Chemotherapy | | |
|--|------------------------|---------------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 601 | 601 | | |
| Units: percentage of subjects with event | | | | |
| number (not applicable) | 40.6 | 34.3 | | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | Rituximab versus Obinutuzumab |
| Comparison groups | Obinutuzumab+Chemotherapy v Rituximab+Chemotherapy |
| Number of subjects included in analysis | 1202 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0055 ^[1] |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.77 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.64 |
| upper limit | 0.93 |

Notes:

[1] - Stratified by chemotherapy regimen and Follicular Lymphoma International Prognostic Index (FLIPI) risk group.

Secondary: Progression-Free Survival in the Overall Study Population, Investigator-Assessed

| | |
|-----------------|--|
| End point title | Progression-Free Survival in the Overall Study Population, Investigator-Assessed |
|-----------------|--|

End point description:

PFS in the overall study population was defined as the time from randomisation until the first documented day of disease progression or death from any cause, whichever occurred first, on the basis of investigator assessments according to the Revised Response Criteria for Malignant Lymphoma. Progression was defined as at least 50% increase in nodal lesions or $\geq 50\%$ increase in any node > 1 centimeter (cm) or $\geq 50\%$ increase in other target measurable lesions (e.g., splenic or hepatic nodules) and/or appearance of any new bone marrow involvement and/or appearance of any new lesion > 1.5 cm or $\geq 50\%$ increase in any previously involved node with a diameter ≤ 1 cm such that it is now > 1.5 cm. Tumour measurements were obtained by CT/MRI. The ITT population was defined as all randomised subjects grouped according to their randomised treatment arm regardless of what treatments were actually received.

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

End point timeframe:

Baseline up to data cut-off (up to approximately 5 years and 2 months)

| End point values | Rituximab+Chemotherapy | Obinutuzumab+Chemotherapy | | |
|--|------------------------|---------------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 699 | 702 | | |
| Units: percentage of subjects with event | | | | |
| number (not applicable) | 41.5 | 34.8 | | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | Rituximab versus Obinutuzumab |
| Comparison groups | Rituximab+Chemotherapy v Obinutuzumab+Chemotherapy |
| Number of subjects included in analysis | 1401 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0028 |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.77 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.65 |
| upper limit | 0.91 |

Secondary: Progression-Free Survival (PFS) (Follicular Lymphoma Population), IRC-Assessed

| | |
|-----------------|--|
| End point title | Progression-Free Survival (PFS) (Follicular Lymphoma Population), IRC-Assessed |
|-----------------|--|

End point description:

PFS in the subjects with follicular lymphoma was defined as the time from randomisation until the first documented day of disease progression or death from any cause, whichever occurred first, on the basis of IRC assessments according to the Revised Response Criteria for Malignant Lymphoma. Progression was defined as at least 50% increase in nodal lesions or $\geq 50\%$ increase in any node > 1 centimeter (cm) or $\geq 50\%$ increase in other target measurable lesions (e.g., splenic or hepatic nodules) and/or appearance of any new bone marrow involvement and/or appearance of any new lesion > 1.5 cm or $\geq 50\%$ increase in any previously involved node with a diameter ≤ 1 cm such that it is now > 1.5 cm. Tumour measurements were obtained by CT/MRI. The FL ITT population was defined as all randomised subjects with follicular histology grouped according to their randomised treatment arm regardless of what treatments were actually received.

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

End point timeframe:

Baseline up to data cut-off (up to approximately 5 years and 2 months)

| End point values | Rituximab+Chemotherapy | Obinutuzumab+Chemotherapy | | |
|--|------------------------|---------------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 601 | 601 | | |
| Units: percentage of subjects with event | | | | |
| number (not applicable) | 23.5 | 18.0 | | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | Rituximab versus Obinutuzumab |
| Comparison groups | Rituximab+Chemotherapy v Obinutuzumab+Chemotherapy |
| Number of subjects included in analysis | 1202 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0118 |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.72 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.56 |
| upper limit | 0.93 |

Secondary: Progression-Free Survival (PFS) (Overall Study Population), Assessed by Independent Review Committee (IRC)

| | |
|-----------------|--|
| End point title | Progression-Free Survival (PFS) (Overall Study Population), Assessed by Independent Review Committee (IRC) |
|-----------------|--|

End point description:

PFS in the overall study population was defined as the time from randomisation until the first documented day of disease progression or death from any cause, whichever occurred first, on the basis of IRC assessments according to the Revised Response Criteria for Malignant Lymphoma. Progression was defined as at least 50% increase in nodal lesions or $\geq 50\%$ increase in any node > 1 centimeter (cm) or $\geq 50\%$ increase in other target measurable lesions (e.g., splenic or hepatic nodules) and/or appearance of any new bone marrow involvement and/or appearance of any new lesion > 1.5 cm or $\geq 50\%$ increase in any previously involved node with a diameter ≤ 1 cm such that it is now > 1.5 cm. Tumour measurements were obtained by CT/MRI. The ITT population was defined as all randomised subjects grouped according to their randomised treatment arm regardless of what treatments were actually received.

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

End point timeframe:

Baseline up to data cut-off (up to approximately 5 years and 2 months)

| End point values | Rituximab+Chemotherapy | Obinutuzumab+Chemotherapy | | |
|--|------------------------|---------------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 699 | 702 | | |
| Units: percentage of subjects with event | | | | |
| number (not applicable) | 24.6 | 18.4 | | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | Rituximab versus Obinutuzumab |
| Comparison groups | Rituximab+Chemotherapy v Obinutuzumab+Chemotherapy |
| Number of subjects included in analysis | 1401 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0038 |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.71 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.57 |
| upper limit | 0.9 |

Secondary: Overall Response (Follicular Lymphoma Population), Investigator-Assessed

| | |
|-----------------|--|
| End point title | Overall Response (Follicular Lymphoma Population), Investigator-Assessed |
|-----------------|--|

End point description:

Percentage of subjects with overall response in the follicular lymphoma population was defined as percentage of subjects with PR or complete response CR determined on the basis of investigator assessments with the use of Revised Response Criteria for Malignant Lymphoma. Tumour assessments were performed with CT/MRI with or without PET. CR was defined as disappearance of all target lesions; PR was defined as $\geq 50\%$ decrease target lesions in up to six dominant lesions identified at baseline, no new lesions and no increase in the size of the liver, spleen, or other nodes. Splenic and hepatic nodules must have regressed by $\geq 50\%$. Overall Response (OR) = CR + PR. The FL ITT population was defined as all randomised subjects with follicular histology grouped according to their randomised treatment arm regardless of what treatments were actually received.

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

End point timeframe:

Baseline up to end of induction period (up to approximately 7 months)

| End point values | Rituximab+Chemotherapy | Obinutuzumab+Chemotherapy | | |
|--|------------------------|---------------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 601 | 601 | | |
| Units: percentage of subjects with event | | | | |
| number (not applicable) | | | | |
| Without PET (n=519, 530) | 86.4 | 88.2 | | |
| With PET (n=242, 254) | 81.2 | 85.5 | | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | With PET |
| Comparison groups | Rituximab+Chemotherapy v Obinutuzumab+Chemotherapy |
| Number of subjects included in analysis | 1202 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.17 |
| Method | Logrank |
| Parameter estimate | Absolute difference in % |
| Point estimate | 4.3 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.8 |
| upper limit | 10.5 |

| | |
|---|--|
| Statistical analysis title | Without PET |
| Comparison groups | Rituximab+Chemotherapy v Obinutuzumab+Chemotherapy |
| Number of subjects included in analysis | 1202 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.3 |
| Method | Logrank |
| Parameter estimate | Absolute difference in % |
| Point estimate | 1.8 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.02 |
| upper limit | 5.68 |

Secondary: Overall Response (Overall Study Population), Investigator-Assessed

| | |
|-----------------|--|
| End point title | Overall Response (Overall Study Population), Investigator-Assessed |
|-----------------|--|

End point description:

Percentage of subjects with overall response in the overall study population was defined as percentage of subjects with partial response (PR) or complete response (CR) determined on the basis of investigator assessments with the use of Revised Response Criteria for Malignant Lymphoma. Tumour assessments were performed with CT/MRI with or without positron emission tomography (PET). CR was defined as disappearance of all target lesions; PR was defined as $\geq 50\%$ decrease target lesions in up to six dominant lesions identified at baseline, no new lesions and no increase in the size of the liver, spleen, or other nodes. Splenic and hepatic nodules must have regressed by $\geq 50\%$; Overall Response (OR) = CR + PR. The ITT population was defined as all randomised subjects grouped according to their randomised treatment arm regardless of what treatments were actually received.

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

End point timeframe:

Baseline up to end of induction period (up to approximately 7 months)

| End point values | Rituximab+Chemotherapy | Obinutuzumab+Chemotherapy | | |
|--|------------------------|---------------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 699 | 702 | | |
| Units: percentage of subjects with event | | | | |
| number (not applicable) | | | | |
| Without PET (n=599, 613) | 85.7 | 87.3 | | |
| With PET (n=270, 274) | 81.8 | 85.4 | | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | Without PET |
| Comparison groups | Rituximab+Chemotherapy v Obinutuzumab+Chemotherapy |
| Number of subjects included in analysis | 1401 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.33 |
| Method | Logrank |
| Parameter estimate | Absolute difference in % |
| Point estimate | 1.6 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -2 |
| upper limit | 5.3 |

| | |
|---|--|
| Statistical analysis title | With PET |
| Comparison groups | Rituximab+Chemotherapy v Obinutuzumab+Chemotherapy |
| Number of subjects included in analysis | 1401 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.17 |
| Method | Logrank |
| Parameter estimate | Absolute difference in % |
| Point estimate | 3.5 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.3 |
| upper limit | 9.4 |

Secondary: Complete Response (Follicular Lymphoma Population), Investigator-Assessed

| | |
|-----------------|---|
| End point title | Complete Response (Follicular Lymphoma Population), Investigator-Assessed |
|-----------------|---|

End point description:

Complete response in the follicular lymphoma population was determined on the basis of investigator assessments with the use of Revised Response Criteria for Malignant Lymphoma. Tumour assessments were performed with CT/MRI with or without PET. CR was defined as disappearance of all target lesions. The FL ITT population was defined as all randomised subjects with follicular histology grouped according to their randomised treatment arm regardless of what treatments were actually received.

| | |
|---|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Baseline up to end of induction period (up to approximately 7 months) | |

| End point values | Rituximab+Chemotherapy | Obinutuzumab+Chemotherapy | | |
|--|------------------------|---------------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 601 | 601 | | |
| Units: percentage of subjects with event | | | | |
| number (not applicable) | | | | |
| Without PET (n=145, 112) | 24.1 | 18.6 | | |
| With PET (n=169, 184) | 56.7 | 62.0 | | |

Statistical analyses

| Statistical analysis title | Without PET |
|---|--|
| Comparison groups | Rituximab+Chemotherapy v Obinutuzumab+Chemotherapy |
| Number of subjects included in analysis | 1202 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.02 |
| Method | Logrank |
| Parameter estimate | Absolute difference in % |
| Point estimate | -5.5 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -10.2 |
| upper limit | -0.78 |

| Statistical analysis title | With PET |
|---|--|
| Comparison groups | Rituximab+Chemotherapy v Obinutuzumab+Chemotherapy |
| Number of subjects included in analysis | 1202 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.32 |
| Method | Logrank |
| Parameter estimate | Absolute difference in % |
| Point estimate | 5.2 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.8 |
| upper limit | 13.3 |

Secondary: Complete Response (Overall Study Population), Investigator-Assessed

| | |
|-----------------|---|
| End point title | Complete Response (Overall Study Population), Investigator-Assessed |
|-----------------|---|

End point description:

Complete response in the overall study population was determined on the basis of investigator assessments with the use of Revised Response Criteria for Malignant Lymphoma. Tumor assessments were performed with CT/MRI with or without PET. CR was defined as disappearance of all target lesions. The ITT population was defined as all randomised subjects grouped according to their randomised treatment arm regardless of what treatments were actually received. Reported is the percentage of subjects with event.

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

End point timeframe:

Baseline up to end of induction period (up to approximately 7 months)

| End point values | Rituximab+Chemotherapy | Obinutuzumab+Chemotherapy | | |
|--|------------------------|---------------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 699 | 702 | | |
| Units: percentage of subjects with event | | | | |
| number (not applicable) | | | | |
| Without PET (n=163, 129) | 23.3 | 18.4 | | |
| With PET (n=188, 196) | 57.0 | 61.1 | | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | Without PET |
| Comparison groups | Rituximab+Chemotherapy v Obinutuzumab+Chemotherapy |
| Number of subjects included in analysis | 1401 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.02 |
| Method | Logrank |
| Parameter estimate | Absolute difference in % |
| Point estimate | -4.9 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -9.3 |
| upper limit | 0.6 |

| | |
|---|--|
| Statistical analysis title | With PET |
| Comparison groups | Rituximab+Chemotherapy v Obinutuzumab+Chemotherapy |
| Number of subjects included in analysis | 1401 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.33 |
| Method | Logrank |
| Parameter estimate | Absolute difference in % |
| Point estimate | 4.1 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -3.6 |
| upper limit | 11.8 |

Secondary: Overall Response (Follicular Lymphoma Population), IRC-Assessed

| | |
|-----------------|---|
| End point title | Overall Response (Follicular Lymphoma Population), IRC-Assessed |
|-----------------|---|

End point description:

Percentage of subjects with overall response in the follicular lymphoma population was defined as percentage of subjects with PR or complete response CR determined on the basis of IRC assessments with the use of Revised Response Criteria for Malignant Lymphoma. Tumour assessments were performed with CT/MRI with or without PET. CR was defined as disappearance of all target lesions; PR was defined as $\geq 50\%$ decrease target lesions in up to six dominant lesions identified at baseline, no new lesions and no increase in the size of the liver, spleen, or other nodes. Splenic and hepatic nodules must have regressed by $\geq 50\%$. Overall Response (OR) = CR + PR. The FL ITT population was defined as all randomised subjects with follicular histology grouped according to their randomised treatment arm regardless of what treatments were actually received.

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

End point timeframe:

Baseline up to end of induction period (up to approximately 7 months)

| End point values | Rituximab+Chemotherapy | Obinutuzumab+Chemotherapy | | |
|--|------------------------|---------------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 601 | 601 | | |
| Units: percentage of subjects with event | | | | |
| number (not applicable) | | | | |
| Without PET (n=529, 549) | 88.0 | 91.3 | | |
| With PET (n=254, 263) | 85.2 | 88.6 | | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | Without PET |
| Comparison groups | Rituximab+Chemotherapy v Obinutuzumab+Chemotherapy |
| Number of subjects included in analysis | 1202 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.052 |
| Method | Logrank |
| Parameter estimate | Absolute difference in % |
| Point estimate | 3.3 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.19 |
| upper limit | 6.85 |

| | |
|---|--|
| Statistical analysis title | With PET |
| Comparison groups | Rituximab+Chemotherapy v Obinutuzumab+Chemotherapy |
| Number of subjects included in analysis | 1202 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.3 |
| Method | Logrank |
| Parameter estimate | Absolute difference in % |
| Point estimate | 3.3 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.3 |
| upper limit | 8.9 |

Secondary: Overall Response (Overall Study Population), IRC-Assessed

| | |
|--|---|
| End point title | Overall Response (Overall Study Population), IRC-Assessed |
| End point description: | |
| <p>Percentage of subjects with overall response in the overall study population was defined as percentage of subjects with PR or CR determined on the basis of IRC assessments with the use of Revised Response Criteria for Malignant Lymphoma. Tumour assessments were performed with CT/MRI with or without PET. CR was defined as disappearance of all target lesions; PR was defined as $\geq 50\%$ decrease target lesions in up to six dominant lesions identified at baseline, no new lesions and no increase in the size of the liver, spleen, or other nodes. Splenic and hepatic nodules must have regressed by $\geq 50\%$; Overall Response (OR) = CR + PR. The ITT population was defined as all randomised subjects grouped according to their randomised treatment arm regardless of what treatments were actually received.</p> | |
| End point type | Secondary |
| End point timeframe: | |
| Baseline up to end of induction period (up to approximately 7 months) | |

| End point values | Rituximab+Chemotherapy | Obinutuzumab+Chemotherapy | | |
|--|------------------------|---------------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 699 | 702 | | |
| Units: percentage of subjects with event number (not applicable) | | | | |
| Without PET (n=606, 631) | 86.7 | 89.9 | | |
| With PET (n=330, 321) | 83.3 | 87.2 | | |

Statistical analyses

| Statistical analysis title | Without PET |
|---|--|
| Comparison groups | Rituximab+Chemotherapy v Obinutuzumab+Chemotherapy |
| Number of subjects included in analysis | 1401 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.049 |
| Method | Logrank |
| Parameter estimate | Absolute difference in % |
| Point estimate | 3.2 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.3 |
| upper limit | 6.6 |

| Statistical analysis title | With PET |
|---|--|
| Comparison groups | Rituximab+Chemotherapy v Obinutuzumab+Chemotherapy |
| Number of subjects included in analysis | 1401 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.22 |
| Method | Logrank |
| Parameter estimate | Absolute difference in % |
| Point estimate | 3.9 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.7 |
| upper limit | 9.5 |

Secondary: Complete Response (Follicular Lymphoma Population), IRC-Assessed

| | |
|-----------------|--|
| End point title | Complete Response (Follicular Lymphoma Population), IRC-Assessed |
|-----------------|--|

End point description:

Complete response in the follicular lymphoma population was determined on the basis of IRC assessments with the use of Revised Response Criteria for Malignant Lymphoma. Tumour assessments were performed with CT/MRI with or without PET. CR was defined as disappearance of all target lesions. The FL ITT population was defined as all randomised subjects with follicular histology grouped according to their randomised treatment arm regardless of what treatments were actually received.

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

End point timeframe:

Baseline up to end of induction period (up to approximately 7 months)

| End point values | Rituximab+Chemotherapy | Obinutuzumab+Chemotherapy | | |
|--|------------------------|---------------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 601 | 601 | | |
| Units: percentage of subjects with event number (not applicable) | | | | |
| Without PET (n=161, 171) | 26.8 | 28.5 | | |
| With PET (n=178, 212) | 59.7 | 71.4 | | |

Statistical analyses

| Statistical analysis title | With PET |
|---|--|
| Comparison groups | Rituximab+Chemotherapy v Obinutuzumab+Chemotherapy |
| Number of subjects included in analysis | 1202 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.006 |
| Method | Logrank |
| Parameter estimate | Absolute difference in % |
| Point estimate | 11.7 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 3.9 |
| upper limit | 19.4 |

| Statistical analysis title | Without PET |
|---|--|
| Comparison groups | Rituximab+Chemotherapy v Obinutuzumab+Chemotherapy |
| Number of subjects included in analysis | 1202 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.58 |
| Method | Logrank |
| Parameter estimate | Absolute difference in % |
| Point estimate | 1.7 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -3.5 |
| upper limit | 6.8 |

Secondary: Complete Response (Overall Study Population), IRC-Assessed

| | |
|--|--|
| End point title | Complete Response (Overall Study Population), IRC-Assessed |
| End point description: | |
| Complete response in the overall study population was determined on the basis of IRC assessments with the use of Revised Response Criteria for Malignant Lymphoma. Tumour assessments were performed with CT/MRI with or without PET. CR was defined as disappearance of all target lesions. The ITT population was defined as all randomised subjects grouped according to their randomised treatment arm regardless of what treatments were actually received. | |
| End point type | Secondary |
| End point timeframe: | |
| Baseline up to end of induction period (up to approximately 7 months) | |

| End point values | Rituximab+Chemotherapy | Obinutuzumab+Chemotherapy | | |
|--|------------------------|---------------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 699 | 702 | | |
| Units: percentage of subjects with event | | | | |
| number (not applicable) | | | | |
| Without PET (n=184, 190) | 26.3 | 27.1 | | |
| With PET (n=196, 223) | 59.4 | 69.5 | | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | With PET |
| Comparison groups | Rituximab+Chemotherapy v Obinutuzumab+Chemotherapy |
| Number of subjects included in analysis | 1401 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.009 |
| Method | Logrank |
| Parameter estimate | Absolute difference in % |
| Point estimate | 10.1 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 2.6 |
| upper limit | 17.6 |

| | |
|---|--|
| Statistical analysis title | Without PET |
| Comparison groups | Rituximab+Chemotherapy v Obinutuzumab+Chemotherapy |
| Number of subjects included in analysis | 1401 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.8 |
| Method | Logrank |
| Parameter estimate | Absolute difference in % |
| Point estimate | 0.7 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -4 |
| upper limit | 5.5 |

Secondary: Overall Survival (Follicular Lymphoma Population)

| | |
|-------------------------|--|
| End point title | Overall Survival (Follicular Lymphoma Population) |
| End point description: | Overall survival in the follicular lymphoma population was defined as the time from the date of randomisation to the date of death from any cause. The FL ITT population was defined as all randomised subjects with follicular histology grouped according to their randomised treatment arm regardless of what treatments were actually received. Reported is the percentage of subjects with event. |
| End point type | Secondary |
| End point timeframe: | |
| Baseline up to 10 years | |

| End point values | Rituximab+Chemotherapy | Obinutuzumab+Chemotherapy | | |
|--|------------------------|---------------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 601 | 601 | | |
| Units: percentage of subjects with event | | | | |
| number (not applicable) | 14.3 | 12.6 | | |

Statistical analyses

| | |
|-----------------------------------|--|
| Statistical analysis title | Rituximab versus Obinutuzumab |
| Comparison groups | Rituximab+Chemotherapy v Obinutuzumab+Chemotherapy |

| | |
|---|-------------------|
| Number of subjects included in analysis | 1202 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.3577 |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.86 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.63 |
| upper limit | 1.18 |

Secondary: Overall Survival (Overall Study Population)

| | |
|---|---|
| End point title | Overall Survival (Overall Study Population) |
| End point description: | |
| Overall survival in the overall study population was defined as the time from the date of randomisation to the date of death from any cause. The ITT population was defined as all randomised subjects grouped according to their randomised treatment arm regardless of what treatments were actually received. Reported is the percentage of subjects with event. | |
| End point type | Secondary |
| End point timeframe: | |
| Baseline up to data cut-off (up to approximately 5 years and 2 months) | |

| End point values | Rituximab+Chemotherapy | Obinutuzumab+Chemotherapy | | |
|--|------------------------|---------------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 699 | 702 | | |
| Units: percentage of subjects with event | | | | |
| number (not applicable) | 10.2 | 8.4 | | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | Rituximab versus Obinutuzumab |
| Comparison groups | Rituximab+Chemotherapy v Obinutuzumab+Chemotherapy |
| Number of subjects included in analysis | 1401 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.25 |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.82 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.58 |
| upper limit | 1.16 |

Secondary: Event-Free Survival (Follicular Lymphoma Population)

| | |
|-----------------|--|
| End point title | Event-Free Survival (Follicular Lymphoma Population) |
|-----------------|--|

End point description:

Event-free survival: time from the date of randomisation to the date to disease progression/relapse, death from any cause, or initiation of a new anti-lymphoma treatment (NALT) on the basis of investigator assessment assessments with the use of Revised Response Criteria for Malignant Lymphoma. Disease progression/relapse was defined as at least 50% increase in nodal lesions or $\geq 50\%$ increase in any node > 1 centimeter (cm) or $\geq 50\%$ increase in other target measurable lesions (e.g., splenic or hepatic nodules) and/or appearance of any new bone marrow involvement and/or appearance of any new lesion > 1.5 cm or $\geq 50\%$ increase in any previously involved node with a diameter ≤ 1 cm such that it is now > 1.5 cm. Tumour measurements were obtained by CT/MRI. FL ITT population: all randomised subjects with follicular histology grouped according to their randomised treatment arm regardless of what treatments were actually received. Reported: percentage of subjects with event

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

End point timeframe:

Baseline up to 10 years

| End point values | Rituximab+Chemotherapy | Obinutuzumab+Chemotherapy | | |
|--|------------------------|---------------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 601 | 601 | | |
| Units: percentage of subjects with event | | | | |
| number (not applicable) | 42.9 | 35.8 | | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | Rituximab versus Obinutuzumab |
| Comparison groups | Rituximab+Chemotherapy v Obinutuzumab+Chemotherapy |
| Number of subjects included in analysis | 1202 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0015 |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.74 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.62 |
| upper limit | 0.89 |

Secondary: Event-Free Survival (Overall Study Population)

| | |
|-----------------|--|
| End point title | Event-Free Survival (Overall Study Population) |
|-----------------|--|

End point description:

Event-free survival was defined as the time from the date of randomisation to the date to disease progression/relapse, death from any cause, or initiation of a new anti-lymphoma treatment (NALT) on the basis of investigator assessment assessments with the use of Revised Response Criteria for Malignant Lymphoma. Disease progression/relapse was defined as at least 50% increase in nodal lesions or $\geq 50\%$ increase in any node > 1 centimeter (cm) or $\geq 50\%$ increase in other target measurable lesions (e.g., splenic or hepatic nodules) and/or appearance of any new bone marrow involvement and/or appearance of any new lesion > 1.5 cm or $\geq 50\%$ increase in any previously involved node with a diameter ≤ 1 cm such that it is now > 1.5 cm. Tumour measurements were obtained by CT/MRI. The ITT population was defined as all randomised subjects grouped according to their randomised treatment arm regardless of what treatments were actually received. Reported: percentage of subjects with event.

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

End point timeframe:

Baseline up to data cut-off (up to approximately 4 years and 7 months)

| End point values | Rituximab+Chemotherapy | Obinutuzumab+Chemotherapy | | |
|--|------------------------|---------------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 699 | 702 | | |
| Units: percentage of subjects with event | | | | |
| number (not applicable) | 30.6 | 22.6 | | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | Rituximab versus Obinutuzumab |
| Comparison groups | Rituximab+Chemotherapy v Obinutuzumab+Chemotherapy |
| Number of subjects included in analysis | 1401 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0004 |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.69 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.56 |
| upper limit | 0.85 |

Secondary: Disease-Free Survival (DFS), (Follicular Lymphoma Population)

| | |
|-----------------|---|
| End point title | Disease-Free Survival (DFS), (Follicular Lymphoma Population) |
|-----------------|---|

End point description:

DFS: time from the date of the first occurrence of a documented CR to the date of disease progression/relapse, or death from any cause on the basis of investigator assessments with the use of Revised Response Criteria for Malignant Lymphoma. Tumour assessments were performed with CT/MRI. CR was defined as disappearance of all target lesions. Progression/relapse was defined as at least 50% increase in nodal lesions or $\geq 50\%$ increase in any node > 1 centimeter (cm) or $\geq 50\%$ increase in other target measurable lesions (e.g., splenic or hepatic nodules) and/or appearance of any new bone marrow involvement and/or appearance of any new lesion > 1.5 cm or $\geq 50\%$ increase in any previously involved node with a diameter ≤ 1 cm such that it is now > 1.5 cm. Subjects with CR within the FL ITT population were included in the analysis. Reported: percentage of subjects with event.

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

End point timeframe:

From first occurrence of documented CR to data cut-off (up to approximately 5 years and 2 months)

| End point values | Rituximab+Chemotherapy | Obinutuzumab+Chemotherapy | | |
|--|------------------------|---------------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 330 | 355 | | |
| Units: percentage of subjects with event | | | | |
| number (not applicable) | 27.9 | 26.3 | | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | Rituximab versus Obinutuzumab |
| Comparison groups | Rituximab+Chemotherapy v Obinutuzumab+Chemotherapy |
| Number of subjects included in analysis | 685 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.95 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.71 |
| upper limit | 1.27 |

Secondary: Disease-Free Survival (DFS) (Overall Study Population)

| | |
|--|--|
| End point title | Disease-Free Survival (DFS) (Overall Study Population) |
| End point description: DFS: time from the date of the first occurrence of a documented CR to the date of disease progression/relapse, or death from any cause on the basis of investigator assessments with the use of Revised Response Criteria for Malignant Lymphoma. Tumour assessments were performed with CT/MRI. CR was defined as disappearance of all target lesions. Progression/relapse was defined as at least 50% increase in nodal lesions or $\geq 50\%$ increase in any node > 1 centimeter (cm) or $\geq 50\%$ increase in other target measurable lesions (e.g., splenic or hepatic nodules) and/or appearance of any new bone marrow involvement and/or appearance of any new lesion > 1.5 cm or $\geq 50\%$ increase in any previously involved node with a diameter ≤ 1 cm such that it is now > 1.5 cm. Subjects with CR within the ITT population were included in the analysis. Reported: percentage of subjects with event. | |
| End point type | Secondary |
| End point timeframe: From first occurrence of documented CR to data cut-off (up to approximately 5 years and 2 months) | |

| End point values | Rituximab+Chemotherapy | Obinutuzumab+Chemotherapy | | |
|--|------------------------|---------------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 320 | 343 | | |
| Units: percentage of subjects with event | | | | |
| number (not applicable) | 14.9 | 11.2 | | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | Rituximab versus Obinutuzumab |
| Comparison groups | Rituximab+Chemotherapy v Obinutuzumab+Chemotherapy |
| Number of subjects included in analysis | 663 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.78 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.5 |
| upper limit | 1.19 |

Secondary: Duration of Response (DOR) (Follicular Lymphoma Population), Investigator-Assessed

| | |
|-----------------|--|
| End point title | Duration of Response (DOR) (Follicular Lymphoma Population), |
|-----------------|--|

End point description:

DOR was defined as the time from first occurrence of a documented CR or PR to disease progression/relapse, or death from any cause. Tumour assessments by CT/MRI. CR: disappearance of all target lesions. PR: $\geq 50\%$ decrease target lesions in up to six dominant lesions identified at baseline, no new lesions, no increase in the size of the liver, spleen, or other nodes. Splenic and hepatic nodules must have regressed by $\geq 50\%$. Progression/relapse was defined as at least 50% increase in nodal lesions or $\geq 50\%$ increase in any node > 1 centimeter (cm) or $\geq 50\%$ increase in other target measurable lesions (e.g., splenic or hepatic nodules) and/or appearance of any new bone marrow involvement and/or appearance of any new lesion > 1.5 cm or $\geq 50\%$ increase in any previously involved node with a diameter ≤ 1 cm such that it is now > 1.5 cm. Subjects with CR or PR within the FL ITT population were included in the analysis. Reported is the percentage of subjects with event.

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

End point timeframe:

From first occurrence of documented CR or PR to data cut-off (up to approximately 5 years and 2 months)

| End point values | Rituximab+Chemotherapy | Obinutuzumab+Chemotherapy | | |
|--|------------------------|---------------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 568 | 571 | | |
| Units: percentage of subjects with event | | | | |
| number (not applicable) | 39.3 | 33.3 | | |

Statistical analyses

| Statistical analysis title | Rituximab versus Obinutuzumab |
|---|--|
| Comparison groups | Rituximab+Chemotherapy v Obinutuzumab+Chemotherapy |
| Number of subjects included in analysis | 1139 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.76 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.63 |
| upper limit | 0.93 |

Secondary: Duration of Response (DOR) (Overall Study Population), Investigator-Assessed

| | |
|-----------------|--|
| End point title | Duration of Response (DOR) (Overall Study Population), Investigator-Assessed |
|-----------------|--|

End point description:

DOR was defined as the time from first occurrence of a documented CR or PR to disease progression/relapse, or death from any cause. Tumour assessments by CT/MRI. CR: disappearance of all

target lesions. PR: $\geq 50\%$ decrease target lesions in up to six dominant lesions identified at baseline, no new lesions and no increase in the size of the liver, spleen, or other nodes. Splenic and hepatic nodules must have regressed by $\geq 50\%$. Progression/relapse was defined as at least 50% increase in nodal lesions or $\geq 50\%$ increase in any node > 1 centimeter (cm) or $\geq 50\%$ increase in other target measurable lesions (e.g., splenic or hepatic nodules) and/or appearance of any new bone marrow involvement and/or appearance of any new lesion > 1.5 cm or $\geq 50\%$ increase in any previously involved node with a diameter ≤ 1 cm such that it is now > 1.5 cm. Subjects with CR or PR within the ITT population were included in the analysis. Reported is the percentage of subjects with event.

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

End point timeframe:

From first occurrence of documented CR or PR to data cut-off (up to approximately 5 years and 2 months)

| End point values | Rituximab+Chemotherapy | Obinutuzumab+Chemotherapy | | |
|--|------------------------|---------------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 656 | 659 | | |
| Units: percentage of subjects with event | | | | |
| number (not applicable) | 25.5 | 18.7 | | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | Rituximab versus Obinutuzumab |
| Comparison groups | Rituximab+Chemotherapy v Obinutuzumab+Chemotherapy |
| Number of subjects included in analysis | 1315 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.69 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.55 |
| upper limit | 0.88 |

Secondary: Time to Next Anti-Lymphoma Treatment (Follicular Lymphoma Population)

| | |
|-----------------|---|
| End point title | Time to Next Anti-Lymphoma Treatment (Follicular Lymphoma Population) |
|-----------------|---|

End point description:

Time to next anti-lymphoma treatment was defined as the time from the date of randomisation to the start date of the next anti-lymphoma treatment or death from any cause. Reported is the percentage of subjects who started next anti-lymphoma treatment. The FL ITT population was defined as all randomised subjects with follicular histology grouped according to their randomised treatment arm regardless of what treatments were actually received. Reported is the percentage of subjects with event.

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

End point timeframe:
Baseline up to 10 years

| End point values | Rituximab+Chemotherapy | Obinutuzumab+Chemotherapy | | |
|--|------------------------|---------------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 601 | 601 | | |
| Units: percentage of subjects with event | | | | |
| number (not applicable) | 34.8 | 26.6 | | |

Statistical analyses

| Statistical analysis title | Rituximab versus Obinutuzumab |
|---|--|
| Comparison groups | Rituximab+Chemotherapy v Obinutuzumab+Chemotherapy |
| Number of subjects included in analysis | 1202 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.71 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.58 |
| upper limit | 0.87 |

Secondary: Time to Next Anti-Lymphoma Treatment (Overall Study Population)

| | |
|-----------------|---|
| End point title | Time to Next Anti-Lymphoma Treatment (Overall Study Population) |
|-----------------|---|

End point description:

Time to next anti-lymphoma treatment was defined as the time from the date of randomisation to the start date of the next anti-lymphoma treatment or death from any cause. Reported is the percentage of subjects who started next anti-lymphoma treatment. The ITT population was defined as all randomised subjects grouped according to their randomised treatment arm regardless of what treatments were actually received. Reported is the percentage of subjects with event.

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

End point timeframe:

Baseline up to data cut-off (up to approximately 5 years and 2 months)

| End point values | Rituximab+Chemotherapy | Obinutuzumab+Chemotherapy | | |
|--|------------------------|---------------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 699 | 702 | | |
| Units: percentage of subjects with event | | | | |
| number (not applicable) | 21.6 | 15.7 | | |

Statistical analyses

| Statistical analysis title | Rituximab versus Obinutuzumab |
|---|--|
| Comparison groups | Rituximab+Chemotherapy v Obinutuzumab+Chemotherapy |
| Number of subjects included in analysis | 1401 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.7 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.54 |
| upper limit | 0.89 |

Secondary: Percentage of Subjects With Adverse Events

| | |
|---|--|
| End point title | Percentage of Subjects With Adverse Events |
| End point description: | |
| An adverse event is any untoward medical occurrence in a subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with the treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a pharmaceutical product, whether or not considered related to the pharmaceutical product. Preexisting conditions which worsen during a study are also considered as adverse events. The safety analysis population included all subjects who received any amount of any study drug and subjects were analysed according to the treatment received. | |
| End point type | Secondary |
| End point timeframe: | |
| Baseline up to 10 years | |

| End point values | Rituximab+Chemotherapy | Obinutuzumab+Chemotherapy | | |
|-------------------------------|------------------------|---------------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 692 | 698 | | |
| Units: percentage of subjects | | | | |
| number (not applicable) | 99.6 | 99.9 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in All Domains of FACT-G (Follicular Lymphoma Population)

| | |
|-----------------|--|
| End point title | Change from Baseline in All Domains of FACT-G (Follicular Lymphoma Population) |
|-----------------|--|

End point description:

FACT-G consists of the following 4 FACT-Lym sub-questionnaires: Physical Well-being (range: 0-28), Social/Family Well-being (range: 0-28), Emotional Well-being (range: 0-24) and Functional Well-being (range: 0-28). Higher scores indicate better outcomes. A positive change from baseline indicates improvement. The FL ITT population was defined as all randomised subjects with follicular histology grouped according to their randomised treatment arm regardless of what treatments were actually received.

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

End point timeframe:

Baseline (Induction Cycle 1, Day 1), end of study (up to approximately 5 years and 2 months)

| End point values | Rituximab+Chemotherapy | Obinutuzumab+Chemotherapy | | |
|---|------------------------|---------------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 601 | 601 | | |
| Units: Units on a scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| Physical Well-being (PW), Baseline (n=557, n=566) | 23.36 (± 4.77) | 23.14 (± 4.85) | | |
| PW Change, Cycle 3, Day 1 (n=511, 496) | -0.91 (± 4.54) | -0.21 (± 4.59) | | |
| PW Change, End Induction (n=482, 480) | -0.06 (± 4.83) | 0.56 (± 5.14) | | |
| PW Change, Maint Month 2 (n=362, 398) | 0.83 (± 4.76) | 1.42 (± 5.09) | | |
| PW Change, Maint Month 12 (n=362, 406) | 1.14 (± 4.29) | 1.34 (± 4.74) | | |
| PW Change, End Maint (n=411, 437) | 0.88 (± 4.54) | 1.33 (± 5.00) | | |
| Social/Family Well-being , Baseline (n=555, 563) | 22.84 (± 4.92) | 23.28 (± 4.77) | | |
| S/FW Change, Cycle 3 Day 1 (n=506, 492) | -0.52 (± 4.03) | -0.67 (± 3.92) | | |
| S/FW Change, End Induction (n=482, 475) | -0.46 (± 4.77) | -0.56 (± 5.00) | | |
| S/FW Change, Maint Month 2 (n=359, 396) | -0.39 (± 4.72) | -0.67 (± 4.68) | | |
| S/FW Change, Maint Month 12 (n=359, 403) | -0.61 (± 5.56) | -0.97 (± 5.34) | | |
| S/FW Change, End Maint (n=410, 436) | -0.93 (± 5.67) | -0.71 (± 5.54) | | |

| | | | | |
|---|----------------|----------------|--|--|
| Emotional Well-being (EW), Baseline (n=556, 563) | 17.64 (± 4.19) | 17.87 (± 4.13) | | |
| EW Change, Cycle 3 Day 1 (n=503, 490) | 1.49 (± 3.40) | 1.35 (± 3.35) | | |
| EW Change, End Induction (n=478, 476) | 1.16 (± 3.90) | 1.14 (± 3.87) | | |
| EW Change, Maint Month 2 (n=359, 396) | 1.77 (± 3.88) | 1.49 (± 4.16) | | |
| EW Change, Maint Month 12 (n=360, 402) | 1.45 (± 3.92) | 1.46 (± 3.88) | | |
| EW Change, End Maint (n=405, 435) | 1.43 (± 3.98) | 1.49 (± 3.99) | | |
| Functional Well-being (FW), Baseline (n=556, 563) | 18.66 (± 6.19) | 18.76 (± 5.98) | | |
| FW Change, Cycle 3 Day 1 (n=504, 488) | -0.30 (± 5.30) | -0.07 (± 5.24) | | |
| FW Change, End Induction (n=480, 476) | 0.44 (± 5.63) | 0.93 (± 5.85) | | |
| FW Change, Maint Month 2 (n=359, 396) | 1.04 (± 5.31) | 1.25 (± 6.02) | | |
| FW Change, Maint Month 12 (n=360, 402) | 1.84 (± 5.54) | 1.65 (± 5.95) | | |
| FW Change, End Maint (n=406, 436) | 1.40 (± 6.12) | 1.72 (± 6.16) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in FACT-Lym Total Outcome Index (TOI) Score (Follicular Lymphoma Population)

| | |
|-----------------|---|
| End point title | Change From Baseline in FACT-Lym Total Outcome Index (TOI) Score (Follicular Lymphoma Population) |
|-----------------|---|

End point description:

The FACT-Lym TOI Score for the follicular lymphoma population was derived from the following 3 individual FACT-Lym questionnaire subscale scores: Physical Well-being (range: 0-28), Functional Well-being (range: 0-28) and Lymphoma (range: 0-60). The FACT-Lym TOI Score is the sum of the 3 individual subscales (range 0-116). Higher scores indicate better outcomes. A positive change from baseline indicates an improvement. The FL ITT population was defined as all randomised subjects with follicular histology grouped according to their randomised treatment arm regardless of what treatments were actually received.

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

End point timeframe:

Baseline (Induction Cycle 1, Day 1), end of study (up to approximately 5 years and 2 months)

| End point values | Rituximab+Chemotherapy | Obinutuzumab+Chemotherapy | | |
|--------------------------------------|------------------------|---------------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 601 | 601 | | |
| Units: Units on a scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| TOI Score, Baseline (n=559, 567) | 86.61 (± 18.16) | 86.94 (± 18.05) | | |

| | | | | |
|---|----------------|----------------|--|--|
| TOI Score Change, Cycle 3 Day 1 (n=514, 497) | 0.46 (± 15.03) | 2.18 (± 15.95) | | |
| TOI Score Change, End Induction (n=485, 481) | 2.91 (± 17.00) | 4.57 (± 16.71) | | |
| TOI Score Change, Maint Month 2 (n=363, 400) | 6.22 (± 16.16) | 7.17 (± 16.57) | | |
| TOI Score Change, Maint Month 12 (n=362, 408) | 7.61 (± 15.62) | 7.20 (± 16.75) | | |
| TOI Score Change, End Maint (n=412, 440) | 6.23 (± 17.06) | 7.44 (± 16.96) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in FACT-Lym Individual Subscale Lymphoma Score (Follicular Population)

| | |
|-----------------|---|
| End point title | Change From Baseline in FACT-Lym Individual Subscale Lymphoma Score (Follicular Population) |
|-----------------|---|

End point description:

The FACT-Lym Individual Subscale Lymphoma Score for the follicular lymphoma population was derived from the Lymphoma subscale questionnaire (range: 0-60). Higher scores indicate better outcomes. A positive change from baseline indicates an improvement. The FL ITT population was defined as all randomised subjects with follicular histology grouped according to their randomised treatment arm regardless of what treatments were actually received.

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

End point timeframe:

Baseline (Induction Cycle 1, Day 1), end of study (up to approximately 5 years and 2 months)

| End point values | Rituximab+Chemotherapy | Obinutuzumab+Chemotherapy | | |
|--|------------------------|---------------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 601 | 601 | | |
| Units: Units on a scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| Lymphoma, Baseline (n=556, 563) | 45.01 (± 9.37) | 45.54 (± 9.29) | | |
| Lymphoma Change, Cycle 3 Day 1 (n=509, 491) | 2.04 (± 7.18) | 2.71 (± 7.46) | | |
| Lymphoma Change, End Induction (n=477, 478) | 2.99 (± 8.63) | 3.01 (± 8.36) | | |
| Lymphoma Change, Maint Month 2 (n=360, 395) | 4.80 (± 8.29) | 4.52 (± 8.32) | | |
| Lymphoma Change, Maint Month 12 (n=360, 404) | 4.93 (± 8.34) | 4.27 (± 8.31) | | |
| Lymphoma Change, End Maint (n=407, 438) | 4.31 (± 8.81) | 4.57 (± 8.54) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Functional Assessment of Cancer Therapy-Lymphoma (FACT-Lym) Total Score (Follicular Population)

| | |
|-----------------|---|
| End point title | Change From Baseline in Functional Assessment of Cancer Therapy-Lymphoma (FACT-Lym) Total Score (Follicular Population) |
|-----------------|---|

End point description:

The FACT-Lym Total Score for the follicular lymphoma population was derived from the following 5 individual FACT-Lym questionnaire subscale scores: Physical Well-being (range: 0-28), Social/Family Well-being (range: 0-28), Emotional Well-being (range: 0-24), Functional Well-being (range: 0-28) and Lymphoma (range: 0-60). The FACT-Lym Total Score is the sum of all 5 individual subscales (range 0-168). Higher scores indicate better outcomes. A positive change from baseline indicates an improvement. The FL ITT population was defined as all randomised subjects with follicular histology grouped according to their randomised treatment arm regardless of what treatments were actually received.

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

End point timeframe:

Baseline (Induction Cycle 1, Day 1), end of study (up to approximately 5 years and 2 months)

| End point values | Rituximab+Chemotherapy | Obinutuzumab+Chemotherapy | | |
|---|------------------------|---------------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 601 | 601 | | |
| Units: Units on a scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| Total Score, Baseline (n=552, 559) | 127.40 (\pm 22.43) | 128.42 (\pm 22.16) | | |
| Total Score Change, Cycle 3 Day 1 (n=499, 484) | 1.98 (\pm 17.01) | 3.21 (\pm 17.12) | | |
| Total Score Change, End Induction (n=471, 471) | 4.18 (\pm 19.75) | 5.10 (\pm 20.03) | | |
| Total Score Change, Maint Month 2 (n=356, 392) | 8.40 (\pm 19.16) | 8.13 (\pm 19.80) | | |
| Total Score Change, Maint Month 12 (n=358, 396) | 8.87 (\pm 19.31) | 7.90 (\pm 19.55) | | |
| Total Score Change, End Maint (n=401, 433) | 7.43 (\pm 19.88) | 8.80 (\pm 20.57) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Euro-Quality of Life-5 Dimensions (EQ-5D) Questionnaire Summary Score (Follicular Lymphoma Population) During Induction Phase

| | |
|-----------------|---|
| End point title | Change From Baseline in Euro-Quality of Life-5 Dimensions (EQ-5D) Questionnaire Summary Score (Follicular Lymphoma Population) During Induction Phase |
|-----------------|---|

End point description:

The EQ-5D is a quality of life questionnaire with five questions, each with three categories (no problem,

moderate problem, severe problems) and a visual analogue scale (VAS) from 0 (worst possible health state) to 100 (best possible health state. Summary score ranges from 0 to 1. Higher scores indicate better outcomes. A positive change from baseline indicates an improvement. The FL ITT population was defined as all randomised subjects with follicular histology grouped according to their randomised treatment arm regardless of what treatments were actually received. 9999=NE=Not estimable based on 0 or 1 subject evaluated.

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

End point timeframe:

Induction: Cycle 1 Day 1 (Baseline), Cycle 3 Day 1, End of Induction (up to 7 months) (1 Cycle=21 or 28 days); Maintenance: 2, 12, 25 months after Day 1 of last induction cycle (Cycle 6 or 8), Follow-up; up to data cut-off (up to 5 years and 2 months)

| End point values | Rituximab+Chemotherapy | Obinutuzumab+Chemotherapy | | |
|--|------------------------|---------------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 601 | 601 | | |
| Units: Units on a scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| Baseline Induction (n=558, 559) | 0.80 (± 0.24) | 0.81 (± 0.21) | | |
| Change Baseline, Cycle 1 Day 1 (n=0, 0) | 9999 (± 9999) | 9999 (± 9999) | | |
| Change Baseline, Cycle 3 Day 1 (n=505, 487) | 0.03 (± 0.21) | 0.03 (± 0.20) | | |
| Change Baseline, Induction Completion (n=468, 466) | 0.04 (± 0.23) | 0.03 (± 0.22) | | |
| Change Baseline, Maint/Obs Month 2 (n=348, 377) | 0.05 (± 0.23) | 0.06 (± 0.22) | | |
| Change Baseline, Maint/Obs Month 12 (n=2, 1) | 0.00 (± 0.00) | -0.20 (± 9999) | | |
| Change Baseline, Maint/Obs Completion (n=0, 1) | 9999 (± 9999) | -0.10 (± 9999) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in EQ-5D Questionnaire Summary Score (Follicular Lymphoma Population) During Maintenance/Observation Phase

| | |
|-----------------|---|
| End point title | Change From Baseline in EQ-5D Questionnaire Summary Score (Follicular Lymphoma Population) During Maintenance/Observation Phase |
|-----------------|---|

End point description:

The EQ-5D is a quality of life questionnaire with five questions, each with three categories (no problem, moderate problem, severe problems) and a visual analogue scale (VAS) from 0 (worst possible health state) to 100 (best possible health state. Summary score ranges from 0 to 1. Higher scores indicate better outcomes. A positive change from baseline indicates an improvement. The FL ITT population was defined as all randomised subjects with follicular histology grouped according to their randomised treatment arm regardless of what treatments were actually received. 9999=NE=Not estimable based on 0 subjects evaluated.

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

End point timeframe:

Induction: Cycle 1 Day 1 (Baseline), Cycle 3 Day 1, End of Induction (up to 7 months) (1 Cycle=21 or 28 days); Maintenance: 2, 12, 25 months after Day 1 of last induction cycle (Cycle 6 or 8), Follow-up;

| End point values | Rituximab+Chemotherapy | Obinutuzumab+Chemotherapy | | |
|--|------------------------|---------------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 601 | 601 | | |
| Units: Units on a scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| Change Baseline, Maint/Obs Month 2 (n=11, 14) | 0.04 (\pm 0.34) | 0.04 (\pm 0.14) | | |
| Change Baseline, Maint/Obs Month 12 (n=354, 395) | 0.06 (\pm 0.24) | 0.06 (\pm 0.21) | | |
| Change Baseline, Maint/Obs Completion (n=402, 421) | 0.03 (\pm 0.23) | 0.05 (\pm 0.23) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in EQ-5D Questionnaire Summary Score (Follicular Lymphoma Population) During Follow Up Phase

| | |
|-----------------|---|
| End point title | Change From Baseline in EQ-5D Questionnaire Summary Score (Follicular Lymphoma Population) During Follow Up Phase |
|-----------------|---|

End point description:

The EQ-5D is a quality of life questionnaire with five questions, each with three categories (no problem, moderate problem, severe problems) and a visual analogue scale (VAS) from 0 (worst possible health state) to 100 (best possible health state). Summary score ranges from 0 to 1. Higher scores indicate better outcomes. A positive change from baseline indicates an improvement. The FL ITT population was defined as all randomised subjects with follicular histology grouped according to their randomised treatment arm regardless of what treatments were actually received.

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

End point timeframe:

Induction: Cycle 1 Day 1 (Baseline), Cycle 3 Day 1, End of Induction (up to 7 months) (1 Cycle=21 or 28 days); Maintenance: 2, 12, 25 months after Day 1 of last induction cycle (Cycle 6 or 8), Follow-up; up to data cut-off (up to 5 years and 2 months)

| End point values | Rituximab+Chemotherapy | Obinutuzumab+Chemotherapy | | |
|--|------------------------|---------------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 601 | 601 | | |
| Units: Units on a scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| Change Baseline, Follow-up Month 36 (n=238, 248) | 0.05 (\pm 0.24) | 0.06 (\pm 0.23) | | |
| Change Baseline, Follow-up Month 48 (n=73, 80) | 0.05 (\pm 0.20) | 0.06 (\pm 0.23) | | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Baseline up to 10 years

Adverse event reporting additional description:

The safety analysis population included all subjects who received any amount of any study drug and subjects were analysed according to the treatment received.

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

Dictionary used

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

| | |
|--------------------|------|
| Dictionary version | 24.0 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|---------------------------|
| Reporting group title | Obinutuzumab+Chemotherapy |
|-----------------------|---------------------------|

Reporting group description:

Participants will receive either 8 cycles of obinutuzumab along with 6 cycles of CHOP (21-day cycle) or 8 cycles of obinutuzumab along with 8 cycles of CVP (21-day cycles) or 6 cycles of obinutuzumab along with 6 cycles of bendamustine (28-day cycle) during induction period. The induction period will be followed by either a maintenance or observation period for responders or non-responders, respectively. Responders will receive obinutuzumab monotherapy every 2 months for 2 years during the maintenance period. Non-responders will receive no protocol specified treatment during the 2-year observation period. Finally, participants will be followed during a 5-year follow-up period. The chemotherapy regimen (CHOP or CVP or bendamustine) for individual participant will be chosen by the site prior to initiation of the study.

| | |
|-----------------------|------------------------|
| Reporting group title | Rituximab+Chemotherapy |
|-----------------------|------------------------|

Reporting group description:

Participants will receive either 8 cycles of rituximab along with 6 cycles of cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) (21-day cycle) or 8 cycles of rituximab along with 8 cycles of cyclophosphamide, vincristine, and prednisone (CVP) (21-day cycles) or 6 cycles of rituximab along with 6 cycles of bendamustine (28-day cycle) during the induction period. The induction period will be followed by either a maintenance or observation period for responders or non-responders, respectively. Responders will receive rituximab monotherapy every 2 months for 2 years during the maintenance period. Non-responders will receive no protocol specified treatment during the 2-year observation period. Finally, participants will be followed during a 5-year follow-up period. The chemotherapy regimen (CHOP or CVP or bendamustine) for individual participant will be chosen by the site prior to initiation of the study.

| Serious adverse events | Obinutuzumab+Chemotherapy | Rituximab+Chemotherapy | |
|---|---------------------------|------------------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 361 / 698 (51.72%) | 309 / 692 (44.65%) | |
| number of deaths (all causes) | 104 | 111 | |
| number of deaths resulting from adverse events | 14 | 6 | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| ADENOCARCINOMA OF COLON | | | |
| subjects affected / exposed | 2 / 698 (0.29%) | 0 / 692 (0.00%) | |
| occurrences causally related to treatment / all | 2 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| CHOLANGIOCARCINOMA | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 698 (0.00%) | 2 / 692 (0.29%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 1 / 2 | |
| RENAL CANCER | | | |
| subjects affected / exposed | 1 / 698 (0.14%) | 0 / 692 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| HEPATIC CANCER | | | |
| subjects affected / exposed | 1 / 698 (0.14%) | 0 / 692 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| KERATOACANTHOMA | | | |
| subjects affected / exposed | 0 / 698 (0.00%) | 1 / 692 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| SQUAMOUS CELL BREAST CARCINOMA | | | |
| subjects affected / exposed | 0 / 698 (0.00%) | 1 / 692 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| ADENOCARCINOMA METASTATIC | | | |
| subjects affected / exposed | 0 / 698 (0.00%) | 1 / 692 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| LENTIGO MALIGNA | | | |
| subjects affected / exposed | 1 / 698 (0.14%) | 0 / 692 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| LARYNGEAL SQUAMOUS CELL CARCINOMA | | | |
| subjects affected / exposed | 1 / 698 (0.14%) | 0 / 692 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| SQUAMOUS CELL CARCINOMA | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 2 / 698 (0.29%) | 1 / 692 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| PITUITARY TUMOUR BENIGN | | | |
| subjects affected / exposed | 0 / 698 (0.00%) | 1 / 692 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| GASTRIC CANCER | | | |
| subjects affected / exposed | 2 / 698 (0.29%) | 1 / 692 (0.14%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 1 / 2 | 0 / 1 | |
| DUCTAL ADENOCARCINOMA OF PANCREAS | | | |
| subjects affected / exposed | 0 / 698 (0.00%) | 1 / 692 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| INTRADUCTAL PROLIFERATIVE BREAST LESION | | | |
| subjects affected / exposed | 1 / 698 (0.14%) | 1 / 692 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| MYELODYSPLASTIC SYNDROME | | | |
| subjects affected / exposed | 4 / 698 (0.57%) | 0 / 692 (0.00%) | |
| occurrences causally related to treatment / all | 4 / 4 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| PAPILLARY THYROID CANCER | | | |
| subjects affected / exposed | 2 / 698 (0.29%) | 0 / 692 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| TRANSITIONAL CELL CARCINOMA | | | |
| subjects affected / exposed | 2 / 698 (0.29%) | 0 / 692 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| VULVOVAGINAL WARTS | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 698 (0.00%) | 1 / 692 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| HODGKIN'S DISEASE NODULAR SCLEROSIS | | | |
| subjects affected / exposed | 1 / 698 (0.14%) | 0 / 692 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| BENIGN LARYNGEAL NEOPLASM | | | |
| subjects affected / exposed | 0 / 698 (0.00%) | 1 / 692 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| BASAL CELL CARCINOMA | | | |
| subjects affected / exposed | 6 / 698 (0.86%) | 3 / 692 (0.43%) | |
| occurrences causally related to treatment / all | 1 / 7 | 1 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| NEUROENDOCRINE CARCINOMA OF THE SKIN | | | |
| subjects affected / exposed | 0 / 698 (0.00%) | 1 / 692 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| ACUTE MYELOID LEUKAEMIA | | | |
| subjects affected / exposed | 2 / 698 (0.29%) | 1 / 692 (0.14%) | |
| occurrences causally related to treatment / all | 2 / 4 | 1 / 1 | |
| deaths causally related to treatment / all | 1 / 2 | 1 / 1 | |
| TUMOUR FLARE | | | |
| subjects affected / exposed | 0 / 698 (0.00%) | 1 / 692 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| SCHWANNOMA | | | |
| subjects affected / exposed | 1 / 698 (0.14%) | 0 / 692 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| INVASIVE DUCTAL BREAST CARCINOMA | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 698 (0.14%) | 1 / 692 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| NON-SMALL CELL LUNG CANCER | | | |
| subjects affected / exposed | 2 / 698 (0.29%) | 2 / 692 (0.29%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 2 | |
| SQUAMOUS CELL CARCINOMA OF SKIN | | | |
| subjects affected / exposed | 5 / 698 (0.72%) | 2 / 692 (0.29%) | |
| occurrences causally related to treatment / all | 0 / 5 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| COLORECTAL CANCER | | | |
| subjects affected / exposed | 0 / 698 (0.00%) | 1 / 692 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| BOWEN'S DISEASE | | | |
| subjects affected / exposed | 0 / 698 (0.00%) | 1 / 692 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| HODGKIN'S DISEASE | | | |
| subjects affected / exposed | 1 / 698 (0.14%) | 0 / 692 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| PROSTATE CANCER | | | |
| subjects affected / exposed | 5 / 698 (0.72%) | 4 / 692 (0.58%) | |
| occurrences causally related to treatment / all | 1 / 5 | 1 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| OESOPHAGEAL CARCINOMA | | | |
| subjects affected / exposed | 1 / 698 (0.14%) | 0 / 692 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| BLADDER TRANSITIONAL CELL CARCINOMA METASTATIC | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 698 (0.14%) | 0 / 692 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| LUNG NEOPLASM MALIGNANT | | | |
| subjects affected / exposed | 0 / 698 (0.00%) | 3 / 692 (0.43%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 3 | |
| NON-HODGKIN'S LYMPHOMA | | | |
| subjects affected / exposed | 0 / 698 (0.00%) | 1 / 692 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 1 / 1 | |
| PANCREATIC CARCINOMA | | | |
| subjects affected / exposed | 0 / 698 (0.00%) | 1 / 692 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| CANCER PAIN | | | |
| subjects affected / exposed | 1 / 698 (0.14%) | 0 / 692 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| INTRAOCULAR MELANOMA | | | |
| subjects affected / exposed | 0 / 698 (0.00%) | 1 / 692 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| MALIGNANT MELANOMA | | | |
| subjects affected / exposed | 1 / 698 (0.14%) | 3 / 692 (0.43%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| ADENOCARCINOMA | | | |
| subjects affected / exposed | 1 / 698 (0.14%) | 1 / 692 (0.14%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| RECTAL ADENOCARCINOMA | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 698 (0.14%) | 1 / 692 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| ACUTE LYMPHOCYTIC LEUKAEMIA | | | |
| subjects affected / exposed | 1 / 698 (0.14%) | 0 / 692 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 1 / 1 | 0 / 0 | |
| GASTRIC ADENOMA | | | |
| subjects affected / exposed | 1 / 698 (0.14%) | 0 / 692 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| TONGUE NEOPLASM MALIGNANT STAGE UNSPECIFIED | | | |
| subjects affected / exposed | 0 / 698 (0.00%) | 1 / 692 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| BREAST CANCER | | | |
| subjects affected / exposed | 6 / 698 (0.86%) | 0 / 692 (0.00%) | |
| occurrences causally related to treatment / all | 2 / 6 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| COLON CANCER | | | |
| subjects affected / exposed | 1 / 698 (0.14%) | 3 / 692 (0.43%) | |
| occurrences causally related to treatment / all | 0 / 1 | 2 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| HORMONE RECEPTOR POSITIVE BREAST CANCER | | | |
| subjects affected / exposed | 1 / 698 (0.14%) | 0 / 692 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| THYROID ADENOMA | | | |
| subjects affected / exposed | 0 / 698 (0.00%) | 1 / 692 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| GASTROINTESTINAL NEOPLASM | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 698 (0.00%) | 1 / 692 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| ACOUSTIC NEUROMA | | | |
| subjects affected / exposed | 1 / 698 (0.14%) | 0 / 692 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| MENINGIOMA | | | |
| subjects affected / exposed | 1 / 698 (0.14%) | 0 / 692 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| BLADDER TRANSITIONAL CELL CARCINOMA | | | |
| subjects affected / exposed | 0 / 698 (0.00%) | 1 / 692 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| LUNG ADENOCARCINOMA | | | |
| subjects affected / exposed | 2 / 698 (0.29%) | 1 / 692 (0.14%) | |
| occurrences causally related to treatment / all | 1 / 2 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 1 | 1 / 1 | |
| NON-SMALL CELL LUNG CANCER STAGE IV | | | |
| subjects affected / exposed | 1 / 698 (0.14%) | 0 / 692 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| UTERINE CANCER | | | |
| subjects affected / exposed | 0 / 698 (0.00%) | 1 / 692 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| HODGKIN'S DISEASE STAGE II | | | |
| subjects affected / exposed | 1 / 698 (0.14%) | 0 / 692 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| RENAL CELL CARCINOMA | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 698 (0.00%) | 1 / 692 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vascular disorders | | | |
| EMBOLISM | | | |
| subjects affected / exposed | 0 / 698 (0.00%) | 3 / 692 (0.43%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| DEEP VEIN THROMBOSIS | | | |
| subjects affected / exposed | 1 / 698 (0.14%) | 2 / 692 (0.29%) | |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| PERIPHERAL ARTERY ANEURYSM | | | |
| subjects affected / exposed | 0 / 698 (0.00%) | 1 / 692 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| PERIPHERAL ISCHAEMIA | | | |
| subjects affected / exposed | 1 / 698 (0.14%) | 0 / 692 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| PELVIC VENOUS THROMBOSIS | | | |
| subjects affected / exposed | 0 / 698 (0.00%) | 1 / 692 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| AXILLARY VEIN THROMBOSIS | | | |
| subjects affected / exposed | 1 / 698 (0.14%) | 0 / 692 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| HYPOTENSION | | | |
| subjects affected / exposed | 7 / 698 (1.00%) | 2 / 692 (0.29%) | |
| occurrences causally related to treatment / all | 5 / 7 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| HYPERTENSIVE URGENCY | | | |

| | | | |
|--|------------------|------------------|--|
| subjects affected / exposed | 0 / 698 (0.00%) | 1 / 692 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| CIRCULATORY COLLAPSE | | | |
| subjects affected / exposed | 1 / 698 (0.14%) | 0 / 692 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| HYPERTENSIVE CRISIS | | | |
| subjects affected / exposed | 2 / 698 (0.29%) | 0 / 692 (0.00%) | |
| occurrences causally related to treatment / all | 2 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pregnancy, puerperium and perinatal conditions | | | |
| ABORTION | | | |
| subjects affected / exposed | 1 / 698 (0.14%) | 0 / 692 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| General disorders and administration site conditions | | | |
| HYPERTHERMIA | | | |
| subjects affected / exposed | 0 / 698 (0.00%) | 1 / 692 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| CHILLS | | | |
| subjects affected / exposed | 4 / 698 (0.57%) | 3 / 692 (0.43%) | |
| occurrences causally related to treatment / all | 4 / 4 | 2 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| PYREXIA | | | |
| subjects affected / exposed | 37 / 698 (5.30%) | 23 / 692 (3.32%) | |
| occurrences causally related to treatment / all | 23 / 43 | 11 / 24 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| CHEST DISCOMFORT | | | |
| subjects affected / exposed | 2 / 698 (0.29%) | 0 / 692 (0.00%) | |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|-----------------|-----------------|--|
| MUCOSAL INFLAMMATION | | | |
| subjects affected / exposed | 1 / 698 (0.14%) | 1 / 692 (0.14%) | |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| MULTIPLE ORGAN DYSFUNCTION SYNDROME | | | |
| subjects affected / exposed | 0 / 698 (0.00%) | 3 / 692 (0.43%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 2 | |
| DEATH | | | |
| subjects affected / exposed | 1 / 698 (0.14%) | 1 / 692 (0.14%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 1 / 1 | 0 / 1 | |
| HYPERPLASIA | | | |
| subjects affected / exposed | 1 / 698 (0.14%) | 0 / 692 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| ILL-DEFINED DISORDER | | | |
| subjects affected / exposed | 1 / 698 (0.14%) | 0 / 692 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| INFUSION SITE EXTRAVASATION | | | |
| subjects affected / exposed | 1 / 698 (0.14%) | 0 / 692 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| ADVERSE DRUG REACTION | | | |
| subjects affected / exposed | 0 / 698 (0.00%) | 1 / 692 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| STENT-GRAFT ENDOLEAK | | | |
| subjects affected / exposed | 0 / 698 (0.00%) | 1 / 692 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| NON-CARDIAC CHEST PAIN | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 2 / 698 (0.29%) | 0 / 692 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| PAIN | | | |
| subjects affected / exposed | 0 / 698 (0.00%) | 2 / 692 (0.29%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| INFLUENZA LIKE ILLNESS | | | |
| subjects affected / exposed | 1 / 698 (0.14%) | 0 / 692 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| CHEST PAIN | | | |
| subjects affected / exposed | 1 / 698 (0.14%) | 4 / 692 (0.58%) | |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| SWELLING FACE | | | |
| subjects affected / exposed | 0 / 698 (0.00%) | 1 / 692 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| CYST RUPTURE | | | |
| subjects affected / exposed | 1 / 698 (0.14%) | 0 / 692 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| GENERAL PHYSICAL HEALTH DETERIORATION | | | |
| subjects affected / exposed | 3 / 698 (0.43%) | 2 / 692 (0.29%) | |
| occurrences causally related to treatment / all | 1 / 3 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 1 | |
| OEDEMA PERIPHERAL | | | |
| subjects affected / exposed | 0 / 698 (0.00%) | 1 / 692 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Immune system disorders | | | |
| HYPOGAMMAGLOBULINAEMIA | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 698 (0.00%) | 2 / 692 (0.29%) | |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| CYTOKINE RELEASE SYNDROME | | | |
| subjects affected / exposed | 2 / 698 (0.29%) | 0 / 692 (0.00%) | |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| HAEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS | | | |
| subjects affected / exposed | 0 / 698 (0.00%) | 1 / 692 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| ANAPHYLACTIC SHOCK | | | |
| subjects affected / exposed | 1 / 698 (0.14%) | 0 / 692 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| DRUG HYPERSENSITIVITY | | | |
| subjects affected / exposed | 0 / 698 (0.00%) | 1 / 692 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| ALLERGY TO ARTHROPOD BITE | | | |
| subjects affected / exposed | 1 / 698 (0.14%) | 0 / 692 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| ANAPHYLACTIC REACTION | | | |
| subjects affected / exposed | 1 / 698 (0.14%) | 0 / 692 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| HYPERSENSITIVITY | | | |
| subjects affected / exposed | 0 / 698 (0.00%) | 3 / 692 (0.43%) | |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Reproductive system and breast disorders | | | |

| | | | |
|---|------------------|-----------------|--|
| PROSTATITIS | | | |
| subjects affected / exposed | 1 / 698 (0.14%) | 2 / 692 (0.29%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| OVARIAN MASS | | | |
| subjects affected / exposed | 1 / 698 (0.14%) | 0 / 692 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| OVARIAN CYST | | | |
| subjects affected / exposed | 1 / 698 (0.14%) | 1 / 692 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| VAGINAL ULCERATION | | | |
| subjects affected / exposed | 0 / 698 (0.00%) | 1 / 692 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| VULVOVAGINAL PAIN | | | |
| subjects affected / exposed | 1 / 698 (0.14%) | 0 / 692 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| PLEURISY | | | |
| subjects affected / exposed | 1 / 698 (0.14%) | 0 / 692 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| BRONCHOSPASM | | | |
| subjects affected / exposed | 1 / 698 (0.14%) | 1 / 692 (0.14%) | |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| DYSPNOEA | | | |
| subjects affected / exposed | 10 / 698 (1.43%) | 8 / 692 (1.16%) | |
| occurrences causally related to treatment / all | 8 / 12 | 4 / 8 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |

| | | | |
|---|-----------------|-----------------|--|
| ACUTE LUNG INJURY | | | |
| subjects affected / exposed | 1 / 698 (0.14%) | 0 / 692 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 1 / 1 | 0 / 0 | |
| ACUTE RESPIRATORY DISTRESS SYNDROME | | | |
| subjects affected / exposed | 2 / 698 (0.29%) | 0 / 692 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| LUNG DISORDER | | | |
| subjects affected / exposed | 1 / 698 (0.14%) | 0 / 692 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| HYPOXIA | | | |
| subjects affected / exposed | 2 / 698 (0.29%) | 0 / 692 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| RESPIRATORY ARREST | | | |
| subjects affected / exposed | 1 / 698 (0.14%) | 0 / 692 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| INTERSTITIAL LUNG DISEASE | | | |
| subjects affected / exposed | 2 / 698 (0.29%) | 4 / 692 (0.58%) | |
| occurrences causally related to treatment / all | 2 / 2 | 4 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| PHARYNGEAL PARAESTHESIA | | | |
| subjects affected / exposed | 1 / 698 (0.14%) | 0 / 692 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| PULMONARY ARTERIAL HYPERTENSION | | | |
| subjects affected / exposed | 1 / 698 (0.14%) | 0 / 692 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| PLEURAL EFFUSION | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 5 / 698 (0.72%) | 5 / 692 (0.72%) | |
| occurrences causally related to treatment / all | 1 / 5 | 0 / 5 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| EMPHYSEMA | | | |
| subjects affected / exposed | 1 / 698 (0.14%) | 1 / 692 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| EPISTAXIS | | | |
| subjects affected / exposed | 1 / 698 (0.14%) | 2 / 692 (0.29%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| LUNG CONSOLIDATION | | | |
| subjects affected / exposed | 0 / 698 (0.00%) | 2 / 692 (0.29%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| PNEUMONIA ASPIRATION | | | |
| subjects affected / exposed | 2 / 698 (0.29%) | 0 / 692 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| ASTHMA | | | |
| subjects affected / exposed | 2 / 698 (0.29%) | 2 / 692 (0.29%) | |
| occurrences causally related to treatment / all | 0 / 2 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| PNEUMONITIS | | | |
| subjects affected / exposed | 1 / 698 (0.14%) | 1 / 692 (0.14%) | |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| PARANASAL CYST | | | |
| subjects affected / exposed | 1 / 698 (0.14%) | 0 / 692 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| COUGH | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 698 (0.00%) | 2 / 692 (0.29%) | |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| DYSпноEA EXERTIONAL | | | |
| subjects affected / exposed | 0 / 698 (0.00%) | 1 / 692 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| RESPIRATORY DISORDER | | | |
| subjects affected / exposed | 0 / 698 (0.00%) | 1 / 692 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| PHARYNGEAL INFLAMMATION | | | |
| subjects affected / exposed | 1 / 698 (0.14%) | 0 / 692 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| PULMONARY OEDEMA | | | |
| subjects affected / exposed | 2 / 698 (0.29%) | 0 / 692 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| HAEMOPTYSIS | | | |
| subjects affected / exposed | 0 / 698 (0.00%) | 1 / 692 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| PULMONARY CONGESTION | | | |
| subjects affected / exposed | 0 / 698 (0.00%) | 1 / 692 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| PNEUMOTHORAX | | | |
| subjects affected / exposed | 1 / 698 (0.14%) | 0 / 692 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| PULMONARY EMBOLISM | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 8 / 698 (1.15%) | 2 / 692 (0.29%) | |
| occurrences causally related to treatment / all | 2 / 11 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| CHRONIC OBSTRUCTIVE PULMONARY DISEASE | | | |
| subjects affected / exposed | 1 / 698 (0.14%) | 3 / 692 (0.43%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 6 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 1 | |
| ACUTE RESPIRATORY FAILURE | | | |
| subjects affected / exposed | 1 / 698 (0.14%) | 0 / 692 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| PLEURITIC PAIN | | | |
| subjects affected / exposed | 1 / 698 (0.14%) | 2 / 692 (0.29%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| RESPIRATORY FAILURE | | | |
| subjects affected / exposed | 3 / 698 (0.43%) | 2 / 692 (0.29%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Psychiatric disorders | | | |
| SUBSTANCE-INDUCED PSYCHOTIC DISORDER | | | |
| subjects affected / exposed | 0 / 698 (0.00%) | 1 / 692 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| DEPRESSION | | | |
| subjects affected / exposed | 3 / 698 (0.43%) | 2 / 692 (0.29%) | |
| occurrences causally related to treatment / all | 0 / 5 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| CONFUSIONAL STATE | | | |
| subjects affected / exposed | 1 / 698 (0.14%) | 1 / 692 (0.14%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| DELIRIUM | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 698 (0.14%) | 0 / 692 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| SUICIDE ATTEMPT | | | |
| subjects affected / exposed | 1 / 698 (0.14%) | 0 / 692 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| ANXIETY | | | |
| subjects affected / exposed | 1 / 698 (0.14%) | 0 / 692 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| EMOTIONAL DISORDER | | | |
| subjects affected / exposed | 0 / 698 (0.00%) | 1 / 692 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| ALCOHOL PROBLEM | | | |
| subjects affected / exposed | 1 / 698 (0.14%) | 0 / 692 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| PSYCHOTIC DISORDER | | | |
| subjects affected / exposed | 1 / 698 (0.14%) | 0 / 692 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| MENTAL STATUS CHANGES | | | |
| subjects affected / exposed | 2 / 698 (0.29%) | 0 / 692 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Product issues | | | |
| DEVICE BREAKAGE | | | |
| subjects affected / exposed | 1 / 698 (0.14%) | 0 / 692 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Investigations | | | |

| | | | |
|--|-----------------|-----------------|--|
| INTERNATIONAL NORMALISED RATIO INCREASED | | | |
| subjects affected / exposed | 1 / 698 (0.14%) | 0 / 692 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| BLOOD CREATININE INCREASED | | | |
| subjects affected / exposed | 1 / 698 (0.14%) | 1 / 692 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| HEPATIC ENZYME INCREASED | | | |
| subjects affected / exposed | 0 / 698 (0.00%) | 1 / 692 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| ASPARTATE AMINOTRANSFERASE INCREASED | | | |
| subjects affected / exposed | 0 / 698 (0.00%) | 1 / 692 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| EASTERN COOPERATIVE ONCOLOGY GROUP PERFORMANCE STATUS WORSENER | | | |
| subjects affected / exposed | 1 / 698 (0.14%) | 0 / 692 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| RESPIROVIRUS TEST POSITIVE | | | |
| subjects affected / exposed | 0 / 698 (0.00%) | 1 / 692 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| WHITE BLOOD CELLS URINE POSITIVE | | | |
| subjects affected / exposed | 0 / 698 (0.00%) | 1 / 692 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| ALANINE AMINOTRANSFERASE INCREASED | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 698 (0.00%) | 1 / 692 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Injury, poisoning and procedural complications | | | |
| CARTILAGE INJURY | | | |
| subjects affected / exposed | 1 / 698 (0.14%) | 0 / 692 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| MENISCUS INJURY | | | |
| subjects affected / exposed | 1 / 698 (0.14%) | 0 / 692 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| PNEUMOTHORAX TRAUMATIC | | | |
| subjects affected / exposed | 1 / 698 (0.14%) | 0 / 692 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| BRAIN CONTUSION | | | |
| subjects affected / exposed | 1 / 698 (0.14%) | 0 / 692 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| THORACIC VERTEBRAL FRACTURE | | | |
| subjects affected / exposed | 0 / 698 (0.00%) | 1 / 692 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| LUMBAR VERTEBRAL FRACTURE | | | |
| subjects affected / exposed | 0 / 698 (0.00%) | 1 / 692 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| HUMERUS FRACTURE | | | |
| subjects affected / exposed | 1 / 698 (0.14%) | 0 / 692 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| FALL | | | |

| | | | |
|---|------------------|------------------|--|
| subjects affected / exposed | 3 / 698 (0.43%) | 1 / 692 (0.14%) | |
| occurrences causally related to treatment / all | 1 / 3 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| MULTIPLE FRACTURES | | | |
| subjects affected / exposed | 0 / 698 (0.00%) | 1 / 692 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| ANASTOMOTIC STENOSIS | | | |
| subjects affected / exposed | 1 / 698 (0.14%) | 0 / 692 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| COMPRESSION FRACTURE | | | |
| subjects affected / exposed | 0 / 698 (0.00%) | 1 / 692 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| LIGAMENT SPRAIN | | | |
| subjects affected / exposed | 1 / 698 (0.14%) | 0 / 692 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| FOOT FRACTURE | | | |
| subjects affected / exposed | 1 / 698 (0.14%) | 0 / 692 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| ACCIDENT | | | |
| subjects affected / exposed | 1 / 698 (0.14%) | 0 / 692 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| INFUSION RELATED REACTION | | | |
| subjects affected / exposed | 36 / 698 (5.16%) | 19 / 692 (2.75%) | |
| occurrences causally related to treatment / all | 42 / 42 | 21 / 21 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| UPPER LIMB FRACTURE | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 698 (0.14%) | 4 / 692 (0.58%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| FACIAL BONES FRACTURE | | | |
| subjects affected / exposed | 0 / 698 (0.00%) | 1 / 692 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| FEMUR FRACTURE | | | |
| subjects affected / exposed | 2 / 698 (0.29%) | 1 / 692 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| POST PROCEDURAL HAEMORRHAGE | | | |
| subjects affected / exposed | 1 / 698 (0.14%) | 1 / 692 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| MEDICATION ERROR | | | |
| subjects affected / exposed | 1 / 698 (0.14%) | 0 / 692 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| SPINAL COMPRESSION FRACTURE | | | |
| subjects affected / exposed | 1 / 698 (0.14%) | 1 / 692 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| ANKLE FRACTURE | | | |
| subjects affected / exposed | 1 / 698 (0.14%) | 2 / 692 (0.29%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| HAND FRACTURE | | | |
| subjects affected / exposed | 1 / 698 (0.14%) | 0 / 692 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| SEROMA | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 698 (0.14%) | 0 / 692 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| ALCOHOL POISONING | | | |
| subjects affected / exposed | 1 / 698 (0.14%) | 0 / 692 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Congenital, familial and genetic disorders | | | |
| HEREDITARY MOTOR AND SENSORY NEUROPATHY | | | |
| subjects affected / exposed | 0 / 698 (0.00%) | 1 / 692 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac disorders | | | |
| CARDIOGENIC SHOCK | | | |
| subjects affected / exposed | 2 / 698 (0.29%) | 1 / 692 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 2 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 2 | 0 / 0 | |
| SINUS TACHYCARDIA | | | |
| subjects affected / exposed | 3 / 698 (0.43%) | 0 / 692 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| TACHYCARDIA | | | |
| subjects affected / exposed | 3 / 698 (0.43%) | 0 / 692 (0.00%) | |
| occurrences causally related to treatment / all | 3 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| CORONARY ARTERY DISEASE | | | |
| subjects affected / exposed | 1 / 698 (0.14%) | 2 / 692 (0.29%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| BRADYCARDIA | | | |
| subjects affected / exposed | 1 / 698 (0.14%) | 0 / 692 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|-----------------|-----------------|--|
| SUPRAVENTRICULAR TACHYCARDIA | | | |
| subjects affected / exposed | 1 / 698 (0.14%) | 1 / 692 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| ARRHYTHMIA | | | |
| subjects affected / exposed | 2 / 698 (0.29%) | 0 / 692 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| VENTRICULAR TACHYCARDIA | | | |
| subjects affected / exposed | 1 / 698 (0.14%) | 0 / 692 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| PALPITATIONS | | | |
| subjects affected / exposed | 0 / 698 (0.00%) | 1 / 692 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| AORTIC VALVE STENOSIS | | | |
| subjects affected / exposed | 0 / 698 (0.00%) | 1 / 692 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| MYOCARDIAL ISCHAEMIA | | | |
| subjects affected / exposed | 1 / 698 (0.14%) | 0 / 692 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| ATRIAL FLUTTER | | | |
| subjects affected / exposed | 1 / 698 (0.14%) | 0 / 692 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| RIGHT VENTRICULAR FAILURE | | | |
| subjects affected / exposed | 1 / 698 (0.14%) | 0 / 692 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| ACUTE MYOCARDIAL INFARCTION | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 4 / 698 (0.57%) | 0 / 692 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 5 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| CARDIO-RESPIRATORY ARREST | | | |
| subjects affected / exposed | 1 / 698 (0.14%) | 0 / 692 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| CORONARY ARTERY STENOSIS | | | |
| subjects affected / exposed | 0 / 698 (0.00%) | 1 / 692 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| CARDIAC ARREST | | | |
| subjects affected / exposed | 1 / 698 (0.14%) | 1 / 692 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| ATRIAL FIBRILLATION | | | |
| subjects affected / exposed | 9 / 698 (1.29%) | 2 / 692 (0.29%) | |
| occurrences causally related to treatment / all | 1 / 11 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| CARDIAC FAILURE CONGESTIVE | | | |
| subjects affected / exposed | 2 / 698 (0.29%) | 0 / 692 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| SINUS BRADYCARDIA | | | |
| subjects affected / exposed | 5 / 698 (0.72%) | 0 / 692 (0.00%) | |
| occurrences causally related to treatment / all | 5 / 5 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| MYOCARDIAL INFARCTION | | | |
| subjects affected / exposed | 1 / 698 (0.14%) | 1 / 692 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| CARDIAC FAILURE | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 2 / 698 (0.29%) | 3 / 692 (0.43%) | |
| occurrences causally related to treatment / all | 2 / 3 | 3 / 3 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| ANGINA PECTORIS | | | |
| subjects affected / exposed | 1 / 698 (0.14%) | 1 / 692 (0.14%) | |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nervous system disorders | | | |
| HAEMORRHAGIC STROKE | | | |
| subjects affected / exposed | 0 / 698 (0.00%) | 1 / 692 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| CEREBRAL ISCHAEMIA | | | |
| subjects affected / exposed | 0 / 698 (0.00%) | 1 / 692 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| LOSS OF CONSCIOUSNESS | | | |
| subjects affected / exposed | 1 / 698 (0.14%) | 0 / 692 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| DEMENTIA | | | |
| subjects affected / exposed | 2 / 698 (0.29%) | 0 / 692 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| LETHARGY | | | |
| subjects affected / exposed | 2 / 698 (0.29%) | 0 / 692 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| TRANSIENT ISCHAEMIC ATTACK | | | |
| subjects affected / exposed | 5 / 698 (0.72%) | 1 / 692 (0.14%) | |
| occurrences causally related to treatment / all | 1 / 5 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| DYSDIADOCHOKINESIS | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 698 (0.00%) | 1 / 692 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| DIZZINESS POSTURAL | | | |
| subjects affected / exposed | 1 / 698 (0.14%) | 0 / 692 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| SUBARACHNOID HAEMORRHAGE | | | |
| subjects affected / exposed | 0 / 698 (0.00%) | 1 / 692 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| CEREBRAL DISORDER | | | |
| subjects affected / exposed | 1 / 698 (0.14%) | 0 / 692 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| PRESYNCOPE | | | |
| subjects affected / exposed | 0 / 698 (0.00%) | 3 / 692 (0.43%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| MONOPARESIS | | | |
| subjects affected / exposed | 1 / 698 (0.14%) | 0 / 692 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| CEREBRAL INFARCTION | | | |
| subjects affected / exposed | 1 / 698 (0.14%) | 0 / 692 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| EPILEPSY | | | |
| subjects affected / exposed | 1 / 698 (0.14%) | 0 / 692 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| FACIAL PARALYSIS | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 698 (0.14%) | 0 / 692 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| ISCHAEMIC STROKE | | | |
| subjects affected / exposed | 1 / 698 (0.14%) | 1 / 692 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| HAEMORRHAGE INTRACRANIAL | | | |
| subjects affected / exposed | 0 / 698 (0.00%) | 1 / 692 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| SPINAL CORD COMPRESSION | | | |
| subjects affected / exposed | 1 / 698 (0.14%) | 0 / 692 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| NEURALGIA | | | |
| subjects affected / exposed | 1 / 698 (0.14%) | 1 / 692 (0.14%) | |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| POLYNEUROPATHY | | | |
| subjects affected / exposed | 0 / 698 (0.00%) | 1 / 692 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 1 / 1 | |
| SYNCOPE | | | |
| subjects affected / exposed | 4 / 698 (0.57%) | 3 / 692 (0.43%) | |
| occurrences causally related to treatment / all | 1 / 4 | 2 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| BRACHIAL PLEXOPATHY | | | |
| subjects affected / exposed | 0 / 698 (0.00%) | 1 / 692 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| DIZZINESS | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 698 (0.14%) | 3 / 692 (0.43%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| ATAXIA | | | |
| subjects affected / exposed | 0 / 698 (0.00%) | 1 / 692 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| CAROTID ARTERY STENOSIS | | | |
| subjects affected / exposed | 0 / 698 (0.00%) | 1 / 692 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| ENCEPHALOPATHY | | | |
| subjects affected / exposed | 0 / 698 (0.00%) | 1 / 692 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| ORTHOSTATIC INTOLERANCE | | | |
| subjects affected / exposed | 1 / 698 (0.14%) | 0 / 692 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| TREMOR | | | |
| subjects affected / exposed | 0 / 698 (0.00%) | 1 / 692 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| HYPERAMMONAEMIC ENCEPHALOPATHY | | | |
| subjects affected / exposed | 0 / 698 (0.00%) | 1 / 692 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| AMYOTROPHIC LATERAL SCLEROSIS | | | |
| subjects affected / exposed | 0 / 698 (0.00%) | 1 / 692 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| PARKINSON'S DISEASE | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 698 (0.00%) | 1 / 692 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| ORTHOSTATIC TREMOR | | | |
| subjects affected / exposed | 0 / 698 (0.00%) | 1 / 692 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| HYPOTONIA | | | |
| subjects affected / exposed | 1 / 698 (0.14%) | 0 / 692 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| SEIZURE | | | |
| subjects affected / exposed | 1 / 698 (0.14%) | 1 / 692 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| CEREBRAL HAEMATOMA | | | |
| subjects affected / exposed | 0 / 698 (0.00%) | 1 / 692 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| CEREBROVASCULAR ACCIDENT | | | |
| subjects affected / exposed | 0 / 698 (0.00%) | 2 / 692 (0.29%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 2 | |
| NERVOUS SYSTEM DISORDER | | | |
| subjects affected / exposed | 0 / 698 (0.00%) | 1 / 692 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| NEUROPATHY PERIPHERAL | | | |
| subjects affected / exposed | 0 / 698 (0.00%) | 1 / 692 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Blood and lymphatic system disorders | | | |
| HAEMOLYSIS | | | |

| | | | |
|---|------------------|------------------|--|
| subjects affected / exposed | 0 / 698 (0.00%) | 1 / 692 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| AUTOIMMUNE HAEMOLYTIC ANAEMIA | | | |
| subjects affected / exposed | 0 / 698 (0.00%) | 1 / 692 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 1 / 1 | |
| HAEMOLYTIC ANAEMIA | | | |
| subjects affected / exposed | 0 / 698 (0.00%) | 1 / 692 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| MYELOSUPPRESSION | | | |
| subjects affected / exposed | 3 / 698 (0.43%) | 0 / 692 (0.00%) | |
| occurrences causally related to treatment / all | 4 / 4 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| NEUTROPENIA | | | |
| subjects affected / exposed | 28 / 698 (4.01%) | 33 / 692 (4.77%) | |
| occurrences causally related to treatment / all | 30 / 31 | 43 / 46 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| IMMUNE THROMBOCYTOPENIA | | | |
| subjects affected / exposed | 1 / 698 (0.14%) | 0 / 692 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| ANAEMIA | | | |
| subjects affected / exposed | 6 / 698 (0.86%) | 1 / 692 (0.14%) | |
| occurrences causally related to treatment / all | 6 / 7 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| DISSEMINATED INTRAVASCULAR COAGULATION | | | |
| subjects affected / exposed | 1 / 698 (0.14%) | 0 / 692 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| FEBRILE NEUTROPENIA | | | |

| | | | |
|---|------------------|------------------|--|
| subjects affected / exposed | 36 / 698 (5.16%) | 23 / 692 (3.32%) | |
| occurrences causally related to treatment / all | 45 / 48 | 28 / 31 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| GRANULOCYTOPENIA | | | |
| subjects affected / exposed | 1 / 698 (0.14%) | 0 / 692 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| THROMBOCYTOPENIA | | | |
| subjects affected / exposed | 5 / 698 (0.72%) | 3 / 692 (0.43%) | |
| occurrences causally related to treatment / all | 12 / 12 | 3 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| LEUKOPENIA | | | |
| subjects affected / exposed | 4 / 698 (0.57%) | 6 / 692 (0.87%) | |
| occurrences causally related to treatment / all | 2 / 4 | 8 / 10 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| SPLENOMEGALY | | | |
| subjects affected / exposed | 2 / 698 (0.29%) | 1 / 692 (0.14%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ear and labyrinth disorders | | | |
| VERTIGO | | | |
| subjects affected / exposed | 1 / 698 (0.14%) | 0 / 692 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| DEAFNESS | | | |
| subjects affected / exposed | 1 / 698 (0.14%) | 0 / 692 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| EAR PAIN | | | |
| subjects affected / exposed | 0 / 698 (0.00%) | 1 / 692 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Eye disorders | | | |

| | | | |
|---|-----------------|-----------------|--|
| CORNEAL OPACITY | | | |
| subjects affected / exposed | 1 / 698 (0.14%) | 0 / 692 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal disorders | | | |
| MELAENA | | | |
| subjects affected / exposed | 1 / 698 (0.14%) | 0 / 692 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| CONSTIPATION | | | |
| subjects affected / exposed | 3 / 698 (0.43%) | 1 / 692 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 3 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| VOMITING | | | |
| subjects affected / exposed | 5 / 698 (0.72%) | 9 / 692 (1.30%) | |
| occurrences causally related to treatment / all | 4 / 5 | 10 / 13 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| ASCITES | | | |
| subjects affected / exposed | 1 / 698 (0.14%) | 2 / 692 (0.29%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| PANCREATITIS ACUTE | | | |
| subjects affected / exposed | 1 / 698 (0.14%) | 1 / 692 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| GASTRITIS | | | |
| subjects affected / exposed | 1 / 698 (0.14%) | 0 / 692 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| INTESTINAL OBSTRUCTION | | | |
| subjects affected / exposed | 4 / 698 (0.57%) | 0 / 692 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 5 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| ILEUS | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 698 (0.14%) | 0 / 692 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| INTESTINAL ISCHAEMIA | | | |
| subjects affected / exposed | 1 / 698 (0.14%) | 1 / 692 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| MOUTH ULCERATION | | | |
| subjects affected / exposed | 1 / 698 (0.14%) | 1 / 692 (0.14%) | |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| RECTAL HAEMORRHAGE | | | |
| subjects affected / exposed | 1 / 698 (0.14%) | 0 / 692 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| HAEMORRHOIDS | | | |
| subjects affected / exposed | 1 / 698 (0.14%) | 0 / 692 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| INTESTINAL POLYP | | | |
| subjects affected / exposed | 1 / 698 (0.14%) | 0 / 692 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| SWOLLEN TONGUE | | | |
| subjects affected / exposed | 1 / 698 (0.14%) | 0 / 692 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| GASTRITIS EROSIVE | | | |
| subjects affected / exposed | 0 / 698 (0.00%) | 1 / 692 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| UPPER GASTROINTESTINAL HAEMORRHAGE | | | |

| | | | |
|---|------------------|-----------------|--|
| subjects affected / exposed | 1 / 698 (0.14%) | 0 / 692 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 1 / 1 | 0 / 0 | |
| GASTRIC HAEMORRHAGE | | | |
| subjects affected / exposed | 1 / 698 (0.14%) | 0 / 692 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 1 / 1 | 0 / 0 | |
| COLITIS | | | |
| subjects affected / exposed | 3 / 698 (0.43%) | 2 / 692 (0.29%) | |
| occurrences causally related to treatment / all | 1 / 3 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| DIARRHOEA | | | |
| subjects affected / exposed | 11 / 698 (1.58%) | 7 / 692 (1.01%) | |
| occurrences causally related to treatment / all | 7 / 12 | 3 / 8 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| PANCREATITIS | | | |
| subjects affected / exposed | 4 / 698 (0.57%) | 1 / 692 (0.14%) | |
| occurrences causally related to treatment / all | 1 / 5 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| ENTEROVESICAL FISTULA | | | |
| subjects affected / exposed | 1 / 698 (0.14%) | 0 / 692 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| GASTROOESOPHAGEAL REFLUX DISEASE | | | |
| subjects affected / exposed | 0 / 698 (0.00%) | 1 / 692 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| HIATUS HERNIA | | | |
| subjects affected / exposed | 0 / 698 (0.00%) | 1 / 692 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| FAECALOMA | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 698 (0.14%) | 0 / 692 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| OBSTRUCTIVE PANCREATITIS | | | |
| subjects affected / exposed | 1 / 698 (0.14%) | 0 / 692 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| GASTROENTERITIS EOSINOPHILIC | | | |
| subjects affected / exposed | 0 / 698 (0.00%) | 1 / 692 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| INTESTINAL VILLI ATROPHY | | | |
| subjects affected / exposed | 0 / 698 (0.00%) | 1 / 692 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| MIKULICZ'S SYNDROME | | | |
| subjects affected / exposed | 0 / 698 (0.00%) | 1 / 692 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| HAEMATEMESIS | | | |
| subjects affected / exposed | 1 / 698 (0.14%) | 0 / 692 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| LARGE INTESTINAL OBSTRUCTION | | | |
| subjects affected / exposed | 0 / 698 (0.00%) | 1 / 692 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| GASTRIC ULCER | | | |
| subjects affected / exposed | 1 / 698 (0.14%) | 0 / 692 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| UMBILICAL HERNIA | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 698 (0.00%) | 1 / 692 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| ABDOMINAL PAIN UPPER | | | |
| subjects affected / exposed | 0 / 698 (0.00%) | 2 / 692 (0.29%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| SUBACUTE PANCREATITIS | | | |
| subjects affected / exposed | 0 / 698 (0.00%) | 1 / 692 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| LARGE INTESTINE POLYP | | | |
| subjects affected / exposed | 1 / 698 (0.14%) | 0 / 692 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| INGUINAL HERNIA | | | |
| subjects affected / exposed | 1 / 698 (0.14%) | 1 / 692 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| CROHN'S DISEASE | | | |
| subjects affected / exposed | 1 / 698 (0.14%) | 0 / 692 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| SMALL INTESTINAL OBSTRUCTION | | | |
| subjects affected / exposed | 2 / 698 (0.29%) | 0 / 692 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| NAUSEA | | | |
| subjects affected / exposed | 5 / 698 (0.72%) | 3 / 692 (0.43%) | |
| occurrences causally related to treatment / all | 5 / 5 | 2 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| ABDOMINAL PAIN | | | |

| | | | |
|---|------------------|-----------------|--|
| subjects affected / exposed | 10 / 698 (1.43%) | 6 / 692 (0.87%) | |
| occurrences causally related to treatment / all | 1 / 11 | 1 / 6 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| DYSPEPSIA | | | |
| subjects affected / exposed | 1 / 698 (0.14%) | 0 / 692 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatobiliary disorders | | | |
| HEPATIC FUNCTION ABNORMAL | | | |
| subjects affected / exposed | 0 / 698 (0.00%) | 1 / 692 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| BILE DUCT STONE | | | |
| subjects affected / exposed | 1 / 698 (0.14%) | 0 / 692 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| DRUG-INDUCED LIVER INJURY | | | |
| subjects affected / exposed | 2 / 698 (0.29%) | 0 / 692 (0.00%) | |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| CHOLECYSTITIS ACUTE | | | |
| subjects affected / exposed | 0 / 698 (0.00%) | 1 / 692 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| HEPATITIS | | | |
| subjects affected / exposed | 1 / 698 (0.14%) | 0 / 692 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| BILE DUCT STENOSIS | | | |
| subjects affected / exposed | 0 / 698 (0.00%) | 1 / 692 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| CHOLANGITIS | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 698 (0.00%) | 1 / 692 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| CHOLELITHIASIS | | | |
| subjects affected / exposed | 1 / 698 (0.14%) | 1 / 692 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| HEPATITIS ACUTE | | | |
| subjects affected / exposed | 1 / 698 (0.14%) | 0 / 692 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| CHOLECYSTITIS | | | |
| subjects affected / exposed | 5 / 698 (0.72%) | 6 / 692 (0.87%) | |
| occurrences causally related to treatment / all | 0 / 6 | 1 / 7 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| HEPATIC CIRRHOSIS | | | |
| subjects affected / exposed | 1 / 698 (0.14%) | 0 / 692 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| BILIARY COLIC | | | |
| subjects affected / exposed | 3 / 698 (0.43%) | 1 / 692 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Skin and subcutaneous tissue disorders | | | |
| RASH | | | |
| subjects affected / exposed | 5 / 698 (0.72%) | 2 / 692 (0.29%) | |
| occurrences causally related to treatment / all | 3 / 5 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| DERMATITIS EXFOLIATIVE GENERALISED | | | |
| subjects affected / exposed | 1 / 698 (0.14%) | 0 / 692 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| DRUG ERUPTION | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 698 (0.00%) | 1 / 692 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| RASH MACULO-PAPULAR | | | |
| subjects affected / exposed | 1 / 698 (0.14%) | 1 / 692 (0.14%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| ACTINIC KERATOSIS | | | |
| subjects affected / exposed | 0 / 698 (0.00%) | 1 / 692 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| DERMATITIS CONTACT | | | |
| subjects affected / exposed | 1 / 698 (0.14%) | 0 / 692 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| URTICARIA | | | |
| subjects affected / exposed | 1 / 698 (0.14%) | 1 / 692 (0.14%) | |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal and urinary disorders | | | |
| NEPHROLITHIASIS | | | |
| subjects affected / exposed | 1 / 698 (0.14%) | 0 / 692 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| RENAL PELVIS FISTULA | | | |
| subjects affected / exposed | 1 / 698 (0.14%) | 0 / 692 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| ACUTE KIDNEY INJURY | | | |
| subjects affected / exposed | 4 / 698 (0.57%) | 2 / 692 (0.29%) | |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| RENAL PAIN | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 698 (0.00%) | 1 / 692 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| RENAL INFARCT | | | |
| subjects affected / exposed | 0 / 698 (0.00%) | 1 / 692 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| RENAL COLIC | | | |
| subjects affected / exposed | 0 / 698 (0.00%) | 1 / 692 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| RENAL FAILURE | | | |
| subjects affected / exposed | 1 / 698 (0.14%) | 2 / 692 (0.29%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| URETERIC OBSTRUCTION | | | |
| subjects affected / exposed | 0 / 698 (0.00%) | 1 / 692 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Musculoskeletal and connective tissue disorders | | | |
| FLANK PAIN | | | |
| subjects affected / exposed | 1 / 698 (0.14%) | 1 / 692 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| PATHOLOGICAL FRACTURE | | | |
| subjects affected / exposed | 1 / 698 (0.14%) | 0 / 692 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| TEMPOROMANDIBULAR JOINT SYNDROME | | | |
| subjects affected / exposed | 1 / 698 (0.14%) | 0 / 692 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| ARTHROPATHY | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 698 (0.14%) | 0 / 692 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| NECK PAIN | | | |
| subjects affected / exposed | 1 / 698 (0.14%) | 1 / 692 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| MYOPATHY | | | |
| subjects affected / exposed | 1 / 698 (0.14%) | 1 / 692 (0.14%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| ROTATOR CUFF SYNDROME | | | |
| subjects affected / exposed | 1 / 698 (0.14%) | 0 / 692 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| MYOSITIS | | | |
| subjects affected / exposed | 1 / 698 (0.14%) | 1 / 692 (0.14%) | |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| PAIN IN EXTREMITY | | | |
| subjects affected / exposed | 0 / 698 (0.00%) | 1 / 692 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| SPINAL PAIN | | | |
| subjects affected / exposed | 1 / 698 (0.14%) | 0 / 692 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| SYNOVITIS | | | |
| subjects affected / exposed | 0 / 698 (0.00%) | 1 / 692 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| MUSCULAR WEAKNESS | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 698 (0.00%) | 1 / 692 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| OSTEITIS DEFORMANS | | | |
| subjects affected / exposed | 0 / 698 (0.00%) | 1 / 692 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| SPINAL STENOSIS | | | |
| subjects affected / exposed | 0 / 698 (0.00%) | 2 / 692 (0.29%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| INTERVERTEBRAL DISC PROTRUSION | | | |
| subjects affected / exposed | 1 / 698 (0.14%) | 1 / 692 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| BACK PAIN | | | |
| subjects affected / exposed | 2 / 698 (0.29%) | 3 / 692 (0.43%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| HAEMARTHROSIS | | | |
| subjects affected / exposed | 0 / 698 (0.00%) | 1 / 692 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| OSTEOARTHRITIS | | | |
| subjects affected / exposed | 2 / 698 (0.29%) | 3 / 692 (0.43%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| SERONEGATIVE ARTHRITIS | | | |
| subjects affected / exposed | 0 / 698 (0.00%) | 1 / 692 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infections and infestations | | | |
| GASTROENTERITIS VIRAL | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 698 (0.00%) | 1 / 692 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| BRONCHITIS | | | |
| subjects affected / exposed | 9 / 698 (1.29%) | 3 / 692 (0.43%) | |
| occurrences causally related to treatment / all | 2 / 9 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| ENTEROCOCCAL INFECTION | | | |
| subjects affected / exposed | 1 / 698 (0.14%) | 0 / 692 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| POST PROCEDURAL INFECTION | | | |
| subjects affected / exposed | 0 / 698 (0.00%) | 1 / 692 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| NEUTROPENIC SEPSIS | | | |
| subjects affected / exposed | 6 / 698 (0.86%) | 5 / 692 (0.72%) | |
| occurrences causally related to treatment / all | 8 / 9 | 7 / 8 | |
| deaths causally related to treatment / all | 1 / 1 | 0 / 1 | |
| INFLUENZA | | | |
| subjects affected / exposed | 4 / 698 (0.57%) | 0 / 692 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 4 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| BREAST ABSCESS | | | |
| subjects affected / exposed | 1 / 698 (0.14%) | 0 / 692 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| MUCOSAL INFECTION | | | |
| subjects affected / exposed | 1 / 698 (0.14%) | 0 / 692 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| OOPHORITIS | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 698 (0.14%) | 0 / 692 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| CHRONIC SINUSITIS | | | |
| subjects affected / exposed | 1 / 698 (0.14%) | 0 / 692 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| CLOSTRIDIUM DIFFICILE COLITIS | | | |
| subjects affected / exposed | 1 / 698 (0.14%) | 0 / 692 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| RHINITIS | | | |
| subjects affected / exposed | 1 / 698 (0.14%) | 0 / 692 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| ORAL HERPES | | | |
| subjects affected / exposed | 1 / 698 (0.14%) | 0 / 692 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| BACTERAEemia | | | |
| subjects affected / exposed | 1 / 698 (0.14%) | 2 / 692 (0.29%) | |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| INFECTED CYST | | | |
| subjects affected / exposed | 1 / 698 (0.14%) | 0 / 692 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| PYELONEPHRITIS | | | |
| subjects affected / exposed | 2 / 698 (0.29%) | 0 / 692 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| PERITONSILLAR ABSCESS | | | |

| | | | |
|---|-----------------|------------------|--|
| subjects affected / exposed | 1 / 698 (0.14%) | 0 / 692 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| COMPLICATED APPENDICITIS | | | |
| subjects affected / exposed | 0 / 698 (0.00%) | 1 / 692 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| HERPES ZOSTER OTICUS | | | |
| subjects affected / exposed | 1 / 698 (0.14%) | 0 / 692 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| INFECTION | | | |
| subjects affected / exposed | 6 / 698 (0.86%) | 10 / 692 (1.45%) | |
| occurrences causally related to treatment / all | 2 / 7 | 3 / 11 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| PULMONARY SEPSIS | | | |
| subjects affected / exposed | 1 / 698 (0.14%) | 0 / 692 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| DIVERTICULITIS | | | |
| subjects affected / exposed | 1 / 698 (0.14%) | 2 / 692 (0.29%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| PARAPHARYNGEAL SPACE INFECTION | | | |
| subjects affected / exposed | 1 / 698 (0.14%) | 0 / 692 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| URINARY TRACT INFECTION | | | |
| subjects affected / exposed | 8 / 698 (1.15%) | 7 / 692 (1.01%) | |
| occurrences causally related to treatment / all | 2 / 8 | 1 / 7 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| NEUROBORRELIOSIS | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 698 (0.00%) | 1 / 692 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| INTERVERTEBRAL DISCITIS | | | |
| subjects affected / exposed | 0 / 698 (0.00%) | 1 / 692 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| SCROTAL ABSCESS | | | |
| subjects affected / exposed | 0 / 698 (0.00%) | 1 / 692 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| SINUSITIS | | | |
| subjects affected / exposed | 1 / 698 (0.14%) | 2 / 692 (0.29%) | |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| CATHETER SITE CELLULITIS | | | |
| subjects affected / exposed | 1 / 698 (0.14%) | 0 / 692 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| DISSEMINATED VARICELLA ZOSTER VIRUS INFECTION | | | |
| subjects affected / exposed | 1 / 698 (0.14%) | 0 / 692 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| SINUSITIS FUNGAL | | | |
| subjects affected / exposed | 1 / 698 (0.14%) | 0 / 692 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| EPIGLOTTITIS | | | |
| subjects affected / exposed | 1 / 698 (0.14%) | 0 / 692 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| HERPES ZOSTER | | | |

| | | | |
|---|------------------|-----------------|--|
| subjects affected / exposed | 9 / 698 (1.29%) | 9 / 692 (1.30%) | |
| occurrences causally related to treatment / all | 6 / 9 | 5 / 9 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| ESCHERICHIA URINARY TRACT INFECTION | | | |
| subjects affected / exposed | 1 / 698 (0.14%) | 0 / 692 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| OTITIS MEDIA CHRONIC | | | |
| subjects affected / exposed | 1 / 698 (0.14%) | 0 / 692 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| MASTOIDITIS | | | |
| subjects affected / exposed | 0 / 698 (0.00%) | 1 / 692 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| SEPSIS | | | |
| subjects affected / exposed | 14 / 698 (2.01%) | 9 / 692 (1.30%) | |
| occurrences causally related to treatment / all | 8 / 18 | 5 / 9 | |
| deaths causally related to treatment / all | 0 / 2 | 0 / 1 | |
| STAPHYLOCOCCAL BACTERAEMIA | | | |
| subjects affected / exposed | 1 / 698 (0.14%) | 0 / 692 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 1 / 1 | 0 / 0 | |
| CYSTITIS | | | |
| subjects affected / exposed | 1 / 698 (0.14%) | 0 / 692 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| CELLULITIS | | | |
| subjects affected / exposed | 4 / 698 (0.57%) | 3 / 692 (0.43%) | |
| occurrences causally related to treatment / all | 1 / 4 | 1 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| CYTOMEGALOVIRUS INFECTION | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 2 / 698 (0.29%) | 0 / 692 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| SEPTIC SHOCK | | | |
| subjects affected / exposed | 0 / 698 (0.00%) | 2 / 692 (0.29%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| CAMPYLOBACTER INFECTION | | | |
| subjects affected / exposed | 2 / 698 (0.29%) | 0 / 692 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Q FEVER | | | |
| subjects affected / exposed | 0 / 698 (0.00%) | 1 / 692 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| VIRAL INFECTION | | | |
| subjects affected / exposed | 1 / 698 (0.14%) | 4 / 692 (0.58%) | |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| VARICELLA ZOSTER SEPSIS | | | |
| subjects affected / exposed | 1 / 698 (0.14%) | 0 / 692 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| ABDOMINAL SEPSIS | | | |
| subjects affected / exposed | 0 / 698 (0.00%) | 1 / 692 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| ENCEPHALITIS ENTEROVIRAL | | | |
| subjects affected / exposed | 1 / 698 (0.14%) | 0 / 692 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| ESCHERICHIA INFECTION | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 698 (0.14%) | 0 / 692 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| SINUSITIS BACTERIAL | | | |
| subjects affected / exposed | 1 / 698 (0.14%) | 0 / 692 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| ATYPICAL PNEUMONIA | | | |
| subjects affected / exposed | 1 / 698 (0.14%) | 3 / 692 (0.43%) | |
| occurrences causally related to treatment / all | 0 / 1 | 2 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| NEUTROPENIC INFECTION | | | |
| subjects affected / exposed | 1 / 698 (0.14%) | 1 / 692 (0.14%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| TUBERCULOSIS | | | |
| subjects affected / exposed | 1 / 698 (0.14%) | 0 / 692 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| ABSCESS INTESTINAL | | | |
| subjects affected / exposed | 1 / 698 (0.14%) | 0 / 692 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| GASTROENTERITIS | | | |
| subjects affected / exposed | 7 / 698 (1.00%) | 1 / 692 (0.14%) | |
| occurrences causally related to treatment / all | 1 / 7 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| PNEUMOCYSTIS JIROVECI PNEUMONIA | | | |
| subjects affected / exposed | 1 / 698 (0.14%) | 0 / 692 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| TUBO-OVARIAN ABSCESS | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 698 (0.14%) | 0 / 692 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| ABSCESS | | | |
| subjects affected / exposed | 0 / 698 (0.00%) | 1 / 692 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| FEBRILE INFECTION | | | |
| subjects affected / exposed | 0 / 698 (0.00%) | 1 / 692 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| SUBCUTANEOUS ABSCESS | | | |
| subjects affected / exposed | 0 / 698 (0.00%) | 2 / 692 (0.29%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| PERIODONTITIS | | | |
| subjects affected / exposed | 1 / 698 (0.14%) | 0 / 692 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| APPENDICITIS | | | |
| subjects affected / exposed | 1 / 698 (0.14%) | 3 / 692 (0.43%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| DEVICE RELATED SEPSIS | | | |
| subjects affected / exposed | 1 / 698 (0.14%) | 0 / 692 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| BK VIRUS INFECTION | | | |
| subjects affected / exposed | 1 / 698 (0.14%) | 0 / 692 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| RHINOVIRUS INFECTION | | | |

| | | | |
|---|------------------|-----------------|--|
| subjects affected / exposed | 1 / 698 (0.14%) | 0 / 692 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| VASCULAR DEVICE INFECTION | | | |
| subjects affected / exposed | 1 / 698 (0.14%) | 1 / 692 (0.14%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| OESOPHAGEAL CANDIDIASIS | | | |
| subjects affected / exposed | 1 / 698 (0.14%) | 0 / 692 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| VIRAL MYOSITIS | | | |
| subjects affected / exposed | 1 / 698 (0.14%) | 0 / 692 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| LOWER RESPIRATORY TRACT INFECTION | | | |
| subjects affected / exposed | 13 / 698 (1.86%) | 9 / 692 (1.30%) | |
| occurrences causally related to treatment / all | 8 / 23 | 2 / 9 | |
| deaths causally related to treatment / all | 1 / 2 | 0 / 0 | |
| OESOPHAGEAL INFECTION | | | |
| subjects affected / exposed | 1 / 698 (0.14%) | 0 / 692 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| ARTHRITIS BACTERIAL | | | |
| subjects affected / exposed | 0 / 698 (0.00%) | 1 / 692 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| PNEUMONIA BACTERIAL | | | |
| subjects affected / exposed | 1 / 698 (0.14%) | 1 / 692 (0.14%) | |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| UROSEPSIS | | | |

| | | | |
|---|------------------|------------------|--|
| subjects affected / exposed | 4 / 698 (0.57%) | 5 / 692 (0.72%) | |
| occurrences causally related to treatment / all | 4 / 5 | 1 / 6 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| PNEUMONIA FUNGAL | | | |
| subjects affected / exposed | 1 / 698 (0.14%) | 0 / 692 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 1 / 1 | 0 / 0 | |
| UPPER RESPIRATORY TRACT INFECTION | | | |
| subjects affected / exposed | 5 / 698 (0.72%) | 3 / 692 (0.43%) | |
| occurrences causally related to treatment / all | 2 / 7 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| OVARIAN BACTERIAL INFECTION | | | |
| subjects affected / exposed | 0 / 698 (0.00%) | 1 / 692 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| PNEUMONIA | | | |
| subjects affected / exposed | 51 / 698 (7.31%) | 43 / 692 (6.21%) | |
| occurrences causally related to treatment / all | 24 / 61 | 24 / 51 | |
| deaths causally related to treatment / all | 2 / 7 | 0 / 2 | |
| SOFT TISSUE INFECTION | | | |
| subjects affected / exposed | 1 / 698 (0.14%) | 0 / 692 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| ARTHRITIS INFECTIVE | | | |
| subjects affected / exposed | 0 / 698 (0.00%) | 1 / 692 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| BACTERIAL TRACHEITIS | | | |
| subjects affected / exposed | 1 / 698 (0.14%) | 0 / 692 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| DEVICE RELATED INFECTION | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 698 (0.14%) | 2 / 692 (0.29%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| PNEUMONIA PNEUMOCOCCAL | | | |
| subjects affected / exposed | 0 / 698 (0.00%) | 1 / 692 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| GASTROENTERITIS ESCHERICHIA COLI | | | |
| subjects affected / exposed | 1 / 698 (0.14%) | 0 / 692 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| RESPIRATORY TRACT INFECTION | | | |
| subjects affected / exposed | 6 / 698 (0.86%) | 5 / 692 (0.72%) | |
| occurrences causally related to treatment / all | 3 / 7 | 9 / 11 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| INFECTIVE EXACERBATION OF CHRONIC OBSTRUCTIVE AIRWAYS DISEASE | | | |
| subjects affected / exposed | 3 / 698 (0.43%) | 2 / 692 (0.29%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| MENINGITIS ENTEROVIRAL | | | |
| subjects affected / exposed | 1 / 698 (0.14%) | 0 / 692 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| HERPES ZOSTER INFECTION NEUROLOGICAL | | | |
| subjects affected / exposed | 0 / 698 (0.00%) | 1 / 692 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| STAPHYLOCOCCAL INFECTION | | | |
| subjects affected / exposed | 1 / 698 (0.14%) | 0 / 692 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|-----------------|-----------------|--|
| ENDOCARDITIS | | | |
| subjects affected / exposed | 0 / 698 (0.00%) | 1 / 692 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| PELVIC ABSCESS | | | |
| subjects affected / exposed | 2 / 698 (0.29%) | 0 / 692 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| PNEUMOCYSTIS JIROVECI | | | |
| INFECTION | | | |
| subjects affected / exposed | 0 / 698 (0.00%) | 1 / 692 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metabolism and nutrition disorders | | | |
| HYPONATRAEMIA | | | |
| subjects affected / exposed | 4 / 698 (0.57%) | 1 / 692 (0.14%) | |
| occurrences causally related to treatment / all | 1 / 4 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| HYPERCALCAEMIA | | | |
| subjects affected / exposed | 2 / 698 (0.29%) | 2 / 692 (0.29%) | |
| occurrences causally related to treatment / all | 0 / 2 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| HYPERGLYCAEMIA | | | |
| subjects affected / exposed | 1 / 698 (0.14%) | 0 / 692 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| DEHYDRATION | | | |
| subjects affected / exposed | 4 / 698 (0.57%) | 2 / 692 (0.29%) | |
| occurrences causally related to treatment / all | 2 / 4 | 1 / 2 | |
| deaths causally related to treatment / all | 1 / 1 | 0 / 0 | |
| HYPOKALAEMIA | | | |
| subjects affected / exposed | 1 / 698 (0.14%) | 1 / 692 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|-----------------|-----------------|--|
| FLUID OVERLOAD | | | |
| subjects affected / exposed | 1 / 698 (0.14%) | 0 / 692 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| TUMOUR LYSIS SYNDROME | | | |
| subjects affected / exposed | 3 / 698 (0.43%) | 1 / 692 (0.14%) | |
| occurrences causally related to treatment / all | 3 / 3 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| DIABETES MELLITUS | | | |
| subjects affected / exposed | 2 / 698 (0.29%) | 0 / 692 (0.00%) | |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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

| Non-serious adverse events | Obinutuzumab+Chemotherapy | Rituximab+Chemotherapy | |
|---|---------------------------|------------------------|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 690 / 698 (98.85%) | 675 / 692 (97.54%) | |
| Vascular disorders | | | |
| HOT FLUSH | | | |
| subjects affected / exposed | 38 / 698 (5.44%) | 25 / 692 (3.61%) | |
| occurrences (all) | 43 | 28 | |
| FLUSHING | | | |
| subjects affected / exposed | 46 / 698 (6.59%) | 40 / 692 (5.78%) | |
| occurrences (all) | 56 | 44 | |
| HYPOTENSION | | | |
| subjects affected / exposed | 44 / 698 (6.30%) | 28 / 692 (4.05%) | |
| occurrences (all) | 48 | 32 | |
| HYPERTENSION | | | |
| subjects affected / exposed | 64 / 698 (9.17%) | 50 / 692 (7.23%) | |
| occurrences (all) | 100 | 70 | |
| General disorders and administration site conditions | | | |
| CHILLS | | | |
| subjects affected / exposed | 126 / 698 (18.05%) | 74 / 692 (10.69%) | |
| occurrences (all) | 172 | 99 | |

| | | | |
|---|--------------------|--------------------|--|
| PYREXIA | | | |
| subjects affected / exposed | 200 / 698 (28.65%) | 150 / 692 (21.68%) | |
| occurrences (all) | 277 | 231 | |
| PAIN | | | |
| subjects affected / exposed | 26 / 698 (3.72%) | 35 / 692 (5.06%) | |
| occurrences (all) | 28 | 40 | |
| CHEST DISCOMFORT | | | |
| subjects affected / exposed | 43 / 698 (6.16%) | 36 / 692 (5.20%) | |
| occurrences (all) | 45 | 43 | |
| FATIGUE | | | |
| subjects affected / exposed | 275 / 698 (39.40%) | 277 / 692 (40.03%) | |
| occurrences (all) | 390 | 392 | |
| INFLUENZA LIKE ILLNESS | | | |
| subjects affected / exposed | 34 / 698 (4.87%) | 35 / 692 (5.06%) | |
| occurrences (all) | 38 | 36 | |
| ASTHENIA | | | |
| subjects affected / exposed | 47 / 698 (6.73%) | 44 / 692 (6.36%) | |
| occurrences (all) | 56 | 55 | |
| MUCOSAL INFLAMMATION | | | |
| subjects affected / exposed | 36 / 698 (5.16%) | 44 / 692 (6.36%) | |
| occurrences (all) | 41 | 55 | |
| OEDEMA PERIPHERAL | | | |
| subjects affected / exposed | 46 / 698 (6.59%) | 40 / 692 (5.78%) | |
| occurrences (all) | 50 | 47 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| PRODUCTIVE COUGH | | | |
| subjects affected / exposed | 42 / 698 (6.02%) | 35 / 692 (5.06%) | |
| occurrences (all) | 53 | 41 | |
| THROAT IRRITATION | | | |
| subjects affected / exposed | 27 / 698 (3.87%) | 37 / 692 (5.35%) | |
| occurrences (all) | 27 | 40 | |
| DYSPNOEA | | | |
| subjects affected / exposed | 112 / 698 (16.05%) | 88 / 692 (12.72%) | |
| occurrences (all) | 131 | 101 | |
| OROPHARYNGEAL PAIN | | | |

| | | | |
|---|---------------------------|---------------------------|--|
| subjects affected / exposed occurrences (all) | 82 / 698 (11.75%) 98 | 73 / 692 (10.55%) 87 | |
| COUGH subjects affected / exposed occurrences (all) | 221 / 698 (31.66%) 305 | 185 / 692 (26.73%) 248 | |
| Psychiatric disorders INSOMNIA subjects affected / exposed occurrences (all) | 113 / 698 (16.19%) 131 | 89 / 692 (12.86%) 98 | |
| ANXIETY subjects affected / exposed occurrences (all) | 44 / 698 (6.30%) 47 | 29 / 692 (4.19%) 31 | |
| Investigations WEIGHT DECREASED subjects affected / exposed occurrences (all) | 35 / 698 (5.01%) 37 | 45 / 692 (6.50%) 49 | |
| Injury, poisoning and procedural complications INFUSION RELATED REACTION subjects affected / exposed occurrences (all) | 416 / 698 (59.60%) 699 | 347 / 692 (50.14%) 569 | |
| Nervous system disorders PERIPHERAL SENSORY NEUROPATHY subjects affected / exposed occurrences (all) | 59 / 698 (8.45%) 68 | 47 / 692 (6.79%) 50 | |
| DYSGEUSIA subjects affected / exposed occurrences (all) | 38 / 698 (5.44%) 42 | 40 / 692 (5.78%) 44 | |
| HEADACHE subjects affected / exposed occurrences (all) | 155 / 698 (22.21%) 229 | 123 / 692 (17.77%) 185 | |
| PARAESTHESIA subjects affected / exposed occurrences (all) | 62 / 698 (8.88%) 71 | 51 / 692 (7.37%) 68 | |
| DIZZINESS subjects affected / exposed occurrences (all) | 75 / 698 (10.74%) 88 | 57 / 692 (8.24%) 69 | |

| | | | |
|---|---------------------------|---------------------------|--|
| NEUROPATHY PERIPHERAL subjects affected / exposed occurrences (all) | 51 / 698 (7.31%) 62 | 49 / 692 (7.08%) 52 | |
| Blood and lymphatic system disorders | | | |
| NEUTROPENIA subjects affected / exposed occurrences (all) | 348 / 698 (49.86%) 885 | 307 / 692 (44.36%) 777 | |
| ANAEMIA subjects affected / exposed occurrences (all) | 75 / 698 (10.74%) 88 | 72 / 692 (10.40%) 95 | |
| THROMBOCYTOPENIA subjects affected / exposed occurrences (all) | 90 / 698 (12.89%) 150 | 52 / 692 (7.51%) 79 | |
| LEUKOPENIA subjects affected / exposed occurrences (all) | 87 / 698 (12.46%) 222 | 91 / 692 (13.15%) 267 | |
| Gastrointestinal disorders | | | |
| CONSTIPATION subjects affected / exposed occurrences (all) | 249 / 698 (35.67%) 326 | 221 / 692 (31.94%) 301 | |
| VOMITING subjects affected / exposed occurrences (all) | 182 / 698 (26.07%) 242 | 151 / 692 (21.82%) 211 | |
| DIARRHOEA subjects affected / exposed occurrences (all) | 207 / 698 (29.66%) 318 | 168 / 692 (24.28%) 253 | |
| DRY MOUTH subjects affected / exposed occurrences (all) | 36 / 698 (5.16%) 40 | 23 / 692 (3.32%) 25 | |
| NAUSEA subjects affected / exposed occurrences (all) | 354 / 698 (50.72%) 594 | 338 / 692 (48.84%) 577 | |
| STOMATITIS subjects affected / exposed occurrences (all) | 54 / 698 (7.74%) 72 | 55 / 692 (7.95%) 71 | |
| ABDOMINAL PAIN | | | |

| | | | |
|--|---------------------------|---------------------------|--|
| subjects affected / exposed occurrences (all) | 69 / 698 (9.89%) 84 | 78 / 692 (11.27%) 95 | |
| ABDOMINAL PAIN UPPER subjects affected / exposed occurrences (all) | 57 / 698 (8.17%) 64 | 53 / 692 (7.66%) 60 | |
| DYSPEPSIA subjects affected / exposed occurrences (all) | 65 / 698 (9.31%) 82 | 50 / 692 (7.23%) 56 | |
| Skin and subcutaneous tissue disorders | | | |
| RASH subjects affected / exposed occurrences (all) | 127 / 698 (18.19%) 162 | 131 / 692 (18.93%) 170 | |
| PRURITUS subjects affected / exposed occurrences (all) | 102 / 698 (14.61%) 124 | 94 / 692 (13.58%) 116 | |
| ERYTHEMA subjects affected / exposed occurrences (all) | 37 / 698 (5.30%) 40 | 37 / 692 (5.35%) 43 | |
| DRY SKIN subjects affected / exposed occurrences (all) | 40 / 698 (5.73%) 44 | 36 / 692 (5.20%) 39 | |
| NIGHT SWEATS subjects affected / exposed occurrences (all) | 32 / 698 (4.58%) 35 | 38 / 692 (5.49%) 46 | |
| ALOPECIA subjects affected / exposed occurrences (all) | 90 / 698 (12.89%) 94 | 77 / 692 (11.13%) 78 | |
| Musculoskeletal and connective tissue disorders | | | |
| MUSCLE SPASMS subjects affected / exposed occurrences (all) | 40 / 698 (5.73%) 46 | 42 / 692 (6.07%) 49 | |
| BACK PAIN subjects affected / exposed occurrences (all) | 99 / 698 (14.18%) 127 | 115 / 692 (16.62%) 143 | |
| BONE PAIN | | | |

| | | | |
|-----------------------------------|--------------------|--------------------|--|
| subjects affected / exposed | 40 / 698 (5.73%) | 44 / 692 (6.36%) | |
| occurrences (all) | 46 | 56 | |
| ARTHRALGIA | | | |
| subjects affected / exposed | 144 / 698 (20.63%) | 127 / 692 (18.35%) | |
| occurrences (all) | 180 | 160 | |
| MYALGIA | | | |
| subjects affected / exposed | 53 / 698 (7.59%) | 38 / 692 (5.49%) | |
| occurrences (all) | 63 | 43 | |
| PAIN IN EXTREMITY | | | |
| subjects affected / exposed | 66 / 698 (9.46%) | 65 / 692 (9.39%) | |
| occurrences (all) | 75 | 79 | |
| Infections and infestations | | | |
| RHINITIS | | | |
| subjects affected / exposed | 59 / 698 (8.45%) | 36 / 692 (5.20%) | |
| occurrences (all) | 71 | 49 | |
| SINUSITIS | | | |
| subjects affected / exposed | 68 / 698 (9.74%) | 47 / 692 (6.79%) | |
| occurrences (all) | 92 | 58 | |
| ORAL HERPES | | | |
| subjects affected / exposed | 46 / 698 (6.59%) | 43 / 692 (6.21%) | |
| occurrences (all) | 54 | 48 | |
| BRONCHITIS | | | |
| subjects affected / exposed | 47 / 698 (6.73%) | 42 / 692 (6.07%) | |
| occurrences (all) | 69 | 53 | |
| LOWER RESPIRATORY TRACT INFECTION | | | |
| subjects affected / exposed | 59 / 698 (8.45%) | 71 / 692 (10.26%) | |
| occurrences (all) | 97 | 105 | |
| RESPIRATORY TRACT INFECTION | | | |
| subjects affected / exposed | 39 / 698 (5.59%) | 35 / 692 (5.06%) | |
| occurrences (all) | 67 | 43 | |
| HERPES ZOSTER | | | |
| subjects affected / exposed | 70 / 698 (10.03%) | 40 / 692 (5.78%) | |
| occurrences (all) | 75 | 46 | |
| NASOPHARYNGITIS | | | |

| | | | |
|------------------------------------|--------------------|--------------------|--|
| subjects affected / exposed | 135 / 698 (19.34%) | 143 / 692 (20.66%) | |
| occurrences (all) | 200 | 224 | |
| CONJUNCTIVITIS | | | |
| subjects affected / exposed | 35 / 698 (5.01%) | 26 / 692 (3.76%) | |
| occurrences (all) | 42 | 30 | |
| UPPER RESPIRATORY TRACT INFECTION | | | |
| subjects affected / exposed | 153 / 698 (21.92%) | 132 / 692 (19.08%) | |
| occurrences (all) | 217 | 189 | |
| PNEUMONIA | | | |
| subjects affected / exposed | 47 / 698 (6.73%) | 46 / 692 (6.65%) | |
| occurrences (all) | 63 | 59 | |
| URINARY TRACT INFECTION | | | |
| subjects affected / exposed | 75 / 698 (10.74%) | 66 / 692 (9.54%) | |
| occurrences (all) | 111 | 100 | |
| Metabolism and nutrition disorders | | | |
| HYPOKALAEMIA | | | |
| subjects affected / exposed | 48 / 698 (6.88%) | 29 / 692 (4.19%) | |
| occurrences (all) | 72 | 43 | |
| DECREASED APPETITE | | | |
| subjects affected / exposed | 98 / 698 (14.04%) | 91 / 692 (13.15%) | |
| occurrences (all) | 114 | 103 | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|---|
| 26 July 2011 | Allow for an early futility analysis of the first 170 randomized patients with follicular lymphoma based on the end-of-induction treatment complete response rates. The statistical methods sections were updated accordingly. Positron emission tomography (PET) was also made mandatory at screening and at end of induction therapy for the first 170 subjects with follicular lymphoma at all sites where PET scanners were available. The determination of minimal residual disease (MRD) based on polymerase chain reaction detection of BCL2/IgH-rearrangements within the malignant clone for all subjects with follicular lymphoma was also implemented. |
| 16 July 2012 | Implementation of a deoxyribonucleic acid (DNA) substudy in those subjects who give consent to the Roche Clinical Repository (RCR) and to DNA collection. |
| 28 May 2013 | Clarification of measuring and assessing the spleen and splenic response for marginal zone lymphoma (MZL) subjects. |
| 22 March 2014 | The Sponsor issued a Dear Investigator Letter (DIL) on 3 February 2014 to inform investigators about a higher incidence of thrombocytopenia and hemorrhagic events during the first cycle in participants with chronic lymphocytic leukemia (CLL) treated with obinutuzumab plus chlorambucil (GClb) as compared with participants treated with rituximab plus chlorambucil (RCIb) or chlorambucil alone. Updates to guidelines regarding management of participants with thrombocytopenia. Evaluation of medical resource utilization was removed from the secondary objectives. The name of the study drug was updated from GA101 to obinutuzumab. |
| 09 June 2017 | The protocol was amended to consider second malignancies as an adverse event of special interest (AESI). The Medical Monitor for the study changed. Biomarker sample storage changed from 15 to 5 years after the completion of the study. |
| 15 February 2020 | The protocol was amended to collect response after progression and administration of new anti-lymphoma treatment (NALT). The Medical Monitor changed. Reference safety information was added. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported