

**Clinical trial results:**

**A Two-Stage Phase III, International, Multi-Center, Randomized, Controlled, Open-Label Study to Investigate the Pharmacokinetics, Efficacy and Safety of Rituximab SC in Combination With CHOP or CVP Versus Rituximab IV in Combination With CHOP or CVP in Patients With Previously Untreated Follicular Lymphoma Followed by Maintenance Treatment With Either Rituximab SC or Rituximab IV**

**Summary**

|                          |                                  |
|--------------------------|----------------------------------|
| EudraCT number           | 2010-021377-36                   |
| Trial protocol           | ES GB BE SK IT DK DE FR FI GR BG |
| Global end of trial date | 31 October 2017                  |

**Results information**

|                                |                  |
|--------------------------------|------------------|
| Result version number          | v4 (current)     |
| This version publication date  | 14 November 2018 |
| First version publication date | 06 August 2015   |
| Version creation reason        |                  |

**Trial information****Trial identification**

|                       |         |
|-----------------------|---------|
| Sponsor protocol code | BO22334 |
|-----------------------|---------|

**Additional study identifiers**

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT01200758 |
| WHO universal trial number (UTN)   | -           |

Notes:

**Sponsors**

|                              |  |
|------------------------------|--|
| Sponsor organisation name    | F. Hoffmann-La Roche AG  |
| Sponsor organisation address | Grenzacherstrasse 124, Basel, Switzerland, CH-4070   |
| Public contact               | Roche Trial Information Hotline, F. Hoffmann-La Roche AG, +41 61 6878333, global.trial_information@roche.com |
| Scientific contact           | Roche Trial Information Hotline, F. Hoffmann-La Roche AG, +41 61 6878333, 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                       | 31 October 2017 |
| Is this the analysis of the primary completion data? | No              |
| Global end of trial reached?                         | Yes             |
| Global end of trial date                             | 31 October 2017 |
| Was the trial ended prematurely?                     | No              |

Notes:

## General information about the trial

Main objective of the trial:

This was a two-stage, Phase III, international, multicenter, randomized, controlled, open-label study to investigate the pharmacokinetic (PK), efficacy, and safety of rituximab subcutaneous (SC) in combination with cyclophosphamide, doxorubicin, vincristine, prednisolone (CHOP) or cyclophosphamide, vincristine, prednisolone (CVP) versus rituximab intravenous (IV) in combination with CHOP or CVP in participants with previously untreated follicular lymphoma (FL) followed by maintenance treatment with either rituximab SC or rituximab IV.

Protection of trial subjects:

The study was conducted in accordance with the principles of the "Declaration of Helsinki" and Good Clinical Practice (GCP).

Background therapy: -

Evidence for comparator: -

|   |                  |
|---|------------------|
| Actual start date of recruitment                          | 15 February 2011 |
| Long term follow-up planned                               | Yes              |
| Long term follow-up rationale                             | Safety           |
| Long term follow-up duration                              | 2 Years          |
| Independent data monitoring committee (IDMC) involvement? | Yes              |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |                        |
|--------------------------------------|------------------------|
| Country: Number of subjects enrolled | Romania: 9             |
| Country: Number of subjects enrolled | Slovakia: 4            |
| Country: Number of subjects enrolled | Spain: 53              |
| Country: Number of subjects enrolled | United Kingdom: 23     |
| Country: Number of subjects enrolled | Belgium: 1             |
| Country: Number of subjects enrolled | Bulgaria: 18           |
| Country: Number of subjects enrolled | Denmark: 23            |
| Country: Number of subjects enrolled | Finland: 10            |
| Country: Number of subjects enrolled | France: 38             |
| Country: Number of subjects enrolled | Germany: 21            |
| Country: Number of subjects enrolled | Greece: 2              |
| Country: Number of subjects enrolled | Italy: 40              |
| Country: Number of subjects enrolled | Thailand: 9            |
| Country: Number of subjects enrolled | Serbia: 17             |
| Country: Number of subjects enrolled | Russian Federation: 14 |
| Country: Number of subjects enrolled | Colombia: 9            |

|                                      |   |
|--------------------------------------|---|
| Country: Number of subjects enrolled | Malaysia: 2                                   |
| Country: Number of subjects enrolled | Australia: 15                                 |
| Country: Number of subjects enrolled | Peru: 4                                       |
| Country: Number of subjects enrolled | South Africa: 2                               |
| Country: Number of subjects enrolled | Bosnia and Herzegovina: 2                     |
| Country: Number of subjects enrolled | Turkey: 8                                     |
| Country: Number of subjects enrolled | Mexico: 13                                    |
| Country: Number of subjects enrolled | Canada: 25                                    |
| Country: Number of subjects enrolled | Brazil: 14                                    |
| Country: Number of subjects enrolled | Singapore: 7                                  |
| Country: Number of subjects enrolled | Macedonia, the former Yugoslav Republic of: 2 |
| Country: Number of subjects enrolled | Croatia: 8                                    |
| Country: Number of subjects enrolled | Georgia: 8                                    |
| Country: Number of subjects enrolled | New Zealand: 9                                |
| Worldwide total number of subjects   | 410   |
| EEA total number of subjects         | 250   |

Notes:

| <b>Subjects enrolled per age group</b>    |     |
|---|-----|
| 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)                      | 301 |
| From 65 to 84 years                       | 103 |
| 85 years and over                         | 6   |

## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details:

Screening/baseline tests were performed within 28 days before randomization. Randomization was centralized in a 1:1 fashion using the Pocock and Simon dynamic randomization algorithm. The study was conducted in 2 stages: Stage I & II. All participants irrespective of the treatment period completion commenced follow-up period in both Stage I and II.

### Period 1

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

### Arms

|                              |   |
|------------------------------|---|
| Are arms mutually exclusive? | Yes   |
| <b>Arm title</b>             | Stage I: Rituximab IV + Chemotherapy (CHOP/CVP) |

Arm description:

Eight cycles of rituximab IV infusion (375 milligrams per square meter [ $\text{mg}/\text{m}^2$ ]; rituximab induction) in combination with up to 8 cycles of CHOP or CVP chemotherapy (as per institutional practice) administered every 3 weeks. Participants achieving at least partial response (PR) during induction, entered rituximab IV maintenance therapy ( $375 \text{ mg}/\text{m}^2$ ) once every 8 weeks for 24 months.

|  |                   |
|--|-------------------|
| Arm type                               | Active comparator |
| Investigational medicinal product name | Rituximab         |
| Investigational medicinal product code |                   |
| Other name                             | MabThera          |
| Pharmaceutical forms                   | Infusion          |
| Routes of administration               | Intravenous use   |

Dosage and administration details:

Participants received  $375 \text{ mg}/\text{m}^2$  rituximab IV every 3 weeks for 8 cycles (the first cycle of rituximab was given on Day 0, Day 1, or Day 2, depending on institutional practice) and then maintenance therapy ( $375 \text{ mg}/\text{m}^2$ ) once every 8 weeks up to 24 months for participants who achieved at least PR.

|                  |   |
|------------------|---|
| <b>Arm title</b> | Stage I: Rituximab SC + Chemotherapy (CHOP/CVP) |
|------------------|---|

Arm description:

First cycle of rituximab IV ( $375 \text{ mg}/\text{m}^2$ ) + 7 cycles of rituximab SC (1400 mg; rituximab induction) in combination with up to 8 cycles of CHOP or CVP chemotherapy (as per institutional practice) administered every 3 weeks. Participants achieving at least PR during induction, entered rituximab SC (1400 mg) maintenance therapy once every 8 weeks for 24 months.

|  |                  |
|--|------------------|
| Arm type                               | Experimental     |
| Investigational medicinal product name | Rituximab        |
| Investigational medicinal product code |                  |
| Other name                             | MabThera         |
| Pharmaceutical forms                   | Injection        |
| Routes of administration               | Subcutaneous use |

Dosage and administration details:

Participants received  $375 \text{ mg}/\text{m}^2$  rituximab IV for Cycle 1 followed by 1400 mg SC every 3 weeks for 7 cycles and then maintenance therapy (1400 mg SC) once every 8 weeks up to 24 months for participants who achieved at least PR.

|                  |  |
|------------------|--|
| <b>Arm title</b> | Stage II: Rituximab IV + Chemotherapy (CHOP/CVP) |
|------------------|--|

Arm description:

Eight cycles of rituximab IV infusion ( $375 \text{ mg}/\text{m}^2$ ; rituximab induction) in combination with up to 8

cycles of CHOP or CVP chemotherapy (as per institutional practice) administered every 3 weeks. Participants achieving at least PR during induction, entered rituximab IV maintenance therapy (375 mg/m<sup>2</sup>) once every 8 weeks for 24 months.

|  |                   |
|--|-------------------|
| Arm type                               | Active comparator |
| Investigational medicinal product name | Rituximab         |
| Investigational medicinal product code |                   |
| Other name                             | MabThera          |
| Pharmaceutical forms                   | Infusion          |
| Routes of administration               | Intravenous use   |

Dosage and administration details:

Participants received 375 mg/m<sup>2</sup> rituximab IV every 3 weeks for 8 cycles (the first cycle of rituximab was given on Day 0, Day 1, or Day 2, depending on institutional practice) and then maintenance therapy (375 mg/m<sup>2</sup>) once every 8 weeks up to 24 months for participants who achieved at least PR.

|                  |  |
|------------------|--|
| <b>Arm title</b> | Stage II: Rituximab SC + Chemotherapy (CHOP/CVP) |
|------------------|--|

Arm description:

First cycle of rituximab IV (375 mg/m<sup>2</sup>) + 7 cycles of rituximab SC (1400 mg; rituximab induction) in combination with up to 8 cycles of CHOP or CVP chemotherapy (as per institutional practice) administered every 3 weeks. Participants achieving at least PR entered rituximab SC (1400 mg) maintenance therapy once every 8 weeks for 24 months.

|  |                  |
|--|------------------|
| Arm type                               | Experimental     |
| Investigational medicinal product name | Rituximab        |
| Investigational medicinal product code |                  |
| Other name                             | MabThera         |
| Pharmaceutical forms                   | Injection        |
| Routes of administration               | Subcutaneous use |

Dosage and administration details:

Participants received 375 mg/m<sup>2</sup> rituximab IV for Cycle 1 followed by 1400 mg SC every 3 weeks for 7 cycles and then maintenance therapy (1400 mg SC) once every 8 weeks up to 24 months for participants who achieved at least PR.

| <b>Number of subjects in period 1</b> | Stage I: Rituximab IV + Chemotherapy (CHOP/CVP) | Stage I: Rituximab SC + Chemotherapy (CHOP/CVP) | Stage II: Rituximab IV + Chemotherapy (CHOP/CVP) |
|---------------------------------------|---|---|--|
| Started                               | 64  | 63  | 141  |
| Completed                             | 46  | 46  | 100  |
| Not completed                         | 18  | 17  | 41   |
| Consent withdrawn by subject          | 1   | 2   | 4  |
| Physician decision                    | 1   | 1   | 5  |
| Disease progression                   | 9   | 7   | 16   |
| Adverse event, non-fatal              | 5   | 5   | 5  |
| Death                                 | -   | 1   | 3  |
| Lost to follow-up                     | -   | -   | 3  |
| Lack of efficacy                      | 2   | 1   | 4  |
| Protocol deviation                    | -   | -   | 1  |

| <b>Number of subjects in period 1</b> | Stage II: Rituximab SC + Chemotherapy (CHOP/CVP) |
|---------------------------------------|--|
| Started                               | 142  |

|                              |    |
|------------------------------|----|
| Completed                    | 92 |
| Not completed                | 50 |
| Consent withdrawn by subject | 1  |
| Physician decision           | 7  |
| Disease progression          | 21 |
| Adverse event, non-fatal     | 9  |
| Death                        | 5  |
| Lost to follow-up            | 1  |
| Lack of efficacy             | 2  |
| Protocol deviation           | 4  |

## Baseline characteristics

### Reporting groups

|                                |                                |
|--------------------------------|--------------------------------|
| Reporting group title          | Overall trial (overall period) |
| Reporting group description: - |                                |

| Reporting group values             | Overall trial (overall period) | Total |  |
|------------------------------------|--------------------------------|-------|--|
| Number of subjects                 | 410                            | 410   |  |
| Age categorical<br>Units: Subjects |                                |       |  |

|   |                 |     |  |
|---|-----------------|-----|--|
| Age Continuous<br>Units: years<br>arithmetic mean<br>standard deviation | 56.5<br>± 12.67 | -   |  |
| Gender, Male/Female<br>Units: Subjects                                  |                 |     |  |
| Female  | 219             | 219 |  |
| Male  | 191             | 191 |  |

### Subject analysis sets

|                            |  |
|----------------------------|--|
| Subject analysis set title | Stage I and II: Rituximab IV + Chemotherapy (CHOP/CVP) |
| Subject analysis set type  | Intention-to-treat                                     |

Subject analysis set description:

Eight cycles of rituximab IV infusion (375 mg/m<sup>2</sup>; rituximab induction) in combination with up to 8 cycles of CHOP or CVP chemotherapy (as per institutional practice) administered every 3 weeks. Participants achieving at least PR during induction, entered rituximab IV maintenance therapy (375 mg/m<sup>2</sup>) once every 8 weeks for 24 months.

|                            |  |
|----------------------------|--|
| Subject analysis set title | Stage I and II: Rituximab SC + Chemotherapy (CHOP/CVP) |
| Subject analysis set type  | Intention-to-treat                                     |

Subject analysis set description:

First cycle rituximab IV infusion (375 mg/m<sup>2</sup>) + 7 cycles of rituximab SC 1400 mg in combination with up to 8 cycles of CHOP or CVP chemotherapy administered every 3 weeks. Participants achieving at least PR entered rituximab SC (1400 mg) maintenance therapy once every 8 weeks for 24 months.

|                            |                    |
|----------------------------|--------------------|
| Subject analysis set title | All Participants   |
| Subject analysis set type  | Intention-to-treat |

Subject analysis set description:

Stage I and II: Rituximab SC + Chemotherapy (CHOP/CVP): First cycle rituximab IV infusion (375 mg/m<sup>2</sup>) + 7 cycles of rituximab SC 1400 mg in combination with up to 8 cycles of CHOP or CVP chemotherapy administered every 3 weeks. Participants achieving at least PR entered rituximab SC (1400 mg) maintenance therapy once every 8 weeks for 24 months. Stage I and II: Rituximab IV + Chemotherapy (CHOP/CVP): Eight cycles of rituximab IV infusion (375 mg/m<sup>2</sup>; rituximab induction) in combination with up to 8 cycles of CHOP or CVP chemotherapy (as per institutional practice) administered every 3 weeks. Participants achieving at least PR during induction, entered rituximab IV maintenance therapy (375 mg/m<sup>2</sup>) once every 8 weeks for 24 months.

| Reporting group values | Stage I and II:<br>Rituximab IV +<br>Chemotherapy<br>(CHOP/CVP) | Stage I and II:<br>Rituximab SC +<br>Chemotherapy<br>(CHOP/CVP) | All Participants |
|------------------------|---|---|------------------|
| Number of subjects     | 205   | 205   | 410              |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| Age categorical<br>Units: Subjects                                      |                 |                 |                 |
| Age Continuous<br>Units: years<br>arithmetic mean<br>standard deviation | 56.9<br>± 12.69 | 56.1<br>± 12.66 | 56.5<br>± 12.67 |
| Gender, Male/Female<br>Units: Subjects                                  |                 |                 |                 |
| Female  | 99              | 120             | 219             |
| Male  | 106             | 85              | 191             |



## End points

### End points reporting groups

|                       |   |
|-----------------------|---|
| Reporting group title | Stage I: Rituximab IV + Chemotherapy (CHOP/CVP) |
|-----------------------|---|

#### Reporting group description:

Eight cycles of rituximab IV infusion (375 milligrams per square meter [ $\text{mg}/\text{m}^2$ ]; rituximab induction) in combination with up to 8 cycles of CHOP or CVP chemotherapy (as per institutional practice) administered every 3 weeks. Participants achieving at least partial response (PR) during induction, entered rituximab IV maintenance therapy ( $375 \text{ mg}/\text{m}^2$ ) once every 8 weeks for 24 months.

|                       |   |
|-----------------------|---|
| Reporting group title | Stage I: Rituximab SC + Chemotherapy (CHOP/CVP) |
|-----------------------|---|

#### Reporting group description:

First cycle of rituximab IV ( $375 \text{ mg}/\text{m}^2$ ) + 7 cycles of rituximab SC (1400 mg; rituximab induction) in combination with up to 8 cycles of CHOP or CVP chemotherapy (as per institutional practice) administered every 3 weeks. Participants achieving at least PR during induction, entered rituximab SC (1400 mg) maintenance therapy once every 8 weeks for 24 months.

|                       |  |
|-----------------------|--|
| Reporting group title | Stage II: Rituximab IV + Chemotherapy (CHOP/CVP) |
|-----------------------|--|

#### Reporting group description:

Eight cycles of rituximab IV infusion ( $375 \text{ mg}/\text{m}^2$ ; rituximab induction) in combination with up to 8 cycles of CHOP or CVP chemotherapy (as per institutional practice) administered every 3 weeks. Participants achieving at least PR during induction, entered rituximab IV maintenance therapy ( $375 \text{ mg}/\text{m}^2$ ) once every 8 weeks for 24 months.

|                       |  |
|-----------------------|--|
| Reporting group title | Stage II: Rituximab SC + Chemotherapy (CHOP/CVP) |
|-----------------------|--|

#### Reporting group description:

First cycle of rituximab IV ( $375 \text{ mg}/\text{m}^2$ ) + 7 cycles of rituximab SC (1400 mg; rituximab induction) in combination with up to 8 cycles of CHOP or CVP chemotherapy (as per institutional practice) administered every 3 weeks. Participants achieving at least PR entered rituximab SC (1400 mg) maintenance therapy once every 8 weeks for 24 months.

|                            |  |
|----------------------------|--|
| Subject analysis set title | Stage I and II: Rituximab IV + Chemotherapy (CHOP/CVP) |
|----------------------------|--|

|                           |                    |
|---------------------------|--------------------|
| Subject analysis set type | Intention-to-treat |
|---------------------------|--------------------|

#### Subject analysis set description:

Eight cycles of rituximab IV infusion ( $375 \text{ mg}/\text{m}^2$ ; rituximab induction) in combination with up to 8 cycles of CHOP or CVP chemotherapy (as per institutional practice) administered every 3 weeks. Participants achieving at least PR during induction, entered rituximab IV maintenance therapy ( $375 \text{ mg}/\text{m}^2$ ) once every 8 weeks for 24 months.

|                            |  |
|----------------------------|--|
| Subject analysis set title | Stage I and II: Rituximab SC + Chemotherapy (CHOP/CVP) |
|----------------------------|--|

|                           |                    |
|---------------------------|--------------------|
| Subject analysis set type | Intention-to-treat |
|---------------------------|--------------------|

#### Subject analysis set description:

First cycle rituximab IV infusion ( $375 \text{ mg}/\text{m}^2$ ) + 7 cycles of rituximab SC 1400 mg in combination with up to 8 cycles of CHOP or CVP chemotherapy administered every 3 weeks. Participants achieving at least PR entered rituximab SC (1400 mg) maintenance therapy once every 8 weeks for 24 months.

|                            |                  |
|----------------------------|------------------|
| Subject analysis set title | All Participants |
|----------------------------|------------------|

|                           |                    |
|---------------------------|--------------------|
| Subject analysis set type | Intention-to-treat |
|---------------------------|--------------------|

#### Subject analysis set description:

Stage I and II: Rituximab SC + Chemotherapy (CHOP/CVP): First cycle rituximab IV infusion ( $375 \text{ mg}/\text{m}^2$ ) + 7 cycles of rituximab SC 1400 mg in combination with up to 8 cycles of CHOP or CVP chemotherapy administered every 3 weeks. Participants achieving at least PR entered rituximab SC (1400 mg) maintenance therapy once every 8 weeks for 24 months. Stage I and II: Rituximab IV + Chemotherapy (CHOP/CVP): Eight cycles of rituximab IV infusion ( $375 \text{ mg}/\text{m}^2$ ; rituximab induction) in combination with up to 8 cycles of CHOP or CVP chemotherapy (as per institutional practice) administered every 3 weeks. Participants achieving at least PR during induction, entered rituximab IV maintenance therapy ( $375 \text{ mg}/\text{m}^2$ ) once every 8 weeks for 24 months.

### Primary: Stage I: Trough Serum Concentrations (Ctough) of IV and SC Rituximab

|                 |   |
|-----------------|---|
| End point title | Stage I: Trough Serum Concentrations (Ctough) of IV and SC Rituximab <sup>[1]</sup> |
|-----------------|---|

#### End point description:

Stage I PK Evaluable Population comprised all participants with data for Ctough available at Cycle 7 and/or observed area under the serum concentration-time curve (AUC) available at Cycle 7. Participants

were analyzed as per treatment received. Number of participants analyzed = participants analyzed for this outcome measure.

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

End point timeframe:

Stage I: Cycle (Cy) 7 Day (D) 21 (within 2 hours predose on Cy8) of induction treatment (1 Cy=3 weeks)

Notes:

[1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Data for this endpoint was provided only for those arms which were planned to be reported

| End point values                                    | Stage I:<br>Rituximab IV +<br>Chemotherapy<br>(CHOP/CVP) | Stage I:<br>Rituximab SC<br>+<br>Chemotherapy<br>(CHOP/CVP) |  |  |
|---|--|---|--|--|
| Subject group type                                  | Reporting group  | Reporting group   |  |  |
| Number of subjects analysed                         | 48   | 54  |  |  |
| Units: micrograms per milliliter (mcg/mL)           |  |   |  |  |
| geometric mean (geometric coefficient of variation) | 83.1 (± 36.7)  | 134.6 (± 43.2)  |  |  |

## Statistical analyses

|                            |                        |
|----------------------------|------------------------|
| Statistical analysis title | Statistical Analysis 1 |
|----------------------------|------------------------|

Statistical analysis description:

Stage I: Rituximab SC + Chemotherapy (CHOP/CVP) vs Stage I: Rituximab IV + Chemotherapy (CHOP/CVP)

|   |   |
|---|---|
| Comparison groups                       | Stage I: Rituximab IV + Chemotherapy (CHOP/CVP) v Stage I: Rituximab SC + Chemotherapy (CHOP/CVP) |
| Number of subjects included in analysis | 102   |
| Analysis specification                  | Pre-specified   |
| Analysis type                           | non-inferiority <sup>[2]</sup>  |
| Parameter estimate                      | Geometric mean ratio  |
| Point estimate                          | 1.62  |
| Confidence interval                     |   |
| level                                   | 90 %  |
| sides                                   | 2-sided   |
| lower limit                             | 1.36  |
| upper limit                             | 1.94  |

Notes:

[2] - Non-inferior Ctrough in SC formulation was demonstrated, if the lower bound of 90% confidence interval (CI) was above 0.8.

## Primary: Stage II: Percentage of Participants With Overall Response at the End of Induction Treatment Assessed Using International Working Group Response Criteria for Non-Hodgkin lymphoma (NHL)

|                 |   |
|-----------------|---|
| End point title | Stage II: Percentage of Participants With Overall Response at the End of Induction Treatment Assessed Using International Working Group Response Criteria for Non-Hodgkin lymphoma (NHL) <sup>[3]</sup> |
|-----------------|---|

End point description:

Overall Response comprised complete response (CR), CR unconfirmed (CRu), or PR. A participant was defined as a responder if they sustained a CR, CRu or PR at the end of induction treatment. Response

assessment was based on clinical examination and computed tomography (CT) scans. Assessment of tumor response was performed according to the International Working Group response criteria for NHL. CR: complete disappearance of all detectable clinical and radiographic evidence of disease and disappearance of all disease-related symptoms if present before therapy; CRu: CR along with regression in lymph node mass by more than ( $>$ ) 75% in the sum of the products of greatest diameters (SPD); PR: Greater than or equal to ( $\geq$ ) 50% decrease in SPD of 6 largest dominant nodes or nodal masses. The 95% CI was estimated for one sample binomial using Pearson-Clopper. Stage II ITT population included all participants who were randomized in Stage II irrespective whether they received study drug or not.

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

End point timeframe:

Stage II: Baseline up to end of induction treatment Cy8 (24 weeks) (1 Cy=3 weeks)

Notes:

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Data for this endpoint was provided only for those arms which were planned to be reported

| End point values                  | Stage II:<br>Rituximab IV +<br>Chemotherapy<br>(CHOP/CVP) | Stage II:<br>Rituximab SC<br>+<br>Chemotherapy<br>(CHOP/CVP) |  |  |
|-----------------------------------|---|--|--|--|
| Subject group type                | Reporting group   | Reporting group  |  |  |
| Number of subjects analysed       | 141   | 142  |  |  |
| Units: percentage of participants |   |  |  |  |
| number (confidence interval 95%)  | 85.1 (78.1 to 90.5)                                       | 80.3 (72.8 to 86.5)  |  |  |

## Statistical analyses

|                            |                        |
|----------------------------|------------------------|
| Statistical analysis title | Statistical Analysis 1 |
|----------------------------|------------------------|

Statistical analysis description:

Stage II: Percentage of Participants With Overall Response at the End of Induction Treatment. The 95% CI for the difference in response rates was estimated using the Hauck-Anderson method.

|   |   |
|---|---|
| Comparison groups                       | Stage II: Rituximab IV + Chemotherapy (CHOP/CVP) v Stage II: Rituximab SC + Chemotherapy (CHOP/CVP) |
| Number of subjects included in analysis | 283   |
| Analysis specification                  | Pre-specified   |
| Analysis type                           | other   |
| P-value                                 | = 0.2835  |
| Method                                  | Chi-squared   |
| Parameter estimate                      | Difference in response rates  |
| Point estimate                          | -4.82   |
| Confidence interval                     |   |
| level                                   | 95 %  |
| sides                                   | 2-sided   |
| lower limit                             | -14   |
| upper limit                             | 4.4   |

|                            |                        |
|----------------------------|------------------------|
| Statistical analysis title | Statistical Analysis 2 |
|----------------------------|------------------------|

Statistical analysis description:

Stage II: Percentage of Participants With Overall Response at the End of Induction Treatment Assessed

|   |   |
|---|---|
| Comparison groups                       | Stage II: Rituximab IV + Chemotherapy (CHOP/CVP) v Stage II: Rituximab SC + Chemotherapy (CHOP/CVP) |
| Number of subjects included in analysis | 283   |
| Analysis specification                  | Pre-specified   |
| Analysis type                           | other   |
| Parameter estimate                      | Odds ratio (OR)   |
| Point estimate                          | 0.71  |
| Confidence interval                     |   |
| level                                   | 95 %  |
| sides                                   | 2-sided   |
| lower limit                             | 0.38  |
| upper limit                             | 1.33  |

### Secondary: Stage I: Percentage of Participants With Overall Response at the End of Induction Treatment Assessed Using International Working Group Response Criteria for NHL

|                 |   |
|-----------------|---|
| End point title | Stage I: Percentage of Participants With Overall Response at the End of Induction Treatment Assessed Using International Working Group Response Criteria for NHL <sup>[4]</sup> |
|-----------------|---|

#### End point description:

Overall Response comprised CR, CRu, or PR. A participant was defined as a responder if they sustained a CR, CRu or PR at the end of induction treatment. Response assessment was based on clinical examination and CT scans. Assessment of tumor response was performed according to the International Working Group response criteria for NHL. CR: complete disappearance of all detectable clinical and radiographic evidence of disease and disappearance of all disease-related symptoms if present before therapy; CRu: CR along with regression in lymph node mass by >75% in the SPD; PR: ≥50% decrease in SPD of 6 largest dominant nodes or nodal masses. The 95% CI was estimated for one sample binomial using Pearson-Clopper. Stage I ITT Population included all participants who were randomized in Stage I irrespective whether they received study drug or not.

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

#### End point timeframe:

Stage I: Baseline up to end of induction treatment Cy8 (24 weeks) (1 Cy=3 weeks)

#### Notes:

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Data for this endpoint was provided only for those arms which were planned to be reported

| End point values                  | Stage I:<br>Rituximab IV +<br>Chemotherapy<br>(CHOP/CVP) | Stage I:<br>Rituximab SC<br>+<br>Chemotherapy<br>(CHOP/CVP) |  |  |
|-----------------------------------|--|---|--|--|
| Subject group type                | Reporting group  | Reporting group   |  |  |
| Number of subjects analysed       | 64   | 63  |  |  |
| Units: percentage of participants |  |   |  |  |
| number (confidence interval 95%)  | 82.8 (71.3 to 91.1)                                      | 90.5 (80.4 to 96.4)   |  |  |

### Statistical analyses

|  |   |
|--|---|
| <b>Statistical analysis title</b>  | Statistical Analysis 1  |
| Statistical analysis description:  |   |
| Stage I: Percentage of Participants With Overall Response at the End of Induction Treatment Assessed Using International Working Group Response Criteria for NHL. The 95% CI for the difference in response rates was estimated using the Hauck-Anderson method. |   |
| Comparison groups  | Stage I: Rituximab IV + Chemotherapy (CHOP/CVP) v Stage I: Rituximab SC + Chemotherapy (CHOP/CVP) |
| Number of subjects included in analysis  | 127   |
| Analysis specification   | Pre-specified   |
| Analysis type  | other   |
| P-value  | = 0.2047  |
| Method   | Chi-squared   |
| Parameter estimate   | Difference in response rates  |
| Point estimate   | 7.66  |
| Confidence interval  |   |
| level  | 95 %  |
| sides  | 2-sided   |
| lower limit  | -5  |
| upper limit  | 20.3  |

|  |   |
|--|---|
| <b>Statistical analysis title</b>  | Statistical Analysis 2  |
| Statistical analysis description:  |   |
| Stage I: Percentage of Participants With Overall Response at the End of Induction Treatment Assessed Using International Working Group Response Criteria for NHL |   |
| Comparison groups  | Stage I: Rituximab IV + Chemotherapy (CHOP/CVP) v Stage I: Rituximab SC + Chemotherapy (CHOP/CVP) |
| Number of subjects included in analysis  | 127   |
| Analysis specification   | Pre-specified   |
| Analysis type  | other   |
| Parameter estimate   | Odds ratio (OR)   |
| Point estimate   | 1.97  |
| Confidence interval  |   |
| level  | 95 %  |
| sides  | 2-sided   |
| lower limit  | 0.68  |
| upper limit  | 5.71  |

**Secondary: Stage I and II (Pooled): Percentage of Participants With Overall Response at the End of Induction Treatment Assessed Using International Working Group Response Criteria for NHL**

|                 |  |
|-----------------|--|
| End point title | Stage I and II (Pooled): Percentage of Participants With Overall Response at the End of Induction Treatment Assessed Using International Working Group Response Criteria for NHL |
|-----------------|--|

End point description:

Overall Response comprised of CR, CRu, or PR. A participant was defined as a responder if they sustained a CR, CRu or PR at the end of induction treatment. Response assessment was based on clinical examination and CT scans. Assessment of tumour response was performed according to the International Working Group response criteria for NHL. CR: complete disappearance of all detectable clinical and radiographic evidence of disease and disappearance of all disease-related symptoms if present before therapy; CRu: CR along with regression in lymph node mass by >75% in SPD; PR:

≥50% decrease in SPD of 6 largest dominant nodes or nodal masses. The 95% CI for the response rates was estimated for one sample binomial using Pearson-Clopper. ITT population.

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

End point timeframe:

Stage I and II: Baseline up to end of induction treatment Cy8 (24 weeks) (1 Cy=3 weeks)

| End point values                  | Stage I and II:<br>Rituximab IV +<br>Chemotherapy<br>(CHOP/CVP) | Stage I and II:<br>Rituximab SC<br>+<br>Chemotherapy<br>(CHOP/CVP) |  |  |
|-----------------------------------|---|--|--|--|
| Subject group type                | Subject analysis set  | Subject analysis set   |  |  |
| Number of subjects analysed       | 205   | 205  |  |  |
| Units: percentage of participants |   |  |  |  |
| number (confidence interval 95%)  | 84.9 (79.2 to<br>89.5)  | 84.4 (78.7 to<br>89.1)   |  |  |

## Statistical analyses

| Statistical analysis title | Statistical Analysis 1 |
|----------------------------|------------------------|
|----------------------------|------------------------|

Statistical analysis description:

Stage I and II: Overall Response of CR, CRu, or PR at the End of Induction Treatment Assessed Using International Working Group Response Criteria for NHL. The 95% CI for the difference in response rates was estimated using the Hauck-Anderson.

|   |  |
|---|--|
| Comparison groups                       | Stage I and II: Rituximab IV + Chemotherapy (CHOP/CVP) v<br>Stage I and II: Rituximab SC + Chemotherapy (CHOP/CVP) |
| Number of subjects included in analysis | 410  |
| Analysis specification                  | Pre-specified  |
| Analysis type                           | other  |
| P-value                                 | = 0.8911   |
| Method                                  | Chi-squared  |
| Parameter estimate                      | Difference in response rates   |
| Point estimate                          | -0.49  |
| Confidence interval                     |  |
| level                                   | 95 %   |
| sides                                   | 2-sided  |
| lower limit                             | -7.7   |
| upper limit                             | 6.8  |

| Statistical analysis title | Statistical Analysis 2 |
|----------------------------|------------------------|
|----------------------------|------------------------|

Statistical analysis description:

Stage I and II (Pooled): Percentage of Participants With Overall Response at the End of Induction Treatment Assessed Using International Working Group Response Criteria for NHL

|                   |  |
|-------------------|--|
| Comparison groups | Stage I and II: Rituximab IV + Chemotherapy (CHOP/CVP) v<br>Stage I and II: Rituximab SC + Chemotherapy (CHOP/CVP) |
|-------------------|--|

|   |                 |
|---|-----------------|
| Number of subjects included in analysis | 410             |
| Analysis specification                  | Pre-specified   |
| Analysis type                           | other           |
| Parameter estimate                      | Odds ratio (OR) |
| Point estimate                          | 0.96            |
| Confidence interval                     |                 |
| level                                   | 95 %            |
| sides                                   | 2-sided         |
| lower limit                             | 0.56            |
| upper limit                             | 1.65            |

### Secondary: Stage I: Percentage of Participants With Complete Response at the End of Induction Treatment Assessed Using International Working Group Response Criteria for NHL

|                 |  |
|-----------------|--|
| End point title | Stage I: Percentage of Participants With Complete Response at the End of Induction Treatment Assessed Using International Working Group Response Criteria for NHL <sup>[5]</sup> |
|-----------------|--|

#### End point description:

Complete Response was comprised CR and CRu. A participant was defined as a responder if they sustained a CR or CRu at the end of induction treatment. Response assessment was based on clinical examination and CT scans. Assessment of tumor response was performed according to the International Working Group response criteria for NHL. CR: complete disappearance of all detectable clinical and radiographic evidence of disease and disappearance of all disease-related symptoms if present before therapy; CRu: CR along with regression in lymph node mass by >75% in SPD. The 95% CI was estimated for one sample binomial using Pearson-Clopper. Stage I ITT population.

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

#### End point timeframe:

Stage I: Baseline up to end of induction treatment Cy8 (24 weeks) (1 Cy=3 weeks)

#### Notes:

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: Data for this endpoint was provided only for those arms which were planned to be reported

| End point values                  | Stage I:<br>Rituximab IV +<br>Chemotherapy<br>(CHOP/CVP) | Stage I:<br>Rituximab SC<br>+<br>Chemotherapy<br>(CHOP/CVP) |  |  |
|-----------------------------------|--|---|--|--|
| Subject group type                | Reporting group  | Reporting group   |  |  |
| Number of subjects analysed       | 64   | 63  |  |  |
| Units: percentage of participants |  |   |  |  |
| number (confidence interval 95%)  | 25.0 (15.0 to 37.4)                                      | 42.9 (30.5 to 56.0)   |  |  |

### Statistical analyses

|                            |                        |
|----------------------------|------------------------|
| Statistical analysis title | Statistical Analysis 2 |
|----------------------------|------------------------|

#### Statistical analysis description:

Stage I: Percentage of Participants With Complete Response at the End of Induction Treatment Assessed Using International Working Group Response Criteria for NHL

|                   |   |
|-------------------|---|
| Comparison groups | Stage I: Rituximab IV + Chemotherapy (CHOP/CVP) v Stage I: Rituximab SC + Chemotherapy (CHOP/CVP) |
|-------------------|---|

|   |                 |
|---|-----------------|
| Number of subjects included in analysis | 127             |
| Analysis specification                  | Pre-specified   |
| Analysis type                           | other           |
| Parameter estimate                      | Odds ratio (OR) |
| Point estimate                          | 2.25            |
| Confidence interval                     |                 |
| level                                   | 95 %            |
| sides                                   | 2-sided         |
| lower limit                             | 1.06            |
| upper limit                             | 4.78            |

|                                   |                        |
|-----------------------------------|------------------------|
| <b>Statistical analysis title</b> | Statistical Analysis 1 |
|-----------------------------------|------------------------|

Statistical analysis description:

Stage I: Percentage of Participants With Complete Response at the End of Induction Treatment Assessed Using International Working Group Response Criteria for NHL. The 95% CI for the difference in response rates was estimated using the Hauck-Anderson method.

|   |   |
|---|---|
| Comparison groups                       | Stage I: Rituximab IV + Chemotherapy (CHOP/CVP) v Stage I: Rituximab SC + Chemotherapy (CHOP/CVP) |
| Number of subjects included in analysis | 127   |
| Analysis specification                  | Pre-specified   |
| Analysis type                           | other   |
| P-value                                 | = 0.0335  |
| Method                                  | Chi-squared   |
| Parameter estimate                      | Difference in response rates  |
| Point estimate                          | 17.86   |
| Confidence interval                     |   |
| level                                   | 95 %  |
| sides                                   | 2-sided   |
| lower limit                             | 0.8   |
| upper limit                             | 35  |

## **Secondary: Stage II: Percentage of Participants With Complete Response at the End of Induction Treatment Assessed Using International Working Group Response Criteria for NHL**

|                 |   |
|-----------------|---|
| End point title | Stage II: Percentage of Participants With Complete Response at the End of Induction Treatment Assessed Using International Working Group Response Criteria for NHL <sup>[6]</sup> |
|-----------------|---|

End point description:

Complete Response comprised of CR and CRu. A participant was defined as a responder if they sustained a CR or CRu at the end of induction treatment. Response assessment was based on clinical examination and CT scans. Assessment of tumor response was performed according to the International Working Group response criteria for NHL. CR: complete disappearance of all detectable clinical and radiographic evidence of disease and disappearance of all disease-related symptoms if present before therapy; CRu: CR along with regression in lymph node mass by >75% in SPD. The 95% CI for the response rates was estimated for one sample binomial using Pearson-Clopper. Stage II ITT population.

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

End point timeframe:

Stage II: Baseline up to end of induction treatment Cy8 (24 weeks) (1 Cy=3 weeks)



Notes:

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.  
Justification: Data for this endpoint was provided only for those arms which were planned to be reported

| End point values                  | Stage II:<br>Rituximab IV +<br>Chemotherapy<br>(CHOP/CVP) | Stage II:<br>Rituximab SC<br>+<br>Chemotherapy<br>(CHOP/CVP) |  |  |
|-----------------------------------|---|--|--|--|
| Subject group type                | Reporting group   | Reporting group  |  |  |
| Number of subjects analysed       | 141   | 142  |  |  |
| Units: percentage of participants |   |  |  |  |
| number (confidence interval 95%)  | 34.8 (26.9 to<br>43.2)                                    | 28.2 (20.9 to<br>36.3)                                       |  |  |

## Statistical analyses

| Statistical analysis title  | Statistical Analysis 1  |
|---|---|
| Statistical analysis description:<br>Stage II: Percentage of Participants With Complete Response at the End of Induction Treatment Assessed Using International Working Group Response Criteria for NHL. The 95% CI for the difference in response rates was estimated using the Hauck-Anderson method. |   |
| Comparison groups   | Stage II: Rituximab IV + Chemotherapy (CHOP/CVP) v Stage II: Rituximab SC + Chemotherapy (CHOP/CVP) |
| Number of subjects included in analysis   | 283   |
| Analysis specification  | Pre-specified   |
| Analysis type   | other   |
| P-value   | = 0.2331  |
| Method  | Chi-squared   |
| Parameter estimate  | Difference in response rates  |
| Point estimate  | -6.58   |
| Confidence interval   |   |
| level   | 95 %  |
| sides   | 2-sided   |
| lower limit   | -17.8   |
| upper limit   | 4.6   |

| Statistical analysis title  | Statistical Analysis 2  |
|---|---|
| Statistical analysis description:<br>Stage II: Percentage of Participants With Complete Response at the End of Induction Treatment Assessed Using International Working Group Response Criteria for NHL |   |
| Comparison groups   | Stage II: Rituximab IV + Chemotherapy (CHOP/CVP) v Stage II: Rituximab SC + Chemotherapy (CHOP/CVP) |

|   |                 |
|---|-----------------|
| Number of subjects included in analysis | 283             |
| Analysis specification                  | Pre-specified   |
| Analysis type                           | other           |
| Parameter estimate                      | Odds ratio (OR) |
| Point estimate                          | 0.74            |
| Confidence interval                     |                 |
| level                                   | 95 %            |
| sides                                   | 2-sided         |
| lower limit                             | 0.44            |
| upper limit                             | 1.22            |

### **Secondary: Stage I and II (Pooled): Percentage of Participants With Complete Response at the End of Induction Treatment Assessed Using International Working Group Response Criteria for NHL**

|                 |   |
|-----------------|---|
| End point title | Stage I and II (Pooled): Percentage of Participants With Complete Response at the End of Induction Treatment Assessed Using International Working Group Response Criteria for NHL |
|-----------------|---|

#### End point description:

Complete Response comprised of CR and CRu. A participant was defined as a responder if they sustained a CR or CRu at the end of induction treatment. Response assessment was based on clinical examination and CT scans. Assessment of tumor response was performed according to the International Working Group response criteria for NHL. CR: complete disappearance of all detectable clinical and radiographic evidence of disease and disappearance of all disease-related symptoms if present before therapy; CRu: CR along with regression in lymph node mass by >75% in SPD. The 95% CI for the response rates was estimated for one sample binomial using Pearson-Clopper. ITT population.

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

#### End point timeframe:

Stage I and II: Baseline up to end of induction treatment Cy8 (24 weeks) (1 Cy=3 weeks)

| <b>End point values</b>           | Stage I and II: Rituximab IV + Chemotherapy (CHOP/CVP) | Stage I and II: Rituximab SC + Chemotherapy (CHOP/CVP) |  |  |
|-----------------------------------|--|--|--|--|
| Subject group type                | Subject analysis set                                   | Subject analysis set                                   |  |  |
| Number of subjects analysed       | 205  | 205  |  |  |
| Units: percentage of participants |  |  |  |  |
| number (confidence interval 95%)  | 31.7 (25.4 to 38.6)                                    | 32.2 (25.9 to 39.1)                                    |  |  |

### **Statistical analyses**

|                                   |                        |
|-----------------------------------|------------------------|
| <b>Statistical analysis title</b> | Statistical Analysis 2 |
|-----------------------------------|------------------------|

#### Statistical analysis description:

Stage I and II (Pooled): Percentage of Participants With Complete Response at the End of Induction Treatment Assessed Using International Working Group Response Criteria for NHL

|                   |   |
|-------------------|---|
| Comparison groups | Stage I and II: Rituximab IV + Chemotherapy (CHOP/CVP) v Stage I and II: Rituximab SC + Chemotherapy (CHOP/CVP) |
|-------------------|---|

|   |                 |
|---|-----------------|
| Number of subjects included in analysis | 410             |
| Analysis specification                  | Pre-specified   |
| Analysis type                           | other           |
| Parameter estimate                      | Odds ratio (OR) |
| Point estimate                          | 1               |
| Confidence interval                     |                 |
| level                                   | 95 %            |
| sides                                   | 2-sided         |
| lower limit                             | 0.66            |
| upper limit                             | 1.51            |

|                                   |                        |
|-----------------------------------|------------------------|
| <b>Statistical analysis title</b> | Statistical Analysis 1 |
|-----------------------------------|------------------------|

Statistical analysis description:

Stage I and II (Pooled): Percentage of Participants With Complete Response at the End of Induction Treatment Assessed Using International Working Group Response Criteria for NHL. The 95% CI for the difference in response rates was estimated using the Hauck-Anderson method.

|   |   |
|---|---|
| Comparison groups                       | Stage I and II: Rituximab IV + Chemotherapy (CHOP/CVP) v Stage I and II: Rituximab SC + Chemotherapy (CHOP/CVP) |
| Number of subjects included in analysis | 410   |
| Analysis specification                  | Pre-specified   |
| Analysis type                           | other   |
| P-value                                 | = 0.9157  |
| Method                                  | Chi-squared   |
| Parameter estimate                      | Difference in response rates  |
| Point estimate                          | 0.49  |
| Confidence interval                     |   |
| level                                   | 95 %  |
| sides                                   | 2-sided   |
| lower limit                             | -8.8  |
| upper limit                             | 9.8   |

### **Secondary: Stage I and II (Pooled): Percentage of Participants With Complete Response at the End of Maintenance Treatment Assessed Using International Working Group Response Criteria for NHL**

|                 |   |
|-----------------|---|
| End point title | Stage I and II (Pooled): Percentage of Participants With Complete Response at the End of Maintenance Treatment Assessed Using International Working Group Response Criteria for NHL |
|-----------------|---|

End point description:

Complete Response comprised of CR and CRu. A participant was defined as a responder if they sustained a CR or CRu at the end of induction treatment. Response assessment was based on clinical examination and CT scans. Assessment of tumor response was performed according to the International Working Group response criteria for NHL. CR: complete disappearance of all detectable clinical and radiographic evidence of disease and disappearance of all disease-related symptoms if present before therapy; CRu: CR along with regression in lymph node mass by >75% in SPD. ITT population; only participants who entered the maintenance phase and received at least 1 cycle of rituximab maintenance treatment from Cycle 9 to Cycle 20 were included in the analysis.

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

End point timeframe:

Stage I and II: Baseline up to 57 days after last maintenance dose (last maintenance dose: maintenance Cy12/Study Cy20 [30 months]) (up to data cutoff of 31 Oct 2017 [up to 6 years]) (1 Cy=8

| <b>End point values</b>           | Stage I and II:<br>Rituximab IV +<br>Chemotherapy<br>(CHOP/CVP) | Stage I and II:<br>Rituximab SC<br>+<br>Chemotherapy<br>(CHOP/CVP) |  |  |
|-----------------------------------|---|--|--|--|
| Subject group type                | Subject analysis set  | Subject analysis set   |  |  |
| Number of subjects analysed       | 178   | 172  |  |  |
| Units: percentage of participants |   |  |  |  |
| number (confidence interval 95%)  | 57.9 (50.4 to<br>65.2)  | 50.6 (42.9 to<br>58.3)   |  |  |

### Statistical analyses

| <b>Statistical analysis title</b>  | Statistical Analysis 2   |
|--|--|
| Statistical analysis description:  |  |
| Stage I and II (Pooled): Percentage of Participants With Complete Response at the End of Maintenance Treatment Assessed Using International Working Group Response Criteria for NHL. |  |
| Comparison groups  | Stage I and II: Rituximab IV + Chemotherapy (CHOP/CVP) v<br>Stage I and II: Rituximab SC + Chemotherapy (CHOP/CVP) |
| Number of subjects included in analysis  | 350  |
| Analysis specification   | Pre-specified  |
| Analysis type  | other  |
| Parameter estimate   | Odds ratio (OR)  |
| Point estimate   | 0.8  |
| Confidence interval  |  |
| level  | 95 %   |
| sides  | 2-sided  |
| lower limit  | 0.52   |
| upper limit  | 1.22   |

| <b>Statistical analysis title</b>   | Statistical Analysis 1   |
|---|--|
| Statistical analysis description:   |  |
| Stage I and II (Pooled): Percentage of Participants With Complete Response at the End of Maintenance Treatment Assessed Using International Working Group Response Criteria for NHL. The 95% CI for the difference in response rates was estimated using the Hauck-Anderson method. |  |
| Comparison groups   | Stage I and II: Rituximab IV + Chemotherapy (CHOP/CVP) v<br>Stage I and II: Rituximab SC + Chemotherapy (CHOP/CVP) |
| Number of subjects included in analysis   | 350  |
| Analysis specification  | Pre-specified  |
| Analysis type   | other  |
| P-value   | = 0.1715   |
| Method  | Chi-squared  |
| Parameter estimate  | Difference in response rates   |
| Point estimate  | -7.28  |

|                     |         |
|---------------------|---------|
| Confidence interval |         |
| level               | 95 %    |
| sides               | 2-sided |
| lower limit         | -18     |
| upper limit         | 3.5     |

### Secondary: Stage I and II (Pooled): Percentage of Participants With Overall Response at the End of Maintenance Treatment Assessed Using International Working Group Response Criteria for NHL

|                 |  |
|-----------------|--|
| End point title | Stage I and II (Pooled): Percentage of Participants With Overall Response at the End of Maintenance Treatment Assessed Using International Working Group Response Criteria for NHL |
|-----------------|--|

#### End point description:

Overall Response comprised of CR, CRu, or PR . A participant was defined as a responder if they sustained a CR, CRu or PR at the end of induction treatment. Response assessment was based on clinical examination and CT scans. Assessment of tumour response was performed according to the International Working Group response criteria for NHL. CR: complete disappearance of all detectable clinical and radiographic evidence of disease and disappearance of all disease-related symptoms if present before therapy; CRu: CR along with regression in lymph node mass by >75% in SPD; PR: ≥50% decrease in SPD of 6 largest dominant nodes or nodal masses. The 95% CI for the response rates was estimated for one sample binomial using Pearson-Clopper. ITT population; only participants who entered the maintenance phase and received at least 1 cycle of rituximab maintenance treatment from Cycle 9 to Cycle 20 were included in the analysis.

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

#### End point timeframe:

Stage I and II: Baseline up to 57 days after last maintenance dose (last maintenance dose: maintenance Cy12/Study Cy20 [30 months]) (1 Cy=8 weeks)

| End point values                  | Stage I and II: Rituximab IV + Chemotherapy (CHOP/CVP) | Stage I and II: Rituximab SC + Chemotherapy (CHOP/CVP) |  |  |
|-----------------------------------|--|--|--|--|
| Subject group type                | Subject analysis set                                   | Subject analysis set                                   |  |  |
| Number of subjects analysed       | 178  | 172  |  |  |
| Units: percentage of participants |  |  |  |  |
| number (confidence interval 95%)  | 78.1 (71.3 to 83.9)                                    | 77.9 (71.0 to 83.9)                                    |  |  |

### Statistical analyses

|                            |                        |
|----------------------------|------------------------|
| Statistical analysis title | Statistical Analysis 1 |
|----------------------------|------------------------|

#### Statistical analysis description:

Stage I and II (Pooled): Percentage of Participants With Overall Response at the End of Maintenance Treatment Assessed Using International Working Group Response Criteria for NHL. The 95% CI for the difference in response rates was estimated using the Hauck-Anderson method.

|                   |   |
|-------------------|---|
| Comparison groups | Stage I and II: Rituximab IV + Chemotherapy (CHOP/CVP) v Stage I and II: Rituximab SC + Chemotherapy (CHOP/CVP) |
|-------------------|---|

|   |                              |
|---|------------------------------|
| Number of subjects included in analysis | 350                          |
| Analysis specification                  | Pre-specified                |
| Analysis type                           | other                        |
| P-value                                 | = 0.9671                     |
| Method                                  | Chi-squared                  |
| Parameter estimate                      | Difference in response rates |
| Point estimate                          | -0.18                        |
| Confidence interval                     |                              |
| level                                   | 95 %                         |
| sides                                   | 2-sided                      |
| lower limit                             | -9.2                         |
| upper limit                             | 8.8                          |

|  |  |
|--|--|
| <b>Statistical analysis title</b>  | Statistical Analysis 2   |
| Statistical analysis description:  |  |
| Stage I and II (Pooled): Percentage of Participants With Overall Response at the End of Maintenance Treatment Assessed Using International Working Group Response Criteria for NHL |  |
| Comparison groups  | Stage I and II: Rituximab IV + Chemotherapy (CHOP/CVP) v<br>Stage I and II: Rituximab SC + Chemotherapy (CHOP/CVP) |
| Number of subjects included in analysis  | 350  |
| Analysis specification   | Pre-specified  |
| Analysis type  | other  |
| Parameter estimate   | Odds ratio (OR)  |
| Point estimate   | 0.99   |
| Confidence interval  |  |
| level  | 95 %   |
| sides  | 2-sided  |
| lower limit  | 0.6  |
| upper limit  | 1.64   |

## **Secondary: Stage I and II (Pooled): Progression-Free Survival (PFS) Assessed Using International Working Group Response Criteria for NHL**

|                 |   |
|-----------------|---|
| End point title | Stage I and II (Pooled): Progression-Free Survival (PFS)<br>Assessed Using International Working Group Response Criteria<br>for NHL |
|-----------------|---|

### End point description:

PFS: time from randomization to PD/relapse or death due to any cause, analyzed using Kaplan-Meier curves. If the specified event (PD/relapse, death) did not occur, PFS was censored at the last tumor assessment date showing no PD, either during treatment or follow-up. Disease progression: Disease progression:  $\geq 50\%$  increase from nadir in the SPD of any previously identified abnormal node or appearance of any new lesion during or at the end of therapy or  $\geq 50\%$  increase in the greatest diameter of any previously identified node  $>1$  cm in its short axis or in the SPD of more than one node. Data for median and corresponding 95% CI were not reached due to  $<50\%$  of participants with event of interest, therefore '99999' are reported. Baseline, D1 of Cy 1-20 (1 Cy=3 weeks for Cy1-8 & 8 weeks for Cy9-20), at early withdrawal, at follow-up, every 12 weeks for 96 weeks or until documented PD/relapse or death (up to median of 27 months; up to data cutoff of 31 Oct 2017 [up to 6 years])

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

### End point timeframe:

Baseline up to disease progression or death up to data cutoff of 31 Oct 2017 (up to 6 years) (See detailed timeframe in Outcome Measure description)

|                                  |  |  |  |  |
|----------------------------------|--|--|--|--|
| <b>End point values</b>          | Stage I and II: Rituximab IV + Chemotherapy (CHOP/CVP) | Stage I and II: Rituximab SC + Chemotherapy (CHOP/CVP) |  |  |
| Subject group type               | Subject analysis set                                   | Subject analysis set                                   |  |  |
| Number of subjects analysed      | 205  | 205  |  |  |
| Units: days                      |  |  |  |  |
| median (confidence interval 95%) | 99999 (99999 to 99999)                                 | 99999 (99999 to 99999)                                 |  |  |

## Statistical analyses

|  |   |
|--|---|
| <b>Statistical analysis title</b>  | Progression-Free Survival (PFS)   |
| Statistical analysis description:<br>Stage 1 and II (Pooled): Progression-Free Survival (PFS) Assessed Using International Working Group Response Criteria for NHL |   |
| Comparison groups  | Stage I and II: Rituximab IV + Chemotherapy (CHOP/CVP) v Stage I and II: Rituximab SC + Chemotherapy (CHOP/CVP) |
| Number of subjects included in analysis  | 410   |
| Analysis specification   | Pre-specified   |
| Analysis type  | other   |
| P-value  | = 0.5526  |
| Method   | Wald test   |
| Parameter estimate   | Hazard ratio (HR)   |
| Point estimate   | 0.9   |
| Confidence interval  |   |
| level  | 95 %  |
| sides  | 2-sided   |
| lower limit  | 0.64  |
| upper limit  | 1.26  |

## Secondary: Stage I and II (Pooled): Percentage of Participants With Disease Progression/Relapse or Death Assessed Using International Working Group Response Criteria for NHL

|   |  |
|---|--|
| End point title   | Stage I and II (Pooled): Percentage of Participants With Disease Progression/Relapse or Death Assessed Using International Working Group Response Criteria for NHL |
| End point description:<br>Disease progression: $\geq 50\%$ increase from nadir in the SPD of any previously identified abnormal node or appearance of any new lesion during or at the end of therapy or $\geq 50\%$ increase in the greatest diameter of any previously identified node $> 1$ cm in its short axis or in the SPD of more than one node. Here, number of participants analyzed = participants who were evaluable for this outcome measure. ITT population. Baseline, D1 of all cycles (Cy 1-20) (1 Cy=3 weeks for Cy1-8 & 8 weeks for Cy9-20), at early withdrawal, at follow-up, every 12 weeks for 96 weeks or until documented disease progression/relapse or death (up to median of 27 months; up to data cutoff of 31 Oct 2017 [up to 6 years]) |  |
| End point type  | Secondary  |

End point timeframe:

Baseline up to disease progression or death up to data cutoff of 31 Oct 2017 (up to 6 years) (See detailed timeframe in Outcome Measure description)

| End point values                  | Stage I and II:<br>Rituximab IV +<br>Chemotherapy<br>(CHOP/CVP) | Stage I and II:<br>Rituximab SC<br>+<br>Chemotherapy<br>(CHOP/CVP) |  |  |
|-----------------------------------|---|--|--|--|
| Subject group type                | Subject analysis set  | Subject analysis set   |  |  |
| Number of subjects analysed       | 205   | 205  |  |  |
| Units: percentage of participants |   |  |  |  |
| number (not applicable)           | 34.6  | 31.7   |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Stage I and II (Pooled): Event-Free Survival Assessed Using International Working Group Response Criteria for NHL

|                 |   |
|-----------------|---|
| End point title | Stage I and II (Pooled): Event-Free Survival Assessed Using International Working Group Response Criteria for NHL |
|-----------------|---|

End point description:

Event-free survival was defined as the time from randomization to disease progression/relapse, death or initiation of new NHL therapy treatment. If the specified event (progression/relapse, death or new NHL treatment) did not occur, event-free survival was censored at the last tumor assessment date either during treatment or follow up. Event-free survival analysis was performed using Kaplan-Meier curves. ITT population. Data for median and upper limit of 95% CI were not reached due to low number (<50%) of participants with event of interest, therefore '99999' are reported to reflect not available (NA) data for median and upper range of 95% CI values. Baseline, D1 of all cycles (Cy 1-20) (1 Cy=3 weeks for Cy1-8 & 8 weeks for Cy9-20), at early withdrawal, at follow-up, every 12 weeks for 96 weeks or until documented disease progression/relapse or death (up to a median of 27 months; up to data cutoff of 31 Oct 2017 [up to 6 years])

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

End point timeframe:

Baseline up to disease progression or death up to data cutoff of 31 Oct 2017 (up to 6 years) (See detailed timeframe in Outcome Measure description)

| End point values                 | Stage I and II:<br>Rituximab IV +<br>Chemotherapy<br>(CHOP/CVP) | Stage I and II:<br>Rituximab SC<br>+<br>Chemotherapy<br>(CHOP/CVP) |  |  |
|----------------------------------|---|--|--|--|
| Subject group type               | Subject analysis set  | Subject analysis set   |  |  |
| Number of subjects analysed      | 205   | 205  |  |  |
| Units: days                      |   |  |  |  |
| median (confidence interval 95%) | 99999 (2126 to 99999)   | 99999 (99999 to 99999)   |  |  |



## Statistical analyses

|  |   |
|--|---|
| <b>Statistical analysis title</b>  | Stage I and II (Pooled): Event-Free Survival  |
| Statistical analysis description:<br>Stage I and II (Pooled): Event-Free Survival Assessed Using International Working Group Response Criteria for NHL |   |
| Comparison groups  | Stage I and II: Rituximab IV + Chemotherapy (CHOP/CVP) v Stage I and II: Rituximab SC + Chemotherapy (CHOP/CVP) |
| Number of subjects included in analysis  | 410   |
| Analysis specification   | Pre-specified   |
| Analysis type  | other   |
| P-value  | = 0.9115  |
| Method   | Wald test   |
| Parameter estimate   | Hazard ratio (HR)   |
| Point estimate   | 0.98  |
| Confidence interval  |   |
| level  | 95 %  |
| sides  | 2-sided   |
| lower limit  | 0.71  |
| upper limit  | 1.36  |

## Secondary: Stage I and II (Pooled): Percentage of Participants With Disease Progression/Relapse, New Anti-Lymphoma Treatment or Death Assessed Using International Working Group Response Criteria for NHL

|                 |   |
|-----------------|---|
| End point title | Stage I and II (Pooled): Percentage of Participants With Disease Progression/Relapse, New Anti-Lymphoma Treatment or Death Assessed Using International Working Group Response Criteria for NHL |
|-----------------|---|

### End point description:

Disease progression:  $\geq 50\%$  increase from nadir in the SPD of any previously identified abnormal node or appearance of any new lesion during or at the end of therapy or  $\geq 50\%$  increase in the greatest diameter of any previously identified node  $>1$  cm in its short axis or in the SPD of more than one node. Here, number of participants analyzed = participants who were evaluable for this outcome measure. ITT population. Baseline, D1 of all cycles (Cy 1-20) (1 Cy=3 weeks for Cy1-8 & 8 weeks for Cy9-20), at early withdrawal, at follow-up, every 12 weeks for 96 weeks or until documented disease progression/relapse or death (up to a median of 27 months; up to data cutoff of 31 Oct 2017 [up to 6 years])

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

### End point timeframe:

Baseline up to disease progression or death up to data cutoff of 31 Oct 2017 (up to 6 years) (See detailed timeframe in Outcome Measure description)

| End point values                  | Stage I and II:<br>Rituximab IV +<br>Chemotherapy<br>(CHOP/CVP) | Stage I and II:<br>Rituximab SC<br>+<br>Chemotherapy<br>(CHOP/CVP) |  |  |
|-----------------------------------|---|--|--|--|
| Subject group type                | Subject analysis set  | Subject analysis set   |  |  |
| Number of subjects analysed       | 205   | 205  |  |  |
| Units: percentage of participants |   |  |  |  |
| number (not applicable)           | 36.1  | 35.1   |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Overall Survival (OS)

|  |                       |
|--|-----------------------|
| End point title  | Overall Survival (OS) |
| End point description:   |                       |
| OS was defined as the time from randomization to death due to any cause. Participants without event were censored at the time of last follow-up information for survival, ie, at the last time known to be alive. ITT population. Data for median and corresponding 95% CI were not reached due to low number (<10%) of participants with event of interest, therefore '99999' are reported to reflect not available (NA) data for median and corresponding 95% CI values. |                       |
| End point type   | Secondary             |
| End point timeframe:   |                       |
| Baseline up to death (up to data cutoff of 31 Oct 2017 [up to 6 years])  |                       |

| End point values                 | Stage I and II:<br>Rituximab IV +<br>Chemotherapy<br>(CHOP/CVP) | Stage I and II:<br>Rituximab SC<br>+<br>Chemotherapy<br>(CHOP/CVP) |  |  |
|----------------------------------|---|--|--|--|
| Subject group type               | Subject analysis set  | Subject analysis set   |  |  |
| Number of subjects analysed      | 205   | 205  |  |  |
| Units: days                      |   |  |  |  |
| median (confidence interval 95%) | 99999 (99999<br>to 99999)                                       | 99999 (99999<br>to 99999)  |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Stage 1: Observed Area Under the Serum Concentration-Time Curve (AUC) of Rituximab

|   |   |
|---|---|
| End point title   | Stage 1: Observed Area Under the Serum Concentration-Time Curve (AUC) of Rituximab <sup>[7]</sup> |
| End point description:  |   |
| AUC is a measure of the serum concentration of the drug over time. It is used to characterize drug absorption. PK evaluable population. Here, number of participants analyzed = participants evaluable for this outcome measure. Predose (within 2 hr) and 24 hrs postdose on Cy 7 (D1,3,7,15), predose (within |   |

2 hr) on Cy 8 D1 (1 Cy=3 weeks); additionally within 15 minutes after end of infusion (infusion duration=30 minutes) on Cy 7 D1 for rituximab IV (up to data cutoff of 11 Apr 2012 [up to 26 months])

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

End point timeframe:

Stage I (Induction): Predose (within 2hr) up to data cutoff of 11 Apr 2012 [up to 26 months] (See detailed timeframe in Outcome Measure description)

Notes:

[7] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Data for this endpoint was provided only for those arms which were planned to be reported

| End point values                                    | Stage I:<br>Rituximab IV +<br>Chemotherapy<br>(CHOP/CVP) | Stage I:<br>Rituximab SC<br>+<br>Chemotherapy<br>(CHOP/CVP) |  |  |
|---|--|---|--|--|
| Subject group type                                  | Reporting group  | Reporting group   |  |  |
| Number of subjects analysed                         | 58   | 55  |  |  |
| Units: mcg*day/mL                                   |  |   |  |  |
| geometric mean (geometric coefficient of variation) | 2734.21 ( $\pm$ 32.51)                                   | 3778.93 ( $\pm$ 37.59)                                      |  |  |

## Statistical analyses

|                            |                           |
|----------------------------|---------------------------|
| Statistical analysis title | Stage 1: AUC of Rituximab |
|----------------------------|---------------------------|

Statistical analysis description:

The ratio of observed rituximab serum was determined as AUC SC/AUC IV during Cycle 7 of induction treatment.

|   |   |
|---|---|
| Comparison groups                       | Stage I: Rituximab IV + Chemotherapy (CHOP/CVP) v Stage I: Rituximab SC + Chemotherapy (CHOP/CVP) |
| Number of subjects included in analysis | 113   |
| Analysis specification                  | Pre-specified   |
| Analysis type                           | other   |
| Parameter estimate                      | Geometric mean ratio  |
| Point estimate                          | 1.38  |
| Confidence interval                     |   |
| level                                   | 90 %  |
| sides                                   | 2-sided   |
| lower limit                             | 1.24  |
| upper limit                             | 1.53  |

## Secondary: Stage I: Maximum Serum Concentrations (Cmax) of IV and SC Rituximab

|                 |  |
|-----------------|--|
| End point title | Stage I: Maximum Serum Concentrations (Cmax) of IV and SC Rituximab <sup>[8]</sup> |
|-----------------|--|

End point description:

Predose (within 2 hr) and 24 hrs postdose on Cy 7 (D1,3,7,15), predose (within 2 hr) on Cy 8 D1 (1 Cy=3 weeks); additionally within 15 minutes after end of infusion (infusion duration=30 minutes) on Cy 7 D1 for rituximab IV (up to data cutoff of 11 Apr 2012 [up to 26 months])

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

End point timeframe:

Stage I (Induction): Predose (within 2hr) up to data cutoff of 11 Apr 2012 [up to 26 months] (See

## Notes:

[8] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Data for this endpoint was provided only for those arms which were planned to be reported

| End point values                                    | Stage I:<br>Rituximab IV +<br>Chemotherapy<br>(CHOP/CVP) | Stage I:<br>Rituximab SC<br>+<br>Chemotherapy<br>(CHOP/CVP) |  |  |
|---|--|---|--|--|
| Subject group type                                  | Reporting group  | Reporting group   |  |  |
| Number of subjects analysed                         | 58   | 59  |  |  |
| Units: mcg/mL                                       |  |   |  |  |
| geometric mean (geometric coefficient of variation) | 250.63 ( $\pm$ 19.66)                                    | 236.82 ( $\pm$ 31.45)                                       |  |  |

### Statistical analyses

| Statistical analysis title              | Stage I: Cmax of IV and SC Rituximab  |
|---|---|
| Comparison groups                       | Stage I: Rituximab IV + Chemotherapy (CHOP/CVP) v Stage I: Rituximab SC + Chemotherapy (CHOP/CVP) |
| Number of subjects included in analysis | 117   |
| Analysis specification                  | Pre-specified   |
| Analysis type                           | other   |
| Parameter estimate                      | Geometric mean ratio  |
| Point estimate                          | 0.941   |
| Confidence interval                     |   |
| level                                   | 95 %  |
| sides                                   | 2-sided   |
| lower limit                             | 0.872   |
| upper limit                             | 1.015   |

### Secondary: Stage I and II (Pooled): Ctrough of Rituximab at Each Induction Treatment Cycle

|                        |   |
|------------------------|---|
| End point title        | Stage I and II (Pooled): Ctrough of Rituximab at Each Induction Treatment Cycle   |
| End point description: | Stage I and II (Induction): Rituximab IV: Predose (within 2 hr) on D1 of Cy1-8 (1 Cy=3 weeks & 4 weeks for Cy8); Rituximab SC: Predose (within 2 hr) on D1 of Cy1 & Cy3-8 (1 Cy=3 weeks and 4 weeks for Cy8), predose (within 2 hr) on D0 of Cy2 (up to data cutoff of 31 Oct 2013 [up to 32 months]) |
| End point type         | Secondary   |
| End point timeframe:   | Stage I and II (induction): Predose (within 2hr) up to data cutoff of 31 Oct 2013 [up to 32 months])<br>(See detailed timeframe in Outcome Measure description)   |

| End point values                                    | Stage I and II:<br>Rituximab IV +<br>Chemotherapy<br>(CHOP/CVP) | Stage I and II:<br>Rituximab SC<br>+<br>Chemotherapy<br>(CHOP/CVP) |  |  |
|---|---|--|--|--|
| Subject group type                                  | Subject analysis set  | Subject analysis set   |  |  |
| Number of subjects analysed                         | 155   | 154  |  |  |
| Units: mcg/mL                                       |   |  |  |  |
| geometric mean (geometric coefficient of variation) |   |  |  |  |
| Cycle 1 (n = 198, 193)                              | 14.00 (± 157.53)  | 12.88 (± 189.70)   |  |  |
| Cycle 2 (n = 197, 190)                              | 30.13 (± 145.36)  | 40.00 (± 124.50)   |  |  |
| Cycle 3 (n = 192, 190)                              | 45.25 (± 110.35)  | 63.83 (± 101.83)   |  |  |
| Cycle 4 (n = 186, 185)                              | 54.06 (± 108.90)  | 81.71 (± 92.28)  |  |  |
| Cycle 5 (n = 185, 185)                              | 64.68 (± 89.90)   | 98.00 (± 71.91)  |  |  |
| Cycle 6 (n = 187, 180)                              | 71.02 (± 87.60)   | 109.56 (± 58.74)   |  |  |
| Cycle 7 (n = 183, 172)                              | 80.7 (± 40.7)   | 122.2 (± 43.8)   |  |  |
| Cycle 8 (n = 52, 54)                                | 77.60 (± 70.53)   | 131.48 (± 50.20)   |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Stage I and II (Pooled): Ctrough of Rituximab at Each Maintenance Treatment Cycle

|                 |   |
|-----------------|---|
| End point title | Stage I and II (Pooled): Ctrough of Rituximab at Each Maintenance Treatment Cycle |
|-----------------|---|

End point description:

Stage I and II (maintenance): D29 of Cy8 (induction; 1 Cy=4 weeks), predose (within 2 hr) on D1 of Cy 9 to 19 (maintenance Cycle 1 to 12 [1 Cy=8 weeks]; up to data cutoff of 11 Jan 2016 [up to 6 years]). ITT Population. Here, number of participants analyzed = participants evaluable for the outcome measure. Here "n" = number of participants evaluable for this outcome measure at specified timepoint.

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

End point timeframe:

Stage I and II (maintenance): Predose (within 2hr) up to data cutoff of 11 Jan 2016 [up to 6 years]) (See detailed timeframe in Outcome Measure description)

| End point values                                    | Stage I and II:<br>Rituximab IV +<br>Chemotherapy<br>(CHOP/CVP) | Stage I and II:<br>Rituximab SC<br>+<br>Chemotherapy<br>(CHOP/CVP) |  |  |
|---|---|--|--|--|
| Subject group type                                  | Subject analysis set  | Subject analysis set   |  |  |
| Number of subjects analysed                         | 174   | 170  |  |  |
| Units: mcg/mL                                       |   |  |  |  |
| geometric mean (geometric coefficient of variation) |   |  |  |  |

|                         |                 |                 |  |  |
|-------------------------|-----------------|-----------------|--|--|
| of variation)           |                 |                 |  |  |
| Cycle 8 (n = 174, 170)  | 37.69 (± 94.30) | 61.31 (± 65.52) |  |  |
| Cycle 9 (n = 171, 168)  | 30.35 (± 75.03) | 49.47 (± 81.23) |  |  |
| Cycle 10 (n = 164, 160) | 28.44 (± 84.64) | 47.27 (± 73.03) |  |  |
| Cycle 11 (n = 164, 157) | 28.77 (± 65.28) | 46.70 (± 66.80) |  |  |
| Cycle 12 (n = 160, 150) | 28.80 (± 56.97) | 44.72 (± 68.74) |  |  |
| Cycle 13 (n = 157, 150) | 28.84 (± 54.04) | 44.32 (± 67.67) |  |  |
| Cycle 14 (n = 153, 147) | 28.09 (± 55.61) | 43.32 (± 67.97) |  |  |
| Cycle 15 (n = 148, 143) | 28.19 (± 52.69) | 44.11 (± 67.92) |  |  |
| Cycle 16 (n = 150, 145) | 28.05 (± 57.19) | 42.96 (± 64.32) |  |  |
| Cycle 17 (n = 149, 143) | 28.24 (± 57.51) | 42.82 (± 65.67) |  |  |
| Cycle 18 (n = 143, 132) | 28.59 (± 62.06) | 44.79 (± 68.56) |  |  |
| Cycle 19 (n = 138, 131) | 27.75 (± 78.26) | 43.69 (± 69.02) |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Stage I and II (Pooled): Rituximab Levels 12 Weeks, 24 Weeks, and 36 Weeks After the Last Rituximab Administration

|                 |  |
|-----------------|--|
| End point title | Stage I and II (Pooled): Rituximab Levels 12 Weeks, 24 Weeks, and 36 Weeks After the Last Rituximab Administration |
|-----------------|--|

End point description:

Safety Analysis Population included all participants who received at least one dose of rituximab, either IV or SC. Participants were analyzed as treated. Here, number of participants analyzed = participants evaluable for the outcome measure. Here "n" = participants who were evaluable for each category, for respective arm groups.

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

End point timeframe:

12 weeks, 24 weeks, and 36 weeks after the last rituximab administration (up to data cutoff of 11 Jan 2016 [up to 6 years])

| End point values              | Stage I and II: Rituximab IV + Chemotherapy (CHOP/CVP) | Stage I and II: Rituximab SC + Chemotherapy (CHOP/CVP) |  |  |
|-------------------------------|--|--|--|--|
| Subject group type            | Subject analysis set                                   | Subject analysis set                                   |  |  |
| Number of subjects analysed   | 117  | 118  |  |  |
| Units: mcg/mL                 |  |  |  |  |
| median (full range (min-max)) |  |  |  |  |

|   |                       |                        |  |  |
|---|-----------------------|------------------------|--|--|
| Week 12: Follow-up Visit 1 (n = 117, 118) | 15.60 (0.70 to 80.40) | 22.35 (0.65 to 107.00) |  |  |
| Week 24: Follow-up Visit 2 (n = 88, 96)   | 2.89 (0.58 to 17.40)  | 5.19 (0.69 to 62.10)   |  |  |
| Week 36: Follow-up Visit 3 (n = 38, 53)   | 1.08 (0.52 to 51.40)  | 2.02 (0.53 to 33.90)   |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Percentage of Participants With B-Cell Depletion by Cycle for Induction Phase

|                 |   |
|-----------------|---|
| End point title | Percentage of Participants With B-Cell Depletion by Cycle for Induction Phase |
|-----------------|---|

End point description:

Depletion is defined as a cluster of differentiation (CD) 19 value <80 cells per cubic millimeter (cells/mm<sup>3</sup>). ITT Population. Here, number of participants analyzed = participants evaluable for the outcome measure. Here "n" = number of participants evaluable for this outcome measure at specified timepoint.

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

End point timeframe:

Time Frame: Stage I and II (induction): for rituximab IV - D1 of Cy 1 to 8 (1 Cy=3 weeks); for rituximab SC - D1 of Cy 1 and Cy 3 to 8, D0 of Cy2

| End point values                      | Stage I and II:<br>Rituximab IV +<br>Chemotherapy<br>(CHOP/CVP) | Stage I and II:<br>Rituximab SC<br>+<br>Chemotherapy<br>(CHOP/CVP) |  |  |
|---------------------------------------|---|--|--|--|
| Subject group type                    | Subject analysis set  | Subject analysis set   |  |  |
| Number of subjects analysed           | 188   | 180  |  |  |
| Units: percentage of participants     |   |  |  |  |
| number (not applicable)               |   |  |  |  |
| Cycle 1 Day 1 - Baseline (n=188, 168) | 51.6  | 54.8   |  |  |
| Cycle 2 Day 0 (n=183, 180)            | 95.1  | 95.0   |  |  |
| Cycle 3 Day 1 (n=175, 175)            | 99.4  | 99.4   |  |  |
| Cycle 4 Day 1 (n=178, 180)            | 99.4  | 100.0  |  |  |
| Cycle 5 Day 1 (n=179, 176)            | 100.0   | 100.0  |  |  |
| Cycle 6 Day 1 (n=173, 175)            | 100.0   | 100.0  |  |  |
| Cycle 7 Day 1 (n=178, 173)            | 100.0   | 100.0  |  |  |
| Cycle 8 Day 1 (n=175, 174)            | 100.0   | 100.0  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Percentage of Participants With B-Cell Depletion by Cycle for

## Maintenance Phase

|                 |   |
|-----------------|---|
| End point title | Percentage of Participants With B-Cell Depletion by Cycle for Maintenance Phase |
|-----------------|---|

End point description:

Depletion is defined as a CD19 value <80 cells/mm<sup>3</sup>. ITT Population. Here, number of participants analyzed = participants evaluable for the outcome measure. Here "n" = number of participants evaluable for this outcome measure at specified timepoint.

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

End point timeframe:

Stage I and II (maintenance): D1 of Cy 9 to 20 (1 Cy=8 weeks) (up to data cutoff of 11 Jan 2016 [up to 6 years])

| End point values                  | Stage I and II:<br>Rituximab IV +<br>Chemotherapy<br>(CHOP/CVP) | Stage I and II:<br>Rituximab SC<br>+<br>Chemotherapy<br>(CHOP/CVP) |  |  |
|-----------------------------------|---|--|--|--|
| Subject group type                | Subject analysis set  | Subject analysis set   |  |  |
| Number of subjects analysed       | 170   | 164  |  |  |
| Units: percentage of participants |   |  |  |  |
| number (not applicable)           |   |  |  |  |
| Cycle 9 Day 1 (n=170, 161)        | 99.4  | 100.0  |  |  |
| Cycle 10 Day 1 (n=165, 164)       | 99.4  | 100.0  |  |  |
| Cycle 11 Day 1 (n=158, 158)       | 99.4  | 100.0  |  |  |
| Cycle 12 Day 1 (n=151, 146)       | 100.0   | 100.0  |  |  |
| Cycle 13 Day 1 (n=149, 141)       | 100.0   | 100.0  |  |  |
| Cycle 14 Day 1 (n=152, 143)       | 100.0   | 100.0  |  |  |
| Cycle 15 Day 1 (n=149, 140)       | 100.0   | 100.0  |  |  |
| Cycle 16 Day 1 (n=142, 141)       | 100.0   | 100.0  |  |  |
| Cycle 17 Day 1 (n=145, 142)       | 100.0   | 100.0  |  |  |
| Cycle 18 Day 1 (n=141, 140)       | 100.0   | 100.0  |  |  |
| Cycle 19 Day 1 (n=140, 138)       | 100.0   | 100.0  |  |  |
| Cycle 20 Day 1 (n=139, 134)       | 100.0   | 100.0  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Stage I and II (Pooled): Percentage of Participants Positive for Human Anti-Chimeric Antibodies (HACAs) to Rituximab

|                 |  |
|-----------------|--|
| End point title | Stage I and II (Pooled): Percentage of Participants Positive for Human Anti-Chimeric Antibodies (HACAs) to Rituximab |
|-----------------|--|

End point description:

Levels of HACA in serum were detected at Day 1 of each cycle up to Cycle 8 and at follow-up visit. Safety Analysis Population: included 6 participants who were randomized under Rituximab SC arm but withdrew after Cy1 and then analyzed under Rituximab IV arm. Here, number of participants analyzed = participants evaluable for the outcome measure. Here "n" = number of participants evaluable for this outcome measure at specified timepoint. Stage I and II: Baseline: pre-dose (72 hours prior) D1 of Cy1, Cy 3-20, D0 of Cy2 (1 Cy=3 weeks for Cy1-8 & 8 weeks for Cy9-20), post-baseline: every 12 weeks after last rituximab administration until 96 weeks (a median of 27 months; up to data cutoff of 11 Jan 2016 [up to 6 years])



|   |           |
|---|-----------|
| End point type  | Secondary |
| End point timeframe:  |           |
| Stage I and II: Baseline, post-baseline (See detailed timeframe in Outcome Measure description) |           |

| End point values                  | Stage I and II:<br>Rituximab IV +<br>Chemotherapy<br>(CHOP/CVP) | Stage I and II:<br>Rituximab SC<br>+<br>Chemotherapy<br>(CHOP/CVP) |  |  |
|-----------------------------------|---|--|--|--|
| Subject group type                | Subject analysis set  | Subject analysis set   |  |  |
| Number of subjects analysed       | 208   | 197  |  |  |
| Units: percentage of participants |   |  |  |  |
| number (not applicable)           |   |  |  |  |
| Baseline (n=208, 191)             | 5.8   | 2.6  |  |  |
| Post-Baseline (n=206, 197)        | 1.5   | 2.0  |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Stage I and II (Pooled): Percentage of Participants Positive for Human Anti-Human Antibodies (HAHAs) to Rituximab

|   |   |
|---|---|
| End point title   | Stage I and II (Pooled): Percentage of Participants Positive for Human Anti-Human Antibodies (HAHAs) to Rituximab |
| End point description:  |   |
| Levels of HAHA in serum were detected at Day 1 of each cycle up to Cycle 8 and at follow-up visit. Safety Analysis Population. Here, number of participants analyzed = participants evaluable for the outcome measure. Here "n" = number of participants evaluable for this outcome measure at specified timepoint. Stage I and II: Baseline: pre-dose (72 hours prior) D1 of Cy1, Cy 3-20, D0 of Cy2 (1 Cy=3 weeks for Cy1-8 & 8 weeks for Cy9-20), post-baseline: every 12 weeks after last rituximab administration until 96 weeks (a median of 27 months; up to data cutoff of 11 Jan 2016 [up to 6 years]) |   |
| End point type  | Secondary   |
| End point timeframe:  |   |
| Stage I and II: Baseline, post-baseline (See detailed timeframe in Outcome Measure description)   |   |

| End point values                  | Stage I and II:<br>Rituximab IV +<br>Chemotherapy<br>(CHOP/CVP) | Stage I and II:<br>Rituximab SC<br>+<br>Chemotherapy<br>(CHOP/CVP) |  |  |
|-----------------------------------|---|--|--|--|
| Subject group type                | Subject analysis set  | Subject analysis set   |  |  |
| Number of subjects analysed       | 68  | 197  |  |  |
| Units: percentage of participants |   |  |  |  |
| number (not applicable)           |   |  |  |  |
| Baseline (n=68, 188)              | 10.3  | 11.2   |  |  |
| Post-Baseline (n=66, 197)         | 7.6   | 13.2   |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Stage I and II (Pooled): Percentage of Responses Showing Time Saved of Staff as Per Physician/Nurse Opinions With Each Administration of Rituximab SC as Compared to Rituximab IV at the End of Cy 8, 15 and 20

|                 |   |
|-----------------|---|
| End point title | Stage I and II (Pooled): Percentage of Responses Showing Time Saved of Staff as Per Physician/Nurse Opinions With Each Administration of Rituximab SC as Compared to Rituximab IV at the End of Cy 8, 15 and 20 |
|-----------------|---|

#### End point description:

All investigator physicians and nurses involved in this study were asked to provide the staff time that could be saved with each administration of rituximab SC as compared with rituximab IV to participants in routine practice after Cy 8, 15, 20 and categorized as less than (<) 1 hr, at least 1 hr but <2 hrs, at least 2 hrs but <3 hrs, at least 3 hrs but <4 hrs,  $\geq 4$  hrs. Staff were asked not to consider the time needed for the first IV administration. ITT Population. Here, number of participants analyzed = participants evaluable for the outcome measure. Here "n" = number of participants evaluable for this outcome measure at specified timepoint. Analysis was done in all participants to show a comparison on the time saved by staffs when administered via SC and IV.

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

#### End point timeframe:

After Cycle 8 of induction treatment (24 weeks) and during the maintenance part of the study after 12 months (i.e., Cycle 15), and after the end of the maintenance treatment, (i.e., Cycle 20) (1 Cycle=4 weeks for Cycle 8 and 8 weeks for Cycles 15 and 20)

| End point values                       | All Participants     |  |  |  |
|--|----------------------|--|--|--|
| Subject group type                     | Subject analysis set |  |  |  |
| Number of subjects analysed            | 166                  |  |  |  |
| Units: percentage of responses         |                      |  |  |  |
| Cycle 8: <1 hour (n=166)               | 11                   |  |  |  |
| Cycle 8: $\geq 1$ to <2 hours (n=166)  | 20                   |  |  |  |
| Cycle 8: $\geq 2$ to <3 hours (n=166)  | 35                   |  |  |  |
| Cycle 8: $\geq 3$ to <4 hours (n=166)  | 18                   |  |  |  |
| Cycle 8: $\geq 4$ hours (n=166)        | 16                   |  |  |  |
| Cycle 15: <1 hour (n=130)              | 13                   |  |  |  |
| Cycle 15: $\geq 1$ to <2 hours (n=130) | 17                   |  |  |  |
| Cycle 15: $\geq 2$ to <3 hours (n=130) | 34                   |  |  |  |
| Cycle 15: $\geq 3$ to <4 hours (n=130) | 14                   |  |  |  |
| Cycle 15: $\geq 4$ hours (n=130)       | 22                   |  |  |  |
| Cycle 20: <1 hour (n=126)              | 14                   |  |  |  |
| Cycle 20: $\geq 1$ to <2 hours (n=126) | 32                   |  |  |  |
| Cycle 20: $\geq 2$ to <3 hours (n=126) | 21                   |  |  |  |
| Cycle 20: $\geq 3$ to <4 hours (n=126) | 13                   |  |  |  |
| Cycle 20: $\geq 4$ hours (n=126)       | 19                   |  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Percentage of Responses Who Showed Rituximab SC Formulation Convenient as Compared to Rituximab IV Formulation as Assessed by Physician/Nurse Opinion

|                 |   |
|-----------------|---|
| End point title | Percentage of Responses Who Showed Rituximab SC Formulation Convenient as Compared to Rituximab IV Formulation as Assessed by Physician/Nurse Opinion |
|-----------------|---|

End point description:

All investigator physicians and nurses involved in this study were asked to complete question i.e. "Which formulation of rituximab (SC or IV) do you think is more convenient?" based on their experience with the rituximab SC and IV formulations across all participants and presented as rituximab SC is much more convenient; rituximab SC is a little more convenient; both formulations are equally convenient; rituximab IV is a little more convenient; and rituximab IV is much more convenient. ITT Population. Here, number of participants analyzed = participants evaluable for the outcome measure. Here "n" = number of participants evaluable for this outcome measure at specified timepoint.

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

End point timeframe:

After Cycle 8 of induction treatment (24 weeks) and during the maintenance part of the study after 12 months (i.e., Cycle 15), and after the end of the maintenance treatment, (i.e., Cycle 20) (1 Cycle=4 weeks for Cycle 8 and 8 weeks for Cycles 15 and 20)

| End point values                                   | All Participants     |  |  |  |
|--|----------------------|--|--|--|
| Subject group type                                 | Subject analysis set |  |  |  |
| Number of subjects analysed                        | 166                  |  |  |  |
| Units: percentage of responses                     |                      |  |  |  |
| Cy8: Rituximab SC much more convenient (n=166)     | 81                   |  |  |  |
| Cy8: Rituximab SC little more convenient (n=166)   | 13                   |  |  |  |
| Cy8: Both formulations equally convenient (n=166)  | 2                    |  |  |  |
| Cy8: Rituximab IV little more convenient (n=166)   | 4                    |  |  |  |
| Cy8: Rituximab IV much more convenient (n=166)     | 0                    |  |  |  |
| Cy15: Rituximab SC much more convenient (n=130)    | 88                   |  |  |  |
| Cy15: Rituximab SC little more convenient (n=130)  | 7                    |  |  |  |
| Cy15: Both formulations equally convenient (n=130) | 5                    |  |  |  |
| Cy15: Rituximab IV little more convenient (n=130)  | 0                    |  |  |  |
| Cy15: Rituximab IV much more convenient (n=130)    | 0                    |  |  |  |

|  |    |  |  |  |
|--|----|--|--|--|
| Cy20: Rituximab SC much more convenient (n=126)    | 88 |  |  |  |
| Cy20: Rituximab SC little more convenient (n=126)  | 9  |  |  |  |
| Cy20: Both formulations equally convenient (n=126) | 2  |  |  |  |
| Cy20: Rituximab IV little more convenient (n=126)  | 1  |  |  |  |
| Cy20: Rituximab IV much more convenient (n=126)    | 0  |  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Percentage of Participants Who Died

|   |                                     |
|---|-------------------------------------|
| End point title   | Percentage of Participants Who Died |
| End point description:<br>ITT population.   |                                     |
| End point type  | Secondary                           |
| End point timeframe:<br>Baseline up to death (up to data cutoff of 31 Oct 2017 [up to 6 years]) |                                     |

| End point values                  | Stage I and II:<br>Rituximab IV +<br>Chemotherapy<br>(CHOP/CVP) | Stage I and II:<br>Rituximab SC<br>+<br>Chemotherapy<br>(CHOP/CVP) |  |  |
|-----------------------------------|---|--|--|--|
| Subject group type                | Subject analysis set  | Subject analysis set   |  |  |
| Number of subjects analysed       | 205   | 205  |  |  |
| Units: percentage of participants |   |  |  |  |
| number (not applicable)           | 12.7  | 8.8  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Baseline up to data cutoff date of 31 Oct 2017 (up to 6 years)

Adverse event reporting additional description:

Safety Analysis Population included all participants who received at least one dose of rituximab, either IV or SC. Safety Analysis Population included 6 participants who were randomized under Rituximab SC arm but withdrew after Cy1 and then analyzed under Rituximab IV arm.

|                 |                |
|-----------------|----------------|
| Assessment type | Non-systematic |
|-----------------|----------------|

### Dictionary used

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

|                    |      |
|--------------------|------|
| Dictionary version | 18.1 |
|--------------------|------|

### Reporting groups

|                       |  |
|-----------------------|--|
| Reporting group title | Stage I and II: Rituximab SC + Chemotherapy (CHOP/CVP) |
|-----------------------|--|

Reporting group description:

First cycle of rituximab IV infusion (375 mg/m<sup>2</sup>) + 7 cycles of rituximab SC (1400 mg; rituximab induction) in combination with up to 8 cycles of CHOP or CVP chemotherapy (as per institutional practice) administered every 3 weeks. Participants achieving at least PR entered rituximab SC (1400 mg) maintenance therapy once every 8 weeks for 24 months.

|                       |  |
|-----------------------|--|
| Reporting group title | Stage I and II: Rituximab IV + Chemotherapy (CHOP/CVP) |
|-----------------------|--|

Reporting group description:

Eight cycles of rituximab IV infusion (375 mg/m<sup>2</sup>; rituximab induction) in combination with up to 8 cycles of CHOP or CVP chemotherapy (as per institutional practice) administered every 3 weeks. Participants achieving at least PR during induction, entered rituximab IV maintenance therapy (375 mg/m<sup>2</sup>) once every 8 weeks for 24 months.

| Serious adverse events  | Stage I and II:<br>Rituximab SC +<br>Chemotherapy<br>(CHOP/CVP) | Stage I and II:<br>Rituximab IV +<br>Chemotherapy<br>(CHOP/CVP) |  |
|---|---|---|--|
| Total subjects affected by serious adverse events                   |   |   |  |
| subjects affected / exposed   | 74 / 197 (37.56%)   | 76 / 210 (36.19%)   |  |
| number of deaths (all causes)                                       | 16  | 28  |  |
| number of deaths resulting from adverse events                      |   |   |  |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |   |   |  |
| Basal cell carcinoma  |   |   |  |
| subjects affected / exposed   | 0 / 197 (0.00%)   | 1 / 210 (0.48%)   |  |
| occurrences causally related to treatment / all                     | 0 / 0   | 0 / 1   |  |
| deaths causally related to treatment / all                          | 0 / 0   | 0 / 0   |  |
| Prostate cancer   |   |   |  |
| subjects affected / exposed   | 1 / 197 (0.51%)   | 1 / 210 (0.48%)   |  |
| occurrences causally related to treatment / all                     | 0 / 1   | 0 / 1   |  |
| deaths causally related to treatment / all                          | 0 / 0   | 0 / 0   |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| Rectal adenocarcinoma                           |                 |                 |  |
| subjects affected / exposed                     | 0 / 197 (0.00%) | 1 / 210 (0.48%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Squamous cell carcinoma of lung                 |                 |                 |  |
| subjects affected / exposed                     | 0 / 197 (0.00%) | 1 / 210 (0.48%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Thyroid cancer                                  |                 |                 |  |
| subjects affected / exposed                     | 0 / 197 (0.00%) | 1 / 210 (0.48%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Squamous cell carcinoma of skin                 |                 |                 |  |
| subjects affected / exposed                     | 1 / 197 (0.51%) | 1 / 210 (0.48%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cervix carcinoma stage 0                        |                 |                 |  |
| subjects affected / exposed                     | 1 / 197 (0.51%) | 0 / 210 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Adenocarcinoma of colon                         |                 |                 |  |
| subjects affected / exposed                     | 1 / 197 (0.51%) | 0 / 210 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Colon cancer                                    |                 |                 |  |
| subjects affected / exposed                     | 1 / 197 (0.51%) | 1 / 210 (0.48%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Kaposi's sarcoma                                |                 |                 |  |
| subjects affected / exposed                     | 1 / 197 (0.51%) | 0 / 210 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Renal cell carcinoma                            |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 197 (0.51%) | 0 / 210 (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 / 197 (0.00%) | 1 / 210 (0.48%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Uterine leiomyoma                               |                 |                 |  |
| subjects affected / exposed                     | 1 / 197 (0.51%) | 0 / 210 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Myelodysplastic syndrome                        |                 |                 |  |
| subjects affected / exposed                     | 0 / 197 (0.00%) | 1 / 210 (0.48%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Adenocarcinoma                                  |                 |                 |  |
| alternative dictionary used:<br>MedDRA 20.1     |                 |                 |  |
| subjects affected / exposed                     | 0 / 197 (0.00%) | 1 / 210 (0.48%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Plasma cell myeloma                             |                 |                 |  |
| alternative dictionary used:<br>MedDRA 20.1     |                 |                 |  |
| subjects affected / exposed                     | 1 / 197 (0.51%) | 0 / 210 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Breast cancer                                   |                 |                 |  |
| alternative dictionary used:<br>MedDRA 20.1     |                 |                 |  |
| subjects affected / exposed                     | 1 / 197 (0.51%) | 0 / 210 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Squamous cell carcinoma                         |                 |                 |  |
| alternative dictionary used:<br>MedDRA 20.1     |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 197 (0.51%) | 0 / 210 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| <b>Vascular disorders</b>                       |                 |                 |  |
| Arterial occlusive disease                      |                 |                 |  |
| subjects affected / exposed                     | 1 / 197 (0.51%) | 0 / 210 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Vena cava thrombosis                            |                 |                 |  |
| subjects affected / exposed                     | 1 / 197 (0.51%) | 0 / 210 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Deep vein thrombosis                            |                 |                 |  |
| subjects affected / exposed                     | 0 / 197 (0.00%) | 1 / 210 (0.48%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hypertensive crisis                             |                 |                 |  |
| subjects affected / exposed                     | 1 / 197 (0.51%) | 1 / 210 (0.48%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Subclavian artery occlusion                     |                 |                 |  |
| subjects affected / exposed                     | 1 / 197 (0.51%) | 0 / 210 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| <b>Surgical and medical procedures</b>          |                 |                 |  |
| Bladder calculus removal                        |                 |                 |  |
| subjects affected / exposed                     | 0 / 197 (0.00%) | 1 / 210 (0.48%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hysterectomy                                    |                 |                 |  |
| subjects affected / exposed                     | 1 / 197 (0.51%) | 0 / 210 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| <b>General disorders and administration</b>     |                 |                 |  |



|   |                 |                 |  |
|---|-----------------|-----------------|--|
| site conditions                                 |                 |                 |  |
| Pyrexia   |                 |                 |  |
| subjects affected / exposed                     | 6 / 197 (3.05%) | 5 / 210 (2.38%) |  |
| occurrences causally related to treatment / all | 1 / 6           | 0 / 5           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Malaise   |                 |                 |  |
| subjects affected / exposed                     | 0 / 197 (0.00%) | 1 / 210 (0.48%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Multi-organ failure                             |                 |                 |  |
| subjects affected / exposed                     | 0 / 197 (0.00%) | 1 / 210 (0.48%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| Death   |                 |                 |  |
| subjects affected / exposed                     | 0 / 197 (0.00%) | 2 / 210 (0.95%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 2           |  |
| Reproductive system and breast disorders        |                 |                 |  |
| Pelvic cyst                                     |                 |                 |  |
| subjects affected / exposed                     | 1 / 197 (0.51%) | 0 / 210 (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 / 197 (0.51%) | 0 / 210 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Uterovaginal prolapse                           |                 |                 |  |
| subjects affected / exposed                     | 1 / 197 (0.51%) | 0 / 210 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Uterine polyp                                   |                 |                 |  |
| alternative dictionary used: MedDRA 20.1        |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 197 (0.51%) | 0 / 210 (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 |                 |                 |  |
| Dyspnoea  |                 |                 |  |
| subjects affected / exposed                     | 2 / 197 (1.02%) | 3 / 210 (1.43%) |  |
| occurrences causally related to treatment / all | 1 / 2           | 2 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pulmonary embolism                              |                 |                 |  |
| subjects affected / exposed                     | 1 / 197 (0.51%) | 4 / 210 (1.90%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 4           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pleural effusion                                |                 |                 |  |
| subjects affected / exposed                     | 1 / 197 (0.51%) | 1 / 210 (0.48%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Acute respiratory failure                       |                 |                 |  |
| subjects affected / exposed                     | 1 / 197 (0.51%) | 1 / 210 (0.48%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 1           | 1 / 1           |  |
| Pneumothorax                                    |                 |                 |  |
| subjects affected / exposed                     | 0 / 197 (0.00%) | 1 / 210 (0.48%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Bronchitis chronic                              |                 |                 |  |
| subjects affected / exposed                     | 0 / 197 (0.00%) | 1 / 210 (0.48%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Psychiatric disorders                           |                 |                 |  |
| Major depression                                |                 |                 |  |
| subjects affected / exposed                     | 0 / 197 (0.00%) | 1 / 210 (0.48%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |

|  |                 |                 |  |
|--|-----------------|-----------------|--|
| Bipolar disorder   |                 |                 |  |
| subjects affected / exposed                                    | 0 / 197 (0.00%) | 1 / 210 (0.48%) |  |
| occurrences causally related to treatment / all                | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all                     | 0 / 0           | 0 / 0           |  |
| Investigations   |                 |                 |  |
| Eastern Cooperative Oncology Group performance status worsened |                 |                 |  |
| subjects affected / exposed                                    | 0 / 197 (0.00%) | 1 / 210 (0.48%) |  |
| occurrences causally related to treatment / all                | 0 / 0           | 0 / 2           |  |
| deaths causally related to treatment / all                     | 0 / 0           | 0 / 0           |  |
| International normalised ratio increased                       |                 |                 |  |
| subjects affected / exposed                                    | 1 / 197 (0.51%) | 0 / 210 (0.00%) |  |
| occurrences causally related to treatment / all                | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all                     | 0 / 0           | 0 / 0           |  |
| Injury, poisoning and procedural complications                 |                 |                 |  |
| Stress fracture  |                 |                 |  |
| subjects affected / exposed                                    | 0 / 197 (0.00%) | 1 / 210 (0.48%) |  |
| occurrences causally related to treatment / all                | 0 / 0           | 0 / 2           |  |
| deaths causally related to treatment / all                     | 0 / 0           | 0 / 0           |  |
| Ankle fracture   |                 |                 |  |
| subjects affected / exposed                                    | 0 / 197 (0.00%) | 1 / 210 (0.48%) |  |
| occurrences causally related to treatment / all                | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all                     | 0 / 0           | 0 / 0           |  |
| Foreign body   |                 |                 |  |
| subjects affected / exposed                                    | 0 / 197 (0.00%) | 1 / 210 (0.48%) |  |
| occurrences causally related to treatment / all                | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all                     | 0 / 0           | 0 / 0           |  |
| Femoral neck fracture  |                 |                 |  |
| subjects affected / exposed                                    | 0 / 197 (0.00%) | 1 / 210 (0.48%) |  |
| occurrences causally related to treatment / all                | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all                     | 0 / 0           | 0 / 0           |  |
| Skull fracture   |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 197 (0.51%) | 0 / 210 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Multiple injuries                               |                 |                 |  |
| subjects affected / exposed                     | 0 / 197 (0.00%) | 1 / 210 (0.48%) |  |
| 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                     | 1 / 197 (0.51%) | 0 / 210 (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                     | 1 / 197 (0.51%) | 0 / 210 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| Traumatic intracranial haemorrhage              |                 |                 |  |
| subjects affected / exposed                     | 0 / 197 (0.00%) | 1 / 210 (0.48%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| Procedural pain                                 |                 |                 |  |
| subjects affected / exposed                     | 1 / 197 (0.51%) | 0 / 210 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Wrist fracture                                  |                 |                 |  |
| subjects affected / exposed                     | 1 / 197 (0.51%) | 0 / 210 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cardiac disorders                               |                 |                 |  |
| Acute coronary syndrome                         |                 |                 |  |
| subjects affected / exposed                     | 0 / 197 (0.00%) | 1 / 210 (0.48%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Atrial fibrillation                             |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 2 / 197 (1.02%) | 0 / 210 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Myocardial infarction                           |                 |                 |  |
| subjects affected / exposed                     | 1 / 197 (0.51%) | 1 / 210 (0.48%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 1           |  |
| Acute myocardial infarction                     |                 |                 |  |
| subjects affected / exposed                     | 1 / 197 (0.51%) | 0 / 210 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cardiac arrest                                  |                 |                 |  |
| subjects affected / exposed                     | 0 / 197 (0.00%) | 1 / 210 (0.48%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cardiac failure congestive                      |                 |                 |  |
| subjects affected / exposed                     | 1 / 197 (0.51%) | 1 / 210 (0.48%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 1           |  |
| Myocardial ischaemia                            |                 |                 |  |
| subjects affected / exposed                     | 0 / 197 (0.00%) | 1 / 210 (0.48%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Bradycardia                                     |                 |                 |  |
| alternative dictionary used:<br>MedDRA 20.1     |                 |                 |  |
| subjects affected / exposed                     | 0 / 197 (0.00%) | 1 / 210 (0.48%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Nervous system disorders                        |                 |                 |  |
| Coma hepatic                                    |                 |                 |  |
| subjects affected / exposed                     | 0 / 197 (0.00%) | 1 / 210 (0.48%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| Migraine  |                  |                  |  |
| subjects affected / exposed                     | 0 / 197 (0.00%)  | 1 / 210 (0.48%)  |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Hydrocephalus                                   |                  |                  |  |
| subjects affected / exposed                     | 1 / 197 (0.51%)  | 0 / 210 (0.00%)  |  |
| occurrences causally related to treatment / all | 1 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Paraesthesia                                    |                  |                  |  |
| subjects affected / exposed                     | 1 / 197 (0.51%)  | 0 / 210 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Sciatica  |                  |                  |  |
| subjects affected / exposed                     | 0 / 197 (0.00%)  | 1 / 210 (0.48%)  |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Cognitive disorder                              |                  |                  |  |
| subjects affected / exposed                     | 0 / 197 (0.00%)  | 2 / 210 (0.95%)  |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Hypoglycaemic coma                              |                  |                  |  |
| subjects affected / exposed                     | 0 / 197 (0.00%)  | 1 / 210 (0.48%)  |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1            |  |
| Transient ischaemic attack                      |                  |                  |  |
| subjects affected / exposed                     | 0 / 197 (0.00%)  | 1 / 210 (0.48%)  |  |
| 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            |                  |                  |  |
| Febrile neutropenia                             |                  |                  |  |
| subjects affected / exposed                     | 12 / 197 (6.09%) | 10 / 210 (4.76%) |  |
| occurrences causally related to treatment / all | 7 / 14           | 5 / 13           |  |
| deaths causally related to treatment / all      | 1 / 2            | 0 / 0            |  |
| Neutropenia                                     |                  |                  |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 6 / 197 (3.05%) | 4 / 210 (1.90%) |  |
| occurrences causally related to treatment / all | 8 / 9           | 2 / 5           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Anaemia   |                 |                 |  |
| subjects affected / exposed                     | 2 / 197 (1.02%) | 1 / 210 (0.48%) |  |
| occurrences causally related to treatment / all | 3 / 4           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Thrombocytopenia                                |                 |                 |  |
| subjects affected / exposed                     | 0 / 197 (0.00%) | 1 / 210 (0.48%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Ear and labyrinth disorders                     |                 |                 |  |
| Vertigo   |                 |                 |  |
| subjects affected / exposed                     | 2 / 197 (1.02%) | 1 / 210 (0.48%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Gastrointestinal disorders                      |                 |                 |  |
| Abdominal pain                                  |                 |                 |  |
| subjects affected / exposed                     | 2 / 197 (1.02%) | 2 / 210 (0.95%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 1 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Constipation                                    |                 |                 |  |
| subjects affected / exposed                     | 0 / 197 (0.00%) | 3 / 210 (1.43%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Ascites   |                 |                 |  |
| subjects affected / exposed                     | 0 / 197 (0.00%) | 1 / 210 (0.48%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Oral lichen planus                              |                 |                 |  |
| subjects affected / exposed                     | 0 / 197 (0.00%) | 1 / 210 (0.48%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pancreatitis                                    |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 197 (0.00%) | 1 / 210 (0.48%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Colitis ulcerative                              |                 |                 |  |
| subjects affected / exposed                     | 1 / 197 (0.51%) | 0 / 210 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Diarrhoea                                       |                 |                 |  |
| subjects affected / exposed                     | 1 / 197 (0.51%) | 0 / 210 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Duodenal ulcer                                  |                 |                 |  |
| subjects affected / exposed                     | 0 / 197 (0.00%) | 1 / 210 (0.48%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Enteritis                                       |                 |                 |  |
| subjects affected / exposed                     | 0 / 197 (0.00%) | 1 / 210 (0.48%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Ileus paralytic                                 |                 |                 |  |
| subjects affected / exposed                     | 1 / 197 (0.51%) | 0 / 210 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Mouth ulceration                                |                 |                 |  |
| subjects affected / exposed                     | 1 / 197 (0.51%) | 0 / 210 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Proctalgia                                      |                 |                 |  |
| subjects affected / exposed                     | 0 / 197 (0.00%) | 1 / 210 (0.48%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Vomiting  |                 |                 |  |



|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 197 (0.51%) | 0 / 210 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Mesenteric vein thrombosis                      |                 |                 |  |
| subjects affected / exposed                     | 0 / 197 (0.00%) | 1 / 210 (0.48%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Colitis   |                 |                 |  |
| subjects affected / exposed                     | 1 / 197 (0.51%) | 0 / 210 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Abdominal wall haematoma                        |                 |                 |  |
| subjects affected / exposed                     | 0 / 197 (0.00%) | 1 / 210 (0.48%) |  |
| 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                     | 0 / 197 (0.00%) | 1 / 210 (0.48%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hepatobiliary disorders                         |                 |                 |  |
| Cholangitis                                     |                 |                 |  |
| subjects affected / exposed                     | 1 / 197 (0.51%) | 0 / 210 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cholecystitis acute                             |                 |                 |  |
| subjects affected / exposed                     | 0 / 197 (0.00%) | 1 / 210 (0.48%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Jaundice  |                 |                 |  |
| subjects affected / exposed                     | 1 / 197 (0.51%) | 0 / 210 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Skin and subcutaneous tissue disorders          |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| Hyperhidrosis                                   |                 |                 |  |
| subjects affected / exposed                     | 0 / 197 (0.00%) | 1 / 210 (0.48%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Lichen planus                                   |                 |                 |  |
| subjects affected / exposed                     | 0 / 197 (0.00%) | 1 / 210 (0.48%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Rash  |                 |                 |  |
| subjects affected / exposed                     | 0 / 197 (0.00%) | 1 / 210 (0.48%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Skin ulcer                                      |                 |                 |  |
| subjects affected / exposed                     | 0 / 197 (0.00%) | 1 / 210 (0.48%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Renal and urinary disorders                     |                 |                 |  |
| Hydronephrosis                                  |                 |                 |  |
| subjects affected / exposed                     | 2 / 197 (1.02%) | 0 / 210 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Urinary retention                               |                 |                 |  |
| subjects affected / exposed                     | 0 / 197 (0.00%) | 1 / 210 (0.48%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Calculus bladder                                |                 |                 |  |
| alternative dictionary used: MedDRA 20.1        |                 |                 |  |
| subjects affected / exposed                     | 0 / 197 (0.00%) | 1 / 210 (0.48%) |  |
| 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 |                 |                 |  |
| Back pain                                       |                 |                 |  |

|   |                  |                 |  |
|---|------------------|-----------------|--|
| subjects affected / exposed                     | 2 / 197 (1.02%)  | 1 / 210 (0.48%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Osteoarthritis                                  |                  |                 |  |
| subjects affected / exposed                     | 0 / 197 (0.00%)  | 2 / 210 (0.95%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Arthralgia                                      |                  |                 |  |
| subjects affected / exposed                     | 2 / 197 (1.02%)  | 0 / 210 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Pain in extremity                               |                  |                 |  |
| subjects affected / exposed                     | 0 / 197 (0.00%)  | 1 / 210 (0.48%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Flank pain                                      |                  |                 |  |
| subjects affected / exposed                     | 1 / 197 (0.51%)  | 0 / 210 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Pathological fracture                           |                  |                 |  |
| subjects affected / exposed                     | 1 / 197 (0.51%)  | 0 / 210 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Arthritis                                       |                  |                 |  |
| subjects affected / exposed                     | 1 / 197 (0.51%)  | 0 / 210 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Infections and infestations                     |                  |                 |  |
| Pneumonia                                       |                  |                 |  |
| subjects affected / exposed                     | 11 / 197 (5.58%) | 7 / 210 (3.33%) |  |
| occurrences causally related to treatment / all | 1 / 13           | 2 / 8           |  |
| deaths causally related to treatment / all      | 0 / 0            | 1 / 1           |  |
| Neutropenic sepsis                              |                  |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 197 (0.51%) | 4 / 210 (1.90%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 4           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cystitis  |                 |                 |  |
| subjects affected / exposed                     | 2 / 197 (1.02%) | 1 / 210 (0.48%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Lower respiratory tract infection               |                 |                 |  |
| subjects affected / exposed                     | 2 / 197 (1.02%) | 2 / 210 (0.95%) |  |
| occurrences causally related to treatment / all | 2 / 2           | 0 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| Urinary tract infection                         |                 |                 |  |
| subjects affected / exposed                     | 2 / 197 (1.02%) | 1 / 210 (0.48%) |  |
| occurrences causally related to treatment / all | 0 / 4           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| Bronchitis                                      |                 |                 |  |
| subjects affected / exposed                     | 1 / 197 (0.51%) | 2 / 210 (0.95%) |  |
| occurrences causally related to treatment / all | 2 / 2           | 0 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Infection                                       |                 |                 |  |
| subjects affected / exposed                     | 0 / 197 (0.00%) | 2 / 210 (0.95%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| Sepsis  |                 |                 |  |
| subjects affected / exposed                     | 3 / 197 (1.52%) | 1 / 210 (0.48%) |  |
| occurrences causally related to treatment / all | 1 / 3           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| Bacterial prostatitis                           |                 |                 |  |
| subjects affected / exposed                     | 1 / 197 (0.51%) | 0 / 210 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Empyema   |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 197 (0.51%) | 0 / 210 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Gastroenteritis norovirus                       |                 |                 |  |
| subjects affected / exposed                     | 0 / 197 (0.00%) | 1 / 210 (0.48%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Giardiasis                                      |                 |                 |  |
| subjects affected / exposed                     | 1 / 197 (0.51%) | 0 / 210 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Meningitis                                      |                 |                 |  |
| subjects affected / exposed                     | 2 / 197 (1.02%) | 0 / 210 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Otitis externa                                  |                 |                 |  |
| subjects affected / exposed                     | 0 / 197 (0.00%) | 1 / 210 (0.48%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pneumocystis jirovecii pneumonia                |                 |                 |  |
| subjects affected / exposed                     | 0 / 197 (0.00%) | 1 / 210 (0.48%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pneumonia mycoplasmal                           |                 |                 |  |
| subjects affected / exposed                     | 1 / 197 (0.51%) | 0 / 210 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Postoperative wound infection                   |                 |                 |  |
| subjects affected / exposed                     | 1 / 197 (0.51%) | 0 / 210 (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                     | 1 / 197 (0.51%) | 1 / 210 (0.48%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Upper respiratory tract infection               |                 |                 |  |
| subjects affected / exposed                     | 1 / 197 (0.51%) | 0 / 210 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Urinary tract infection bacterial               |                 |                 |  |
| subjects affected / exposed                     | 1 / 197 (0.51%) | 0 / 210 (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 / 197 (0.51%) | 1 / 210 (0.48%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Urosepsis                                       |                 |                 |  |
| subjects affected / exposed                     | 2 / 197 (1.02%) | 0 / 210 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cellulitis                                      |                 |                 |  |
| subjects affected / exposed                     | 1 / 197 (0.51%) | 1 / 210 (0.48%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Abscess   |                 |                 |  |
| subjects affected / exposed                     | 0 / 197 (0.00%) | 1 / 210 (0.48%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Chronic hepatitis B                             |                 |                 |  |
| subjects affected / exposed                     | 1 / 197 (0.51%) | 0 / 210 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Bacteraemia                                     |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 197 (0.51%) | 0 / 210 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hepatitis viral                                 |                 |                 |  |
| subjects affected / exposed                     | 1 / 197 (0.51%) | 0 / 210 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Erysipelas                                      |                 |                 |  |
| subjects affected / exposed                     | 1 / 197 (0.51%) | 0 / 210 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Intestinal sepsis                               |                 |                 |  |
| subjects affected / exposed                     | 0 / 197 (0.00%) | 1 / 210 (0.48%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pulmonary tuberculosis                          |                 |                 |  |
| subjects affected / exposed                     | 0 / 197 (0.00%) | 1 / 210 (0.48%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| Respiratory tract infection fungal              |                 |                 |  |
| subjects affected / exposed                     | 0 / 197 (0.00%) | 1 / 210 (0.48%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pyelonephritis                                  |                 |                 |  |
| subjects affected / exposed                     | 0 / 197 (0.00%) | 1 / 210 (0.48%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Creutzfeldt–Jakob disease                       |                 |                 |  |
| subjects affected / exposed                     | 1 / 197 (0.51%) | 0 / 210 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 1 / 1           | 0 / 0           |  |
| Cellulitis gangrenous                           |                 |                 |  |
| alternative dictionary used:<br>MedDRA 20.1     |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 197 (0.00%) | 1 / 210 (0.48%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Metabolism and nutrition disorders              |                 |                 |  |
| Tumour lysis syndrome                           |                 |                 |  |
| subjects affected / exposed                     | 1 / 197 (0.51%) | 0 / 210 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hyponatraemia                                   |                 |                 |  |
| subjects affected / exposed                     | 2 / 197 (1.02%) | 0 / 210 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |

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

| <b>Non-serious adverse events</b>                     | Stage I and II:<br>Rituximab SC +<br>Chemotherapy<br>(CHOP/CVP) | Stage I and II:<br>Rituximab IV +<br>Chemotherapy<br>(CHOP/CVP) |  |
|---|---|---|--|
| Total subjects affected by non-serious adverse events |   |   |  |
| subjects affected / exposed                           | 186 / 197 (94.42%)  | 187 / 210 (89.05%)  |  |
| Vascular disorders                                    |   |   |  |
| Hypertension  |   |   |  |
| subjects affected / exposed                           | 12 / 197 (6.09%)  | 13 / 210 (6.19%)  |  |
| occurrences (all)                                     | 15  | 13  |  |
| Nervous system disorders                              |   |   |  |
| Paraesthesia  |   |   |  |
| subjects affected / exposed                           | 30 / 197 (15.23%)   | 27 / 210 (12.86%)   |  |
| occurrences (all)                                     | 43  | 32  |  |
| Dizziness   |   |   |  |
| subjects affected / exposed                           | 16 / 197 (8.12%)  | 15 / 210 (7.14%)  |  |
| occurrences (all)                                     | 47  | 17  |  |
| Neuropathy peripheral                                 |   |   |  |
| subjects affected / exposed                           | 24 / 197 (12.18%)   | 30 / 210 (14.29%)   |  |
| occurrences (all)                                     | 34  | 39  |  |
| Headache  |   |   |  |



|   |                   |                   |  |
|---|-------------------|-------------------|--|
| subjects affected / exposed                             | 27 / 197 (13.71%) | 20 / 210 (9.52%)  |  |
| occurrences (all)                                       | 35                | 31                |  |
| Hypoaesthesia   |                   |                   |  |
| alternative dictionary used:<br>MedDRA 20.1             |                   |                   |  |
| subjects affected / exposed                             | 10 / 197 (5.08%)  | 7 / 210 (3.33%)   |  |
| occurrences (all)                                       | 13                | 8                 |  |
| General disorders and administration<br>site conditions |                   |                   |  |
| Fatigue   |                   |                   |  |
| subjects affected / exposed                             | 42 / 197 (21.32%) | 38 / 210 (18.10%) |  |
| occurrences (all)                                       | 58                | 48                |  |
| Injection site erythema                                 |                   |                   |  |
| subjects affected / exposed                             | 27 / 197 (13.71%) | 0 / 210 (0.00%)   |  |
| occurrences (all)                                       | 125               | 0                 |  |
| Pyrexia   |                   |                   |  |
| subjects affected / exposed                             | 29 / 197 (14.72%) | 29 / 210 (13.81%) |  |
| occurrences (all)                                       | 38                | 41                |  |
| Asthenia  |                   |                   |  |
| subjects affected / exposed                             | 35 / 197 (17.77%) | 27 / 210 (12.86%) |  |
| occurrences (all)                                       | 53                | 44                |  |
| Chills  |                   |                   |  |
| subjects affected / exposed                             | 16 / 197 (8.12%)  | 18 / 210 (8.57%)  |  |
| occurrences (all)                                       | 17                | 21                |  |
| Mucosal inflammation                                    |                   |                   |  |
| subjects affected / exposed                             | 9 / 197 (4.57%)   | 12 / 210 (5.71%)  |  |
| occurrences (all)                                       | 14                | 14                |  |
| Injection site pain                                     |                   |                   |  |
| subjects affected / exposed                             | 16 / 197 (8.12%)  | 0 / 210 (0.00%)   |  |
| occurrences (all)                                       | 16                | 0                 |  |
| Chest pain  |                   |                   |  |
| subjects affected / exposed                             | 14 / 197 (7.11%)  | 7 / 210 (3.33%)   |  |
| occurrences (all)                                       | 16                | 9                 |  |
| Oedema peripheral                                       |                   |                   |  |
| subjects affected / exposed                             | 10 / 197 (5.08%)  | 13 / 210 (6.19%)  |  |
| occurrences (all)                                       | 13                | 17                |  |
| Influenza like illness                                  |                   |                   |  |

|  |                      |                        |  |
|--|----------------------|------------------------|--|
| subjects affected / exposed<br>occurrences (all) | 5 / 197 (2.54%)<br>6 | 12 / 210 (5.71%)<br>15 |  |
| Blood and lymphatic system disorders             |                      |                        |  |
| Neutropenia                                      |                      |                        |  |
| subjects affected / exposed                      | 65 / 197 (32.99%)    | 57 / 210 (27.14%)      |  |
| occurrences (all)                                | 165                  | 159                    |  |
| Anaemia  |                      |                        |  |
| subjects affected / exposed                      | 30 / 197 (15.23%)    | 26 / 210 (12.38%)      |  |
| occurrences (all)                                | 66                   | 34                     |  |
| Leukopenia                                       |                      |                        |  |
| subjects affected / exposed                      | 13 / 197 (6.60%)     | 23 / 210 (10.95%)      |  |
| occurrences (all)                                | 21                   | 44                     |  |
| Gastrointestinal disorders                       |                      |                        |  |
| Nausea   |                      |                        |  |
| subjects affected / exposed                      | 65 / 197 (32.99%)    | 47 / 210 (22.38%)      |  |
| occurrences (all)                                | 113                  | 89                     |  |
| Vomiting   |                      |                        |  |
| subjects affected / exposed                      | 29 / 197 (14.72%)    | 27 / 210 (12.86%)      |  |
| occurrences (all)                                | 52                   | 31                     |  |
| Diarrhoea  |                      |                        |  |
| subjects affected / exposed                      | 34 / 197 (17.26%)    | 35 / 210 (16.67%)      |  |
| occurrences (all)                                | 47                   | 49                     |  |
| Constipation                                     |                      |                        |  |
| subjects affected / exposed                      | 50 / 197 (25.38%)    | 55 / 210 (26.19%)      |  |
| occurrences (all)                                | 66                   | 87                     |  |
| Abdominal pain                                   |                      |                        |  |
| subjects affected / exposed                      | 29 / 197 (14.72%)    | 25 / 210 (11.90%)      |  |
| occurrences (all)                                | 43                   | 32                     |  |
| Dyspepsia  |                      |                        |  |
| subjects affected / exposed                      | 16 / 197 (8.12%)     | 14 / 210 (6.67%)       |  |
| occurrences (all)                                | 19                   | 22                     |  |
| Abdominal pain upper                             |                      |                        |  |
| subjects affected / exposed                      | 11 / 197 (5.58%)     | 11 / 210 (5.24%)       |  |
| occurrences (all)                                | 14                   | 16                     |  |
| Stomatitis                                       |                      |                        |  |

|  |                        |                        |  |
|--|------------------------|------------------------|--|
| subjects affected / exposed<br>occurrences (all) | 12 / 197 (6.09%)<br>15 | 11 / 210 (5.24%)<br>13 |  |
| Respiratory, thoracic and mediastinal disorders  |                        |                        |  |
| Cough  |                        |                        |  |
| subjects affected / exposed                      | 49 / 197 (24.87%)      | 32 / 210 (15.24%)      |  |
| occurrences (all)                                | 60                     | 47                     |  |
| Oropharyngeal pain                               |                        |                        |  |
| subjects affected / exposed                      | 17 / 197 (8.63%)       | 17 / 210 (8.10%)       |  |
| occurrences (all)                                | 29                     | 18                     |  |
| Dyspnoea   |                        |                        |  |
| subjects affected / exposed                      | 21 / 197 (10.66%)      | 13 / 210 (6.19%)       |  |
| occurrences (all)                                | 24                     | 16                     |  |
| Skin and subcutaneous tissue disorders           |                        |                        |  |
| Pruritus   |                        |                        |  |
| subjects affected / exposed                      | 20 / 197 (10.15%)      | 25 / 210 (11.90%)      |  |
| occurrences (all)                                | 22                     | 26                     |  |
| Erythema   |                        |                        |  |
| subjects affected / exposed                      | 19 / 197 (9.64%)       | 11 / 210 (5.24%)       |  |
| occurrences (all)                                | 34                     | 13                     |  |
| Alopecia   |                        |                        |  |
| subjects affected / exposed                      | 28 / 197 (14.21%)      | 23 / 210 (10.95%)      |  |
| occurrences (all)                                | 29                     | 25                     |  |
| Rash   |                        |                        |  |
| subjects affected / exposed                      | 20 / 197 (10.15%)      | 14 / 210 (6.67%)       |  |
| occurrences (all)                                | 28                     | 18                     |  |
| Psychiatric disorders                            |                        |                        |  |
| Insomnia   |                        |                        |  |
| subjects affected / exposed                      | 19 / 197 (9.64%)       | 19 / 210 (9.05%)       |  |
| occurrences (all)                                | 22                     | 21                     |  |
| Anxiety  |                        |                        |  |
| alternative dictionary used:<br>MedDRA 20.1      |                        |                        |  |
| subjects affected / exposed                      | 11 / 197 (5.58%)       | 7 / 210 (3.33%)        |  |
| occurrences (all)                                | 13                     | 8                      |  |
| Musculoskeletal and connective tissue disorders  |                        |                        |  |

|                                   |                   |                   |  |
|-----------------------------------|-------------------|-------------------|--|
| Bone pain                         |                   |                   |  |
| subjects affected / exposed       | 20 / 197 (10.15%) | 16 / 210 (7.62%)  |  |
| occurrences (all)                 | 26                | 22                |  |
| Back pain                         |                   |                   |  |
| subjects affected / exposed       | 18 / 197 (9.14%)  | 25 / 210 (11.90%) |  |
| occurrences (all)                 | 19                | 29                |  |
| Myalgia                           |                   |                   |  |
| subjects affected / exposed       | 16 / 197 (8.12%)  | 10 / 210 (4.76%)  |  |
| occurrences (all)                 | 20                | 17                |  |
| Muscle spasms                     |                   |                   |  |
| subjects affected / exposed       | 17 / 197 (8.63%)  | 7 / 210 (3.33%)   |  |
| occurrences (all)                 | 21                | 7                 |  |
| Pain in extremity                 |                   |                   |  |
| subjects affected / exposed       | 22 / 197 (11.17%) | 11 / 210 (5.24%)  |  |
| occurrences (all)                 | 25                | 13                |  |
| Arthralgia                        |                   |                   |  |
| subjects affected / exposed       | 26 / 197 (13.20%) | 22 / 210 (10.48%) |  |
| occurrences (all)                 | 27                | 35                |  |
| Infections and infestations       |                   |                   |  |
| Upper respiratory tract infection |                   |                   |  |
| subjects affected / exposed       | 30 / 197 (15.23%) | 26 / 210 (12.38%) |  |
| occurrences (all)                 | 51                | 39                |  |
| Urinary tract infection           |                   |                   |  |
| subjects affected / exposed       | 16 / 197 (8.12%)  | 28 / 210 (13.33%) |  |
| occurrences (all)                 | 23                | 49                |  |
| Nasopharyngitis                   |                   |                   |  |
| subjects affected / exposed       | 22 / 197 (11.17%) | 25 / 210 (11.90%) |  |
| occurrences (all)                 | 29                | 31                |  |
| Bronchitis                        |                   |                   |  |
| subjects affected / exposed       | 15 / 197 (7.61%)  | 15 / 210 (7.14%)  |  |
| occurrences (all)                 | 18                | 23                |  |
| Sinusitis                         |                   |                   |  |
| subjects affected / exposed       | 14 / 197 (7.11%)  | 10 / 210 (4.76%)  |  |
| occurrences (all)                 | 16                | 15                |  |
| Conjunctivitis                    |                   |                   |  |

|                             |                  |                  |  |
|-----------------------------|------------------|------------------|--|
| subjects affected / exposed | 9 / 197 (4.57%)  | 12 / 210 (5.71%) |  |
| occurrences (all)           | 10               | 15               |  |
| Pneumonia                   |                  |                  |  |
| subjects affected / exposed | 12 / 197 (6.09%) | 4 / 210 (1.90%)  |  |
| occurrences (all)           | 12               | 5                |  |
| Influenza                   |                  |                  |  |
| subjects affected / exposed | 9 / 197 (4.57%)  | 14 / 210 (6.67%) |  |
| occurrences (all)           | 10               | 16               |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date            | Amendment  |
|-----------------|--|
| 19 March 2012   | - Added additional flexibility in the protocol for the number of cycles of CHOP chemotherapy to reflect institutional practice based on the PRIMA study. -- Added guidance to clarify acceptable timeframe for dose delays during maintenance treatment. -- Provided clarification on acceptable malignancy types and remission time periods that render a participant eligible. - Removed past hepatitis C virus (HCV) exposure from the exclusion criteria because only anecdotal reports in the literature of HCV reactivation and no clear links established that rituximab is involved in HCV reactivation in previously infected HCV participant. Thus, exclusion of participants with a history of HCV infection was, on balance, not considered necessary. -- Removed bone marrow aspirate and biopsy at unscheduled visit for ethical reasons. -- Added that following drug administration, any participant experiencing a severe or serious adverse event, which is considered immunogenic and possibly related to rituximab administration, serum samples for rituximab PK, anti-rituximab, (and following Cycle 2 for participants randomized in the SC arm anti-rHuPH20) were to be collected within 7 days of the event becoming known to the investigator to ensure participant safety was monitored thoroughly. - Clarified that anti-rHuPH20 sampling should only be performed in participants receiving rituximab SC formulation, as only this formulation includes rHuPH20 excipient. |
| 15 October 2012 | Added possibility of performing safety snapshot(s) during the study to address potential health authority or regulatory questions.   |

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? Yes

| Date            | Interruption  | Restart date |
|-----------------|---|--------------|
| 21 October 2011 | Temporary stop on recruitment occurred between Stage 1 and Stage 2 whilst PK non-inferiority was confirmed by the 1400 mg Stage 1 dose. | 16 July 2012 |

Notes:

### Limitations and caveats

None reported