



## Clinical trial results:

### Phase II Trial to Evaluate the Efficacy of Obinutuzumab (RO5072759) + Bendamustine Treatment in Patients With Refractory or Relapsed Chronic Lymphocytic Leukemia

#### Summary

|                          |                  |
|--------------------------|------------------|
| EudraCT number           | 2013-003388-79   |
| Trial protocol           | ES               |
| Global end of trial date | 19 November 2018 |

#### Results information

|                                |                  |
|--------------------------------|------------------|
| Result version number          | v1 (current)     |
| This version publication date  | 27 November 2019 |
| First version publication date | 27 November 2019 |

#### Trial information

##### Trial identification

|                       |         |
|-----------------------|---------|
| Sponsor protocol code | ML29167 |
|-----------------------|---------|

##### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT02071225 |
| 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               | F. Hoffmann-La Roche AG, F. Hoffmann-La Roche AG, +41 616878333, global.trial_information@roche.com  |
| Scientific contact           | F. Hoffmann-La Roche AG, F. Hoffmann-La Roche AG, + 41 616878333, global.trial_information@roche.com |

Notes:

#### Paediatric regulatory details

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

Notes:

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**Results analysis stage**

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|                                                      |                  |
|------------------------------------------------------|------------------|
| Analysis stage                                       | Final            |
| Date of interim/final analysis                       | 19 November 2018 |
| Is this the analysis of the primary completion data? | No               |
| Global end of trial reached?                         | Yes              |
| Global end of trial date                             | 19 November 2018 |
| Was the trial ended prematurely?                     | No               |

Notes:

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**General information about the trial**

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Main objective of the trial:

To evaluate the efficacy of obinutuzumab and bendamustine treatment in subjects with refractory or relapsed chronic lymphocytic leukemia (CLL).

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

|                                                           |                  |
|-----------------------------------------------------------|------------------|
| Actual start date of recruitment                          | 09 April 2014    |
| Long term follow-up planned                               | Yes              |
| Long term follow-up rationale                             | Safety, Efficacy |
| Long term follow-up duration                              | 55 Months        |
| Independent data monitoring committee (IDMC) involvement? | No               |

Notes:

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**Population of trial subjects**

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**Subjects enrolled per country**

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|                                      |           |
|--------------------------------------|-----------|
| Country: Number of subjects enrolled | Spain: 72 |
| Worldwide total number of subjects   | 72        |
| EEA total number of subjects         | 72        |

Notes:

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**Subjects enrolled per age group**

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|                                           |    |
|-------------------------------------------|----|
| 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)                      | 26 |
| From 65 to 84 years                       | 46 |
| 85 years and over                         | 0  |

## Subject disposition

### Recruitment

Recruitment details:

A total of 72 subjects were recruited at 20 sites in Spain.

### Pre-assignment

Screening details:

Subjects enrolled in the study had documented CD20-positive B-cell type relapsed or refractory chronic lymphocytic leukemia (CLL).

### Period 1

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

### Arms

|                  |                             |
|------------------|-----------------------------|
| <b>Arm title</b> | Obinutuzumab + Bendamustine |
|------------------|-----------------------------|

Arm description:

Subjects received obinutuzumab and bendamustine in 28-days cycles for a maximum of 6 cycles.

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

Dosage and administration details:

70 milligrams per square meter (mg/m<sup>2</sup>) given by intravenous (IV) infusion on Days 2 and 3 of Cycle 1 and on Days 1 and 2 of subsequent cycles.

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

Dosage and administration details:

1000 mg given by IV infusion on Days 1, 8, and 15 of Cycle 1 and on Day 1 of subsequent cycles.

| Number of subjects in period 1 | Obinutuzumab + Bendamustine |
|--------------------------------|-----------------------------|
| Started                        | 72                          |
| Completed                      | 42                          |
| Not completed                  | 30                          |
| Withdrawal of Consent          | 2                           |
| Protocol Deviation             | 1                           |
| Death                          | 25                          |
| Lost to follow-up              | 2                           |



## Baseline characteristics

### Reporting groups

|                       |                             |
|-----------------------|-----------------------------|
| Reporting group title | Obinutuzumab + Bendamustine |
|-----------------------|-----------------------------|

Reporting group description:

Subjects received obinutuzumab and bendamustine in 28-days cycles for a maximum of 6 cycles.

| Reporting group values | Obinutuzumab + Bendamustine | Total |  |
|------------------------|-----------------------------|-------|--|
| Number of subjects     | 72                          | 72    |  |
| Age categorical        |                             |       |  |
| Units: Subjects        |                             |       |  |
| Adults (18-64 years)   | 26                          | 26    |  |
| From 65-84 years       | 46                          | 46    |  |
| Age Continuous         |                             |       |  |
| Units: years           |                             |       |  |
| median                 | 67.9                        |       |  |
| full range (min-max)   | 42.5 to 83.1                | -     |  |
| Sex: Female, Male      |                             |       |  |
| Units: Subjects        |                             |       |  |
| Female                 | 24                          | 24    |  |
| Male                   | 48                          | 48    |  |

## End points

### End points reporting groups

|                                                                                              |                             |
|----------------------------------------------------------------------------------------------|-----------------------------|
| Reporting group title                                                                        | Obinutuzumab + Bendamustine |
| Reporting group description:                                                                 |                             |
| Subjects received obinutuzumab and bendamustine in 28-days cycles for a maximum of 6 cycles. |                             |

### Primary: Overall Response Rate (ORR) as Assessed by the Investigator Using the International Workshop on Chronic Lymphocytic Leukemia (IWCLL) 2008 Criteria

|                 |                                                                                                                                                                   |
|-----------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| End point title | Overall Response Rate (ORR) as Assessed by the Investigator Using the International Workshop on Chronic Lymphocytic Leukemia (IWCLL) 2008 Criteria <sup>[1]</sup> |
|-----------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------|

#### End point description:

ORR was defined as percentage of subjects achieving Complete Response (CR), incomplete CR (CRi) or Partial Response (PR). CR: lymphocytes below  $4 \times 10^9/L$ , absence of lymphadenopathy, hepatomegaly and splenomegaly, absence of disease or constitutional symptoms, neutrophils  $> 1.5 \times 10^9/L$ , platelets  $> 100 \times 10^9/L$ , hemoglobin  $> 110 \text{ g/L}$ , bone marrow at least normocellular for age. CRi: CR with persistent cytopenia, i.e. anemia, thrombocytopenia and/or neutropenia. PR: reduction  $\geq 50\%$  of the lymphocyte count AND reduction  $\geq 50\%$  of the lymphadenopathy OR reduction  $\geq 50\%$  of the size of the liver if enlarged at baseline OR reduction  $\geq 50\%$  of the size of the spleen if enlarged at baseline PLUS one of the following: neutrophils  $> 1.5 \times 10^9/L$ , platelets  $> 100 \times 10^9/L$ , hemoglobin  $> 110 \text{ g/L}$  or increase  $\geq 50\%$  compared to pre-treatment. Efficacy population included all subjects, who received at least one dose of both treatments (bendamustine and obinutuzumab).

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

#### End point timeframe:

2-3 months after last dose of the study treatment (up to approximately 9 months)

#### Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No statistical analyses were planned for this one arm study.

|                                  |                             |  |  |  |
|----------------------------------|-----------------------------|--|--|--|
| <b>End point values</b>          | Obinutuzumab + Bendamustine |  |  |  |
| Subject group type               | Reporting group             |  |  |  |
| Number of subjects analysed      | 70                          |  |  |  |
| Units: percentage of subjects    |                             |  |  |  |
| number (confidence interval 95%) | 78.6 (66.8 to 87.1)         |  |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Best Response Rate (BRR) as Assessed by the Investigator Using the IWCLL 2008 Criteria

|                 |                                                                                        |
|-----------------|----------------------------------------------------------------------------------------|
| End point title | Best Response Rate (BRR) as Assessed by the Investigator Using the IWCLL 2008 Criteria |
|-----------------|----------------------------------------------------------------------------------------|

#### End point description:

Best overall response was defined as percentage of subjects achieving a BR of CR, CRi and PR. CR: lymphocytes below  $4 \times 10^9/L$ , absence of lymphadenopathy, hepatomegaly and splenomegaly, absence

of disease or constitutional symptoms, neutrophils  $>1.5 \times 10^9/L$ , platelets  $>100 \times 10^9/L$ , hemoglobin  $>110$  g/L, bone marrow at least normocellular for age. CRi: CR with persistent cytopenia, i.e. anemia, thrombocytopenia and/or neutropenia. PR: reduction  $\geq 50\%$  of the lymphocyte count AND reduction  $\geq 50\%$  of the lymphadenopathy OR reduction  $\geq 50\%$  of the size of liver if enlarged at baseline OR reduction  $\geq 50\%$  of the size of the spleen if enlarged at baseline PLUS one of the following: neutrophils  $>1.5 \times 10^9/L$ , platelets  $>100 \times 10^9/L$ , hemoglobin  $>110$  g/L or increase  $\geq 50\%$  compared to pre-treatment. Efficacy population included all subjects, who received at least one dose of both treatments (bendamustine and obinutuzumab). Reported here is the number of subjects for whom data for BR achieved were available.

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

End point timeframe:

During study treatment and until 6 months after end of study treatment at approximately 12 months

|                               |                                   |  |  |  |
|-------------------------------|-----------------------------------|--|--|--|
| <b>End point values</b>       | Obinutuzumab<br>+<br>Bendamustine |  |  |  |
| Subject group type            | Reporting group                   |  |  |  |
| Number of subjects analysed   | 54                                |  |  |  |
| Units: percentage of subjects |                                   |  |  |  |
| number (not applicable)       |                                   |  |  |  |
| CR                            | 46.3                              |  |  |  |
| CRi                           | 1.9                               |  |  |  |
| PR                            | 42.6                              |  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Progression Free Survival (PFS)

|                 |                                 |
|-----------------|---------------------------------|
| End point title | Progression Free Survival (PFS) |
|-----------------|---------------------------------|

End point description:

PFS is defined as the time from the start of treatment to disease progression (DP), relapse or death from any cause, whichever occurs first, as assessed by the investigator. DP: at least one of the following characteristics: increase  $\geq 50\%$  in lymphocytes up to at least  $5 \times 10^9/L$ , appearance of new palpable lymph nodes, increase  $\geq 50\%$  of the longest diameter of any previous area of clinically significant lymphadenopathy, increase  $\geq 50\%$  of the size of the liver and/or spleen, transformation to a more aggressive histology, after treatment progression of any cytopenia: decrease of hemoglobin levels of more than 20 g/L or to below 100 g/L and/or decrease of platelet counts by more than 50% or to below  $100 \times 10^9/L$  and/or decrease in the neutrophil counts by more than 50% or to below  $1.0 \times 10^9/L$  if the marrow biopsy also shows infiltration of clonal CLL cells. Efficacy population included all subjects, who received at least one dose of both treatments (bendamustine and obinutuzumab).

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

End point timeframe:

From start of treatment up to disease progression or relapse or death, whichever occurred first (up to approximately 4.5 years)

|                                  |                                   |  |  |  |
|----------------------------------|-----------------------------------|--|--|--|
| <b>End point values</b>          | Obinutuzumab<br>+<br>Bendamustine |  |  |  |
| Subject group type               | Reporting group                   |  |  |  |
| Number of subjects analysed      | 70                                |  |  |  |
| Units: months                    |                                   |  |  |  |
| median (confidence interval 95%) | 24.14 (20.81<br>to 27.47)         |  |  |  |

## 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 the start of study treatment to death from any cause. Efficacy population included all subjects, who received at least one dose of both treatments (bendamustine and obinutuzumab). Here, 99999 indicates that median of OS for efficacy population was not reached. |                       |
| End point type                                                                                                                                                                                                                                                                                       | Secondary             |
| End point timeframe:                                                                                                                                                                                                                                                                                 |                       |
| From start of treatment up to death of any cause (up to approximately 4.5 years)                                                                                                                                                                                                                     |                       |

|                                  |                                   |  |  |  |
|----------------------------------|-----------------------------------|--|--|--|
| <b>End point values</b>          | Obinutuzumab<br>+<br>Bendamustine |  |  |  |
| Subject group type               | Reporting group                   |  |  |  |
| Number of subjects analysed      | 70                                |  |  |  |
| Units: months                    |                                   |  |  |  |
| median (confidence interval 95%) | 99999 (99999<br>to 99999)         |  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Event Free Survival (EFS)

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                           |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------|
| End point title                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | Event Free Survival (EFS) |
| End point description:                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |                           |
| EFS was defined as the time from the start of treatment to DP/relapse, death from any cause or start of a new anti-leukemia therapy. DP: at least one of the following characteristics: increase $\geq 50\%$ in lymphocytes up to at least $5 \times 10^9/L$ , appearance of new palpable lymph nodes, increase $\geq 50\%$ of the longest diameter of any previous area of clinically significant lymphadenopathy, increase $\geq 50\%$ of the size of the liver and/or spleen, transformation to a more aggressive histology, after treatment, progression of any cytopenia: decrease of hemoglobin levels of more than 20 g/L or to below 100 g/L and/or decrease of platelet counts by more than 50% or to below $100 \times 10^9/L$ and/or decrease in the neutrophil counts by more than 50% or to below $1.0 \times 10^9/L$ if the marrow biopsy also shows infiltration of clonal CLL cells. Efficacy population included all subjects, who received at least one dose of both treatments (bendamustine and obinutuzumab). |                           |



|                                                                                                                                                                         |           |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------|
| End point type                                                                                                                                                          | Secondary |
| End point timeframe:                                                                                                                                                    |           |
| From start of treatment up to disease progression or relapse or death or start of a new anti-leukemic therapy, whichever occurred first (up to approximately 4.5 years) |           |

|                                  |                             |  |  |  |
|----------------------------------|-----------------------------|--|--|--|
| <b>End point values</b>          | Obinutuzumab + Bendamustine |  |  |  |
| Subject group type               | Reporting group             |  |  |  |
| Number of subjects analysed      | 70                          |  |  |  |
| Units: months                    |                             |  |  |  |
| median (confidence interval 95%) | 24.14 (19.96 to 28.32)      |  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Disease Free Survival (DFS)

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |                             |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------|
| End point title                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | Disease Free Survival (DFS) |
| End point description:                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |                             |
| DFS was defined for all subjects who achieved CRi or CR. DFS lasted from the date on which CRi or CR was recorded until date on which first DP or death from any cause occurred. DP: at least one: increase $\geq 50\%$ in lymphocytes up to at least $5 \times 10^9/L$ , appearance of new palpable lymph nodes, increase $\geq 50\%$ of longest diameter of any previous area of clinically significant lymphadenopathy, increase $\geq 50\%$ of size of liver and/or spleen, transformation to a more aggressive histology, after treatment, progression of any cytopenia: decrease of hemoglobin levels of more than 20 g/L or to below 100 g/L and/or decrease of platelet counts by more than 50% or to below $100 \times 10^9/L$ and/or decrease in neutrophil counts by more than 50% or to below $1.0 \times 10^9/L$ if marrow biopsy also shows infiltration of clonal CLL cells. Efficacy population included all subjects, who received at least one dose of both treatments (bendamustine and obinutuzumab). Included in the analysis are subjects who achieved CRi or CR. |                             |
| End point type                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | Secondary                   |
| End point timeframe:                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                             |
| From occurrence of complete response up to disease progression or death, whichever occurred first (up to approximately 4.5 years)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |                             |

|                                  |                             |  |  |  |
|----------------------------------|-----------------------------|--|--|--|
| <b>End point values</b>          | Obinutuzumab + Bendamustine |  |  |  |
| Subject group type               | Reporting group             |  |  |  |
| Number of subjects analysed      | 25                          |  |  |  |
| Units: months                    |                             |  |  |  |
| median (confidence interval 95%) | 23.02 (21.38 to 24.66)      |  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Duration of Response (DR)

|                 |                           |
|-----------------|---------------------------|
| End point title | Duration of Response (DR) |
|-----------------|---------------------------|

End point description:

DR was defined for subjects with CRi, CR or PR. DR spanned from date on which response was recorded until the date on which DP or death from any cause occurred. DP: at least one: increase  $\geq 50\%$  in lymphocytes up to at least  $5 \times 10^9/L$ , appearance of new palpable lymph nodes, increase  $\geq 50\%$  of the longest diameter of any previous area of clinically significant lymphadenopathy, increase  $\geq 50\%$  of size of liver and/or spleen, transformation to a more aggressive histology, after treatment, progression of any cytopenia: decrease of hemoglobin levels of more than 20 g/L or to below 100 g/L and/or decrease of platelet counts by more than 50% or to below  $100 \times 10^9/L$  and/or decrease in neutrophil counts by more than 50% or to below  $1.0 \times 10^9/L$  if marrow biopsy also shows infiltration of clonal CLL cells. Efficacy population included all subjects, who received at least one dose of both treatments (bendamustine and obinutuzumab). Included in the analysis are subjects who achieved CRi, CR or PR.

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

End point timeframe:

From occurrence of CR or PR up to disease progression or death, whichever occurred first (up to approximately 4.5 years)

|                                  |                                   |  |  |  |
|----------------------------------|-----------------------------------|--|--|--|
| <b>End point values</b>          | Obinutuzumab<br>+<br>Bendamustine |  |  |  |
| Subject group type               | Reporting group                   |  |  |  |
| Number of subjects analysed      | 54                                |  |  |  |
| Units: months                    |                                   |  |  |  |
| median (confidence interval 95%) | 21.41 (17.60<br>to 25.22)         |  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Time to Re-treatment/New Anti-leukemia Therapy

|                 |                                                |
|-----------------|------------------------------------------------|
| End point title | Time to Re-treatment/New Anti-leukemia Therapy |
|-----------------|------------------------------------------------|

End point description:

Time to re-treatment/new leukemia therapy was defined as the time between the start of treatment and the date of the first administration of re-treatment or new leukemia therapy. Efficacy population included all subjects, who received at least one dose of both treatments (bendamustine and obinutuzumab). Here, 99999 indicates that median of time to re-treatment for efficacy population was not reached.

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

End point timeframe:

Up to 4.5 years

|                                  |                                   |  |  |  |
|----------------------------------|-----------------------------------|--|--|--|
| <b>End point values</b>          | Obinutuzumab<br>+<br>Bendamustine |  |  |  |
| Subject group type               | Reporting group                   |  |  |  |
| Number of subjects analysed      | 70                                |  |  |  |
| Units: months                    |                                   |  |  |  |
| median (confidence interval 95%) | 99999 (99999<br>to 99999)         |  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Percentage of Subjects With Minimal Residual Disease (MRD) Negativity

|                                                                                                                                                                                                                                                                                                                                                                       |                                                                       |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------|
| End point title                                                                                                                                                                                                                                                                                                                                                       | Percentage of Subjects With Minimal Residual Disease (MRD) Negativity |
| End point description:                                                                                                                                                                                                                                                                                                                                                |                                                                       |
| MRD negativity was defined as the presence of less than 1 cell of CLL per 10,000 leukocytes (= category 0, <0.01%) assessed in bone marrow (BM) and peripheral blood (PB) by flow cytometry after the end of the treatment at the final response assessment. Intent-to-treat (ITT) population included all subjects, who received at least one dose of any treatment. |                                                                       |
| End point type                                                                                                                                                                                                                                                                                                                                                        | Secondary                                                             |
| End point timeframe:                                                                                                                                                                                                                                                                                                                                                  |                                                                       |
| At approximately 9 months                                                                                                                                                                                                                                                                                                                                             |                                                                       |

|                               |                                   |  |  |  |
|-------------------------------|-----------------------------------|--|--|--|
| <b>End point values</b>       | Obinutuzumab<br>+<br>Bendamustine |  |  |  |
| Subject group type            | Reporting group                   |  |  |  |
| Number of subjects analysed   | 72                                |  |  |  |
| Units: percentage of subjects |                                   |  |  |  |
| number (not applicable)       |                                   |  |  |  |
| MRD in BM: Cat 0              | 36.4                              |  |  |  |
| MRD in PB: Cat 0              | 53.4                              |  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Percentage of Subjects With Adverse Events (AEs) and Serious Adverse Events (SAEs)

|                                                                                                                                                                                                                                                                                                                                                                                                           |                                                                                    |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------|
| End point title                                                                                                                                                                                                                                                                                                                                                                                           | Percentage of Subjects With Adverse Events (AEs) and Serious Adverse Events (SAEs) |
| End point description:                                                                                                                                                                                                                                                                                                                                                                                    |                                                                                    |
| An AE is any untoward medical occurrence in a subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with the treatment. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a pharmaceutical product, whether or not |                                                                                    |

considered related to the pharmaceutical product. Preexisting conditions which worsen during a study are also considered as AEs. An SAE was any AE that was any of the following: fatal, life-threatening, required or prolonged inpatient hospitalisation, resulted in persistent or significant disability/incapacity, was a congenital anomaly/ birth defect, and was considered a significant medical event by the investigator. Safety population included all subjects, who received at least one dose of any treatment.

|                               |           |
|-------------------------------|-----------|
| End point type                | Secondary |
| End point timeframe:          |           |
| Up to approximately 4.5 years |           |

|                               |                                   |  |  |  |
|-------------------------------|-----------------------------------|--|--|--|
| <b>End point values</b>       | Obinutuzumab<br>+<br>Bendamustine |  |  |  |
| Subject group type            | Reporting group                   |  |  |  |
| Number of subjects analysed   | 72                                |  |  |  |
| Units: percentage of subjects |                                   |  |  |  |
| number (not applicable)       |                                   |  |  |  |
| AEs                           | 94.4                              |  |  |  |
| SAEs                          | 51.4                              |  |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Percentage of Subjects With AEs of Special Interest (AESIs)

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                                                             |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------|
| End point title                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | Percentage of Subjects With AEs of Special Interest (AESIs) |
| End point description:                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |                                                             |
| AESIs included any of the following: SAEs associated with the infusion of obinutuzumab: obinutuzumab serious infusion-related reactions, which were defined as AEs occurring during or within 24 hours following the administration of an infusion of obinutuzumab and considered related to obinutuzumab; serious infection; serious neutropenia; any tumor lysis syndrome (TLS); second malignancies. Safety population included all subjects, who received at least one dose of any treatment. |                                                             |
| End point type                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | Secondary                                                   |
| End point timeframe:                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                                                             |
| Up to approximately 4.5 years                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                                                             |

|                               |                                   |  |  |  |
|-------------------------------|-----------------------------------|--|--|--|
| <b>End point values</b>       | Obinutuzumab<br>+<br>Bendamustine |  |  |  |
| Subject group type            | Reporting group                   |  |  |  |
| Number of subjects analysed   | 72                                |  |  |  |
| Units: percentage of subjects |                                   |  |  |  |
| number (not applicable)       | 45.8                              |  |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Percentage of Subjects With Infusion-related Reactions (IRRs)

|                 |                                                               |
|-----------------|---------------------------------------------------------------|
| End point title | Percentage of Subjects With Infusion-related Reactions (IRRs) |
|-----------------|---------------------------------------------------------------|

End point description:

IRRs were defined as AEs occurring during or within 24 hours following the administration of an infusion and considered related to drug treatment. Safety population included all subjects, who received at least one dose of any treatment.

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

End point timeframe:

Up to end of treatment at 6 months

|                               |                                   |  |  |  |
|-------------------------------|-----------------------------------|--|--|--|
| <b>End point values</b>       | Obinutuzumab<br>+<br>Bendamustine |  |  |  |
| Subject group type            | Reporting group                   |  |  |  |
| Number of subjects analysed   | 72                                |  |  |  |
| Units: percentage of subjects |                                   |  |  |  |
| number (not applicable)       | 20.8                              |  |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Percentage of Subjects Who Discontinued Treatment Prematurely

|                 |                                                               |
|-----------------|---------------------------------------------------------------|
| End point title | Percentage of Subjects Who Discontinued Treatment Prematurely |
|-----------------|---------------------------------------------------------------|

End point description:

Safety population included all subjects, who received at least one dose of any treatment.

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

End point timeframe:

Up to end of treatment at 6 months

|                               |                                   |  |  |  |
|-------------------------------|-----------------------------------|--|--|--|
| <b>End point values</b>       | Obinutuzumab<br>+<br>Bendamustine |  |  |  |
| Subject group type            | Reporting group                   |  |  |  |
| Number of subjects analysed   | 72                                |  |  |  |
| Units: percentage of subjects |                                   |  |  |  |
| number (not applicable)       | 41.7                              |  |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Percentage of Subjects With Previous/Concomitant Diseases

End point title Percentage of Subjects With Previous/Concomitant Diseases

End point description:

Safety population included all subjects, who received at least one dose of any treatment.

End point type Secondary

End point timeframe:

Up to approximately 4.5 years

| End point values              | Obinutuzumab<br>+<br>Bendamustine |  |  |  |
|-------------------------------|-----------------------------------|--|--|--|
| Subject group type            | Reporting group                   |  |  |  |
| Number of subjects analysed   | 72                                |  |  |  |
| Units: percentage of subjects |                                   |  |  |  |
| number (not applicable)       | 97.2                              |  |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Percentage of Subjects With Concomitant Medication

End point title Percentage of Subjects With Concomitant Medication

End point description:

Concomitant therapies included any medication (prescription medication, over-the-counter medications, herbal/homeopathic remedies, nutritional supplements) used by subjects in the 7 days prior to screening until the end of treatment. The following treatments were not permitted during the study treatment period: investigational or unauthorized or unapproved medicinal products, immunotherapy or radioimmunotherapy (other than the trial immunotherapy, obinutuzumab), chemotherapy (other than the trial chemotherapy, bendamustine) and radiotherapy. Safety population included all subjects, who received at least one dose of any treatment.

End point type Secondary

End point timeframe:

From 7 days prior to screening to the end of treatment at 6 months

| End point values              | Obinutuzumab<br>+<br>Bendamustine |  |  |  |
|-------------------------------|-----------------------------------|--|--|--|
| Subject group type            | Reporting group                   |  |  |  |
| Number of subjects analysed   | 72                                |  |  |  |
| Units: percentage of subjects |                                   |  |  |  |
| number (not applicable)       | 54.2                              |  |  |  |

## **Statistical analyses**

---

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Up to approximately 4.5 years

Adverse event reporting additional description:

Safety population included all subjects, who received at least one dose of any treatment.

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

### Dictionary used

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

|                    |      |
|--------------------|------|
| Dictionary version | 20.1 |
|--------------------|------|

### Reporting groups

|                       |                             |
|-----------------------|-----------------------------|
| Reporting group title | Obinutuzumab + Bendamustine |
|-----------------------|-----------------------------|

Reporting group description:

Subjects received obinutuzumab and bendamustine in 28-days cycles for a maximum of 6 cycles.

| Serious adverse events                                              | Obinutuzumab + Bendamustine |  |  |
|---------------------------------------------------------------------|-----------------------------|--|--|
| Total subjects affected by serious adverse events                   |                             |  |  |
| subjects affected / exposed                                         | 37 / 72 (51.39%)            |  |  |
| number of deaths (all causes)                                       | 25                          |  |  |
| number of deaths resulting from adverse events                      | 2                           |  |  |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                             |  |  |
| Gastrointestinal stromal tumour                                     |                             |  |  |
| subjects affected / exposed                                         | 1 / 72 (1.39%)              |  |  |
| occurrences causally related to treatment / all                     | 1 / 1                       |  |  |
| deaths causally related to treatment / all                          | 0 / 0                       |  |  |
| Glioblastoma multiforme                                             |                             |  |  |
| subjects affected / exposed                                         | 1 / 72 (1.39%)              |  |  |
| occurrences causally related to treatment / all                     | 0 / 1                       |  |  |
| deaths causally related to treatment / all                          | 0 / 1                       |  |  |
| Laryngeal squamous cell carcinoma                                   |                             |  |  |
| subjects affected / exposed                                         | 1 / 72 (1.39%)              |  |  |
| occurrences causally related to treatment / all                     | 0 / 1                       |  |  |
| deaths causally related to treatment / all                          | 0 / 0                       |  |  |
| Lung neoplasm malignant                                             |                             |  |  |



|                                                 |                 |  |  |
|-------------------------------------------------|-----------------|--|--|
| subjects affected / exposed                     | 1 / 72 (1.39%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 1           |  |  |
| Squamous cell carcinoma of lung                 |                 |  |  |
| subjects affected / exposed                     | 1 / 72 (1.39%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Vascular disorders                              |                 |  |  |
| Hypertensive crisis                             |                 |  |  |
| subjects affected / exposed                     | 1 / 72 (1.39%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Cardiac disorders                               |                 |  |  |
| Dyspnoea                                        |                 |  |  |
| subjects affected / exposed                     | 1 / 72 (1.39%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Blood and lymphatic system disorders            |                 |  |  |
| Neutropenia                                     |                 |  |  |
| subjects affected / exposed                     | 9 / 72 (12.50%) |  |  |
| occurrences causally related to treatment / all | 11 / 12         |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Febrile neutropenia                             |                 |  |  |
| subjects affected / exposed                     | 8 / 72 (11.11%) |  |  |
| occurrences causally related to treatment / all | 6 / 10          |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Acute myeloid leukaemia                         |                 |  |  |
| subjects affected / exposed                     | 1 / 72 (1.39%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 1           |  |  |
| Acute myelomonocytic leukaemia                  |                 |  |  |
| subjects affected / exposed                     | 1 / 72 (1.39%)  |  |  |
| occurrences causally related to treatment / all | 1 / 1           |  |  |
| deaths causally related to treatment / all      | 1 / 1           |  |  |

|                                                      |                 |  |  |
|------------------------------------------------------|-----------------|--|--|
| Haemophagocytic lymphohistiocytosis                  |                 |  |  |
| subjects affected / exposed                          | 1 / 72 (1.39%)  |  |  |
| occurrences causally related to treatment / all      | 0 / 1           |  |  |
| deaths causally related to treatment / all           | 0 / 0           |  |  |
| Thrombocytopenia                                     |                 |  |  |
| subjects affected / exposed                          | 1 / 72 (1.39%)  |  |  |
| occurrences causally related to treatment / all      | 1 / 1           |  |  |
| deaths causally related to treatment / all           | 0 / 0           |  |  |
| General disorders and administration site conditions |                 |  |  |
| Pyrexia                                              |                 |  |  |
| subjects affected / exposed                          | 8 / 72 (11.11%) |  |  |
| occurrences causally related to treatment / all      | 3 / 8           |  |  |
| deaths causally related to treatment / all           | 0 / 0           |  |  |
| Infusion related reaction                            |                 |  |  |
| subjects affected / exposed                          | 2 / 72 (2.78%)  |  |  |
| occurrences causally related to treatment / all      | 2 / 2           |  |  |
| deaths causally related to treatment / all           | 0 / 0           |  |  |
| Multiple organ dysfunction syndrome                  |                 |  |  |
| subjects affected / exposed                          | 2 / 72 (2.78%)  |  |  |
| occurrences causally related to treatment / all      | 0 / 2           |  |  |
| deaths causally related to treatment / all           | 0 / 2           |  |  |
| Cachexia                                             |                 |  |  |
| subjects affected / exposed                          | 1 / 72 (1.39%)  |  |  |
| occurrences causally related to treatment / all      | 0 / 1           |  |  |
| deaths causally related to treatment / all           | 0 / 0           |  |  |
| Malaise                                              |                 |  |  |
| subjects affected / exposed                          | 1 / 72 (1.39%)  |  |  |
| occurrences causally related to treatment / all      | 0 / 1           |  |  |
| deaths causally related to treatment / all           | 0 / 1           |  |  |
| Mucosal inflammation                                 |                 |  |  |
| subjects affected / exposed                          | 1 / 72 (1.39%)  |  |  |
| occurrences causally related to treatment / all      | 0 / 1           |  |  |
| deaths causally related to treatment / all           | 0 / 0           |  |  |

|                                                 |                 |  |  |
|-------------------------------------------------|-----------------|--|--|
| Gastrointestinal disorders                      |                 |  |  |
| Diarrhoea                                       |                 |  |  |
| subjects affected / exposed                     | 2 / 72 (2.78%)  |  |  |
| occurrences causally related to treatment / all | 2 / 3           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Gastroenteritis                                 |                 |  |  |
| subjects affected / exposed                     | 1 / 72 (1.39%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Upper gastrointestinal haemorrhage              |                 |  |  |
| subjects affected / exposed                     | 1 / 72 (1.39%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Respiratory, thoracic and mediastinal disorders |                 |  |  |
| Bronchiolitis                                   |                 |  |  |
| subjects affected / exposed                     | 1 / 72 (1.39%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Interstitial lung disease                       |                 |  |  |
| subjects affected / exposed                     | 1 / 72 (1.39%)  |  |  |
| occurrences causally related to treatment / all | 1 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Infections and infestations                     |                 |  |  |
| Pneumonia                                       |                 |  |  |
| subjects affected / exposed                     | 8 / 72 (11.11%) |  |  |
| occurrences causally related to treatment / all | 2 / 9           |  |  |
| deaths causally related to treatment / all      | 0 / 2           |  |  |
| Respiratory tract infection                     |                 |  |  |
| subjects affected / exposed                     | 6 / 72 (8.33%)  |  |  |
| occurrences causally related to treatment / all | 2 / 6           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Septic shock                                    |                 |  |  |

|                                                 |                |  |  |  |
|-------------------------------------------------|----------------|--|--|--|
| subjects affected / exposed                     | 3 / 72 (4.17%) |  |  |  |
| occurrences causally related to treatment / all | 1 / 4          |  |  |  |
| deaths causally related to treatment / all      | 1 / 1          |  |  |  |
| Bronchitis                                      |                |  |  |  |
| subjects affected / exposed                     | 2 / 72 (2.78%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 4          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |
| Sepsis                                          |                |  |  |  |
| subjects affected / exposed                     | 2 / 72 (2.78%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 2          |  |  |  |
| deaths causally related to treatment / all      | 0 / 1          |  |  |  |
| Abdominal Sepsis                                |                |  |  |  |
| subjects affected / exposed                     | 1 / 72 (1.39%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |
| Bronchopulmonary aspergillosis                  |                |  |  |  |
| subjects affected / exposed                     | 1 / 72 (1.39%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |
| Lung Infection                                  |                |  |  |  |
| subjects affected / exposed                     | 1 / 72 (1.39%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |
| Periorbital cellulitis                          |                |  |  |  |
| subjects affected / exposed                     | 1 / 72 (1.39%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |
| Respiratory syncytial virus infection           |                |  |  |  |
| subjects affected / exposed                     | 1 / 72 (1.39%) |  |  |  |
| occurrences causally related to treatment / all | 1 / 1          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |
| Rotavirus infection                             |                |  |  |  |

|                                                 |                |  |  |
|-------------------------------------------------|----------------|--|--|
| subjects affected / exposed                     | 1 / 72 (1.39%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Serratia sepsis                                 |                |  |  |
| subjects affected / exposed                     | 1 / 72 (1.39%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Tuberculosis                                    |                |  |  |
| subjects affected / exposed                     | 1 / 72 (1.39%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 1          |  |  |
| Upper respiratory tract infection               |                |  |  |
| subjects affected / exposed                     | 1 / 72 (1.39%) |  |  |
| occurrences causally related to treatment / all | 1 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Urinary tract infection                         |                |  |  |
| subjects affected / exposed                     | 1 / 72 (1.39%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Metabolism and nutrition disorders              |                |  |  |
| Hyponatraemia                                   |                |  |  |
| subjects affected / exposed                     | 1 / 72 (1.39%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |

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

|                                                       |                             |  |  |
|-------------------------------------------------------|-----------------------------|--|--|
| <b>Non-serious adverse events</b>                     | Obinutuzumab + Bendamustine |  |  |
| Total subjects affected by non-serious adverse events |                             |  |  |
| subjects affected / exposed                           | 67 / 72 (93.06%)            |  |  |
| Vascular disorders                                    |                             |  |  |
| Hypotension                                           |                             |  |  |
| subjects affected / exposed                           | 4 / 72 (5.56%)              |  |  |
| occurrences (all)                                     | 4                           |  |  |

|                                                      |                  |  |  |
|------------------------------------------------------|------------------|--|--|
| Cardiac disorders                                    |                  |  |  |
| Dyspnoea                                             |                  |  |  |
| subjects affected / exposed                          | 6 / 72 (8.33%)   |  |  |
| occurrences (all)                                    | 7                |  |  |
| Chest pain                                           |                  |  |  |
| subjects affected / exposed                          | 4 / 72 (5.56%)   |  |  |
| occurrences (all)                                    | 4                |  |  |
| Nervous system disorders                             |                  |  |  |
| Headache                                             |                  |  |  |
| subjects affected / exposed                          | 4 / 72 (5.56%)   |  |  |
| occurrences (all)                                    | 4                |  |  |
| Tremor                                               |                  |  |  |
| subjects affected / exposed                          | 4 / 72 (5.56%)   |  |  |
| occurrences (all)                                    | 4                |  |  |
| Blood and lymphatic system disorders                 |                  |  |  |
| Neutropenia                                          |                  |  |  |
| subjects affected / exposed                          | 48 / 72 (66.67%) |  |  |
| occurrences (all)                                    | 147              |  |  |
| Thrombocytopenia                                     |                  |  |  |
| subjects affected / exposed                          | 30 / 72 (41.67%) |  |  |
| occurrences (all)                                    | 51               |  |  |
| Anaemia                                              |                  |  |  |
| subjects affected / exposed                          | 14 / 72 (19.44%) |  |  |
| occurrences (all)                                    | 35               |  |  |
| General disorders and administration site conditions |                  |  |  |
| Asthenia                                             |                  |  |  |
| subjects affected / exposed                          | 28 / 72 (38.89%) |  |  |
| occurrences (all)                                    | 37               |  |  |
| Pyrexia                                              |                  |  |  |
| subjects affected / exposed                          | 27 / 72 (37.50%) |  |  |
| occurrences (all)                                    | 38               |  |  |
| Infusion related reaction                            |                  |  |  |
| subjects affected / exposed                          | 13 / 72 (18.06%) |  |  |
| occurrences (all)                                    | 14               |  |  |
| Gastrointestinal disorders                           |                  |  |  |

|                                                                                                              |                        |  |  |
|--------------------------------------------------------------------------------------------------------------|------------------------|--|--|
| Nausea<br>subjects affected / exposed<br>occurrences (all)                                                   | 17 / 72 (23.61%)<br>22 |  |  |
| Diarrhoea<br>subjects affected / exposed<br>occurrences (all)                                                | 16 / 72 (22.22%)<br>22 |  |  |
| Constipation<br>subjects affected / exposed<br>occurrences (all)                                             | 9 / 72 (12.50%)<br>11  |  |  |
| Vomiting<br>subjects affected / exposed<br>occurrences (all)                                                 | 8 / 72 (11.11%)<br>10  |  |  |
| Abdominal pain<br>subjects affected / exposed<br>occurrences (all)                                           | 5 / 72 (6.94%)<br>6    |  |  |
| Abdominal pain upper<br>subjects affected / exposed<br>occurrences (all)                                     | 4 / 72 (5.56%)<br>4    |  |  |
| Hepatobiliary disorders<br>Hypertransaminasaemia<br>subjects affected / exposed<br>occurrences (all)         | 4 / 72 (5.56%)<br>4    |  |  |
| Respiratory, thoracic and mediastinal disorders<br>Cough<br>subjects affected / exposed<br>occurrences (all) | 11 / 72 (15.28%)<br>13 |  |  |
| Nasopharyngitis<br>subjects affected / exposed<br>occurrences (all)                                          | 9 / 72 (12.50%)<br>9   |  |  |
| Skin and subcutaneous tissue disorders<br>Pruritus<br>subjects affected / exposed<br>occurrences (all)       | 9 / 72 (12.50%)<br>9   |  |  |
| Rash<br>subjects affected / exposed<br>occurrences (all)                                                     | 6 / 72 (8.33%)<br>6    |  |  |

|                                                                                                                                                                                                                                                                            |                                                                                          |  |  |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------|--|--|
| Infections and infestations<br>Respiratory tract infection<br>subjects affected / exposed<br>occurrences (all)<br><br>Urinary tract infection<br>subjects affected / exposed<br>occurrences (all)<br><br>Herpes zoster<br>subjects affected / exposed<br>occurrences (all) | 19 / 72 (26.39%)<br><br>23<br><br>6 / 72 (8.33%)<br><br>7<br><br>5 / 72 (6.94%)<br><br>6 |  |  |
| Metabolism and nutrition disorders<br>Decreased appetite<br>subjects affected / exposed<br>occurrences (all)                                                                                                                                                               | 5 / 72 (6.94%)<br><br>7                                                                  |  |  |



## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date            | Amendment                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
|-----------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 27 March 2014   | <p>Protocol was amended to reflect changes in the safety profile of obinutuzumab with regard to a higher incidence of thrombocytopenia and haemorrhagic events during the first cycle in patients with CLL treated with obinutuzumab plus chlorambucil, as compared to patients treated with rituximab plus chlorambucil or chlorambucil alone, in the phase 3 pivotal study BO21004/2009-012476-28. Patients who experienced Grade 3 or 4 neutropenia were to be monitored until neutrophil values returned to at least Grade 2. The use of G-CSF was allowed for treatment of neutropenia in this study. Primary prophylaxis with G-CSF was recommended according to the American Society of Clinical Oncology (ASCO), the European Organisation for Research and Treatment of Cancer (EORTC), and European Society for Medical Oncology (ESMO) guidelines, namely for patients who were <math>\geq 60</math> years old and/or with co-morbidities. Severe and life-threatening thrombocytopenia including acute thrombocytopenia (occurring within 24 hours after the infusion) had been observed during treatment with obinutuzumab. Fatal haemorrhagic events had also been reported in subjects treated with obinutuzumab. It seemed that the first cycle was the greatest risk of haemorrhage in obinutuzumab-treated subjects. A clear relationship between thrombocytopenia and haemorrhagic events had not been established. Subjects treated with concomitant medication, which could possibly worsen thrombocytopenia-related events such as platelet inhibitors and anticoagulants, could be at greater risk of bleeding. Subjects were to be closely monitored for thrombocytopenia, especially during the first cycle; regular laboratory tests were to be performed until the event resolved, and dose delays were to be considered in case of severe or life-threatening thrombocytopenia. Transfusion of blood products (i.e. platelet transfusion) according to institutional practice was at the discretion of the treating physician.</p> |
| 29 January 2015 | <p>Protocol was amended to add clarity to elements that were causing confusion at study sites based on experiences and to correct errors. Additional guidance was added to improve management and increase the safety of patients. The amendment also sought to communicate the risk of tumor lysis syndrome (TLS) and reinforced adherence to the protocol when treating subjects in the study: Guidance was clarified to improve the management and emphasis on the monitoring of patients who were at high risk for tumor lysis syndrome (TLS). Bendamustine is contraindicated in subjects with severe blood count alterations. Therefore, subjects who received bendamustine had to have a leukocyte count <math>&gt; 3,000/\text{mL}</math> at baseline. Patients with polymphocytic transformation could not be enrolled in the study. For Grade 3 or 4 adverse events when obinutuzumab was administered on Days 1, 2, 8 and 15, up to 2 weeks delay for infusions was allowed during Cycle 1. For subsequent obinutuzumab cycles, a maximum dose delay of 4 weeks was permitted per cycle due to toxicity. A maximum of 8 weeks of cumulative delay due to toxicity was allowed in total per subjects. In patients receiving chemotherapy, chemotherapy had to be similarly delayed matching any obinutuzumab delay and vice versa. Premedication guidance was clarified according to the recommendations for management of Infusion Related Reactions in the obinutuzumab safety reference document. In order to collect more robust data in this broader patient population, immunoglobulins and beta2-microglobulin were now to be tested. Concerning the study visits there was to be a visit of End of Treatment 28 days after last study drug administration, as well as the Final Response Assessment Visit 2-3 months after last study drug administration.</p>                                                                                                                                                                               |

|                 |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
|-----------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 06 October 2015 | Protocol was amended in order to extend the exploratory study of the prognostic markers as well as to be consistent with updated safety information regarding gastrointestinal (GI) perforation as an important identified risk associated with obinutuzumab. Cases of GI perforation were reported in patients receiving obinutuzumab, mainly in Non-Hodgkin Lymphoma (NHL). Patients with GI involvement had to be monitored for signs of GI perforation.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
| 31 March 2016   | Protocol was amended to implement additional risk minimization measures in patients with chronic lymphocytic leukemia (CLL) at risk of tumor lysis syndrome (TLS) treated with a combination of obinutuzumab and bendamustine. These measures included additional monitoring and laboratory assessments during Cycle 1. If the Howard criteria for TLS were fulfilled (two or more electrolyte laboratory abnormalities present simultaneously) or if a medically relevant laboratory abnormality in TLS-related parameters or a sign of clinical TLS (e.g. increased serum creatinine or cardiac dysrhythmia) were noted, study drugs were to be withheld and patients were to be hospitalized and adequately treated until normalisation of laboratory abnormalities. After normalisation, treatment could be restarted. Patients were to be informed about symptoms or signs of TLS and advised to contact the investigator immediately if any such symptoms occurred. |
| 31 May 2017     | Protocol was amended to consider second malignancies as an adverse event of special interest (AESI) and report these events indefinitely, regardless of relationship to study treatment (even if the study has been closed).                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |

Notes:

## Interruptions (globally)

Were there any global interruptions to the trial? No

## Limitations and caveats

None reported