



Clinical trial results:

A Phase 3, Double-blind, Randomized Study to Compare the Efficacy and Safety of Rituximab Plus Lenalidomide (CC-5013) Versus Rituximab Plus Placebo in Subjects With Relapsed/Refractory Indolent Lymphoma Summary

| | |
|--------------------------|----------------------|
| EudraCT number | 2013-001245-14 |
| Trial protocol | GB BE CZ IT PT ES PL |
| Global end of trial date | 26 January 2022 |

Results information

| | |
|--------------------------------|------------------|
| Result version number | v1 (current) |
| This version publication date | 11 February 2023 |
| First version publication date | 11 February 2023 |

Trial information

Trial identification

| | |
|-----------------------|-----------------|
| Sponsor protocol code | CC-5013-NHL-007 |
|-----------------------|-----------------|

Additional study identifiers

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

Notes:

Sponsors

| | |
|------------------------------|-------------------------------------------------------------------------------------------------|
| Sponsor organisation name | Bristol-Myers Squibb |
| Sponsor organisation address | Chaussée de la Hulpe 185, Brussels, Belgium, 1170 |
| Public contact | EU Study Start-Up Unit, Bristol-Myers Squibb International Corporation, Clinical.Trials@bms.com |
| Scientific contact | Bristol-Myers Squibb Study Director, Bristol-Myers Squibb, Clinical.Trials@bms.com |

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

| | |
|------------------------------------------------------|-----------------|
| Analysis stage | Final |
| Date of interim/final analysis | 11 April 2022 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 26 January 2022 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

Compare the efficacy and safety of rituximab plus lenalidomide (R²) versus rituximab plus placebo in subjects with relapsed/refractory indolent lymphoma.

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and in compliance with all International Conference on Harmonization Good Clinical Practice Guidelines. All the local regulatory requirements pertinent to safety of trial participants were followed.

Background therapy: -

Evidence for comparator: -

| | |
|-----------------------------------------------------------|------------------|
| Actual start date of recruitment | 21 November 2013 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|------------------------|
| Country: Number of subjects enrolled | Belgium: 22 |
| Country: Number of subjects enrolled | Brazil: 42 |
| Country: Number of subjects enrolled | China: 75 |
| Country: Number of subjects enrolled | Czechia: 33 |
| Country: Number of subjects enrolled | France: 7 |
| Country: Number of subjects enrolled | Germany: 5 |
| Country: Number of subjects enrolled | Israel: 3 |
| Country: Number of subjects enrolled | Italy: 43 |
| Country: Number of subjects enrolled | Japan: 36 |
| Country: Number of subjects enrolled | Poland: 10 |
| Country: Number of subjects enrolled | Portugal: 13 |
| Country: Number of subjects enrolled | Russian Federation: 11 |
| Country: Number of subjects enrolled | Spain: 10 |
| Country: Number of subjects enrolled | Turkey: 8 |
| Country: Number of subjects enrolled | United States: 40 |
| Worldwide total number of subjects | 358 |
| EEA total number of subjects | 143 |

Notes:

| Subjects enrolled per age group | |
|-------------------------------------------|-----|
| In utero | 0 |
| Preterm newborn - gestational age < 37 wk | 0 |
| Newborns (0-27 days) | 0 |
| Infants and toddlers (28 days-23 months) | 0 |
| Children (2-11 years) | 0 |
| Adolescents (12-17 years) | 0 |
| Adults (18-64 years) | 203 |
| From 65 to 84 years | 149 |
| 85 years and over | 6 |

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

358 randomized and 356 treated

Period 1

| | |
|------------------------------|---------------------------------------------------------------|
| Period 1 title | Pre-Treatment |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |
| Roles blinded | Subject, Investigator, Monitor, Data analyst, Carer, Assessor |

Arms

| | |
|------------------------------|-----|
| Are arms mutually exclusive? | Yes |
|------------------------------|-----|

| | |
|------------------|--------------------------------------------|
| Arm title | Rituximab + Lenalidomide (R ²) |
|------------------|--------------------------------------------|

Arm description:

Participants received rituximab 375 mg/m² intravenously (IV) every week in Cycle 1 (Days 1, 8, 15 and 22) and on Day 1 of every 28-day cycle from Cycles 2 to 5 plus lenalidomide 20 mg by mouth (PO) once daily on Days 1 to 21 every 28 days up to 12 cycles (21-day treatment and 7-day rest period); if creatinine clearance (CrCl) was ≥ 30 mL/min but < 60 mL/min, participants received lenalidomide 10 mg capsules on days 1 to 21 every 28 days.

| | |
|----------------------------------------|--------------|
| Arm type | Experimental |
| Investigational medicinal product name | Lenalidomide |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Capsule |
| Routes of administration | Oral use |

Dosage and administration details:

20 mg once daily on Days 1 to 21 every 28 days up to 12 cycles (21-day treatment and 7-day rest period); if creatinine clearance (CrCl) was ≥ 30 mL/min but < 60 mL/min, participants received lenalidomide 10 mg on days 1 to 21 every 28 days.

| | |
|----------------------------------------|-----------------------|
| Investigational medicinal product name | Rituximab |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

375 mg/m² every week in Cycle 1 (Days 1, 8, 15 and 22) and on Day 1 of every 28-day cycle from Cycles 2 to 5

| | |
|------------------|---------------------|
| Arm title | Rituximab + Placebo |
|------------------|---------------------|

Arm description:

Participants received rituximab 375 mg/m² IV every week in Cycle 1 (Days 1, 8, 15 and 22) and on Day 1 of every 28-day cycle from cycle 2 to 5 plus placebo (identically matched capsule) once daily on Days 1 to 21 of every 28-day cycle up to 12 cycles.

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

Dosage and administration details:

375 mg/m² every week in Cycle 1 (Days 1, 8, 15 and 22) and on Day 1 of every 28-day cycle from Cycles 2 to 5

| | |
|----------------------------------------|----------|
| Investigational medicinal product name | Placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Capsule |
| Routes of administration | Oral use |

Dosage and administration details:

once daily on Days 1 to 21 of every 28-day cycle up to 12 cycles.

| Number of subjects in period 1 | Rituximab + Lenalidomide (R ²) | Rituximab + Placebo |
|---------------------------------------|--------------------------------------------|---------------------|
| Started | 178 | 180 |
| Completed | 176 | 180 |
| Not completed | 2 | 0 |
| Adverse event, serious fatal | 1 | - |
| Adverse Event unrelated to Study Drug | 1 | - |

Period 2

| | |
|------------------------------|---------------------------------------------------------------|
| Period 2 title | Treatment |
| Is this the baseline period? | No |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |
| Roles blinded | Subject, Investigator, Monitor, Data analyst, Carer, Assessor |

Arms

| | |
|------------------------------|--------------------------------------------|
| Are arms mutually exclusive? | Yes |
| Arm title | Rituximab + Lenalidomide (R ²) |

Arm description:

Participants received rituximab 375 mg/m² intravenously (IV) every week in Cycle 1 (Days 1, 8, 15 and 22) and on Day 1 of every 28-day cycle from Cycles 2 to 5 plus lenalidomide 20 mg by mouth (PO) once daily on Days 1 to 21 every 28 days up to 12 cycles (21-day treatment and 7-day rest period); if creatinine clearance (CrCl) was ≥ 30 mL/min but < 60 mL/min, participants received lenalidomide 10 mg capsules on days 1 to 21 every 28 days.

| | |
|----------------------------------------|--------------|
| Arm type | Experimental |
| Investigational medicinal product name | Lenalidomide |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Capsule |
| Routes of administration | Oral use |

Dosage and administration details:

20 mg once daily on Days 1 to 21 every 28 days up to 12 cycles (21-day treatment and 7-day rest period); if creatinine clearance (CrCl) was ≥ 30 mL/min but < 60 mL/min, participants received lenalidomide 10 mg on days 1 to 21 every 28 days.

| | |
|----------------------------------------|-----------------------|
| Investigational medicinal product name | Rituximab |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

375 mg/m² every week in Cycle 1 (Days 1, 8, 15 and 22) and on Day 1 of every 28-day cycle from Cycles 2 to 5

| | |
|------------------|---------------------|
| Arm title | Rituximab + Placebo |
|------------------|---------------------|

Arm description:

Participants received rituximab 375 mg/m² IV every week in Cycle 1 (Days 1, 8, 15 and 22) and on Day 1 of every 28-day cycle from cycle 2 to 5 plus placebo (identically matched capsule) once daily on Days 1 to 21 of every 28-day cycle up to 12 cycles.

| | |
|----------------------------------------|----------|
| Arm type | Control |
| Investigational medicinal product name | Placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Capsule |
| Routes of administration | Oral use |

Dosage and administration details:

once daily on Days 1 to 21 of every 28-day cycle up to 12 cycles.

| | |
|----------------------------------------|-----------------------|
| Investigational medicinal product name | Rituximab |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

375 mg/m² every week in Cycle 1 (Days 1, 8, 15 and 22) and on Day 1 of every 28-day cycle from Cycles 2 to 5

| Number of subjects in period 2 | Rituximab + Lenalidomide (R ²) | Rituximab + Placebo |
|---------------------------------------|--------------------------------------------|---------------------|
| Started | 176 | 180 |
| Completed | 124 | 110 |
| Not completed | 52 | 70 |
| Adverse event, serious fatal | 2 | - |
| Consent withdrawn by subject | 13 | 7 |
| Adverse event, non-fatal | 14 | 8 |
| Progressive Disease | 21 | 54 |
| Other reasons | 2 | 1 |

Baseline characteristics

Reporting groups

| | |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------|
| Reporting group title | Rituximab + Lenalidomide (R ²) |
| Reporting group description: Participants received rituximab 375 mg/m ² intravenously (IV) every week in Cycle 1 (Days 1, 8, 15 and 22) and on Day 1 of every 28-day cycle from Cycles 2 to 5 plus lenalidomide 20 mg by mouth (PO) once daily on Days 1 to 21 every 28 days up to 12 cycles (21-day treatment and 7-day rest period); if creatinine clearance (CrCl) was ≥ 30 mL/min but < 60 mL/min, participants received lenalidomide 10 mg capsules on days 1 to 21 every 28 days. | |
| Reporting group title | Rituximab + Placebo |
| Reporting group description: Participants received rituximab 375 mg/m ² IV every week in Cycle 1 (Days 1, 8, 15 and 22) and on Day 1 of every 28-day cycle from cycle 2 to 5 plus placebo (identically matched capsule) once daily on Days 1 to 21 of every 28-day cycle up to 12 cycles. | |

| Reporting group values | Rituximab + Lenalidomide (R ²) | Rituximab + Placebo | Total |
|-------------------------------------------------------------------------|--------------------------------------------|---------------------|-------|
| Number of subjects | 178 | 180 | 358 |
| Age categorical Units: | | | |
| Age Continuous Units: years arithmetic mean standard deviation | 62.30 ± 11.227 | 61.48 ± 11.160 | - |
| Sex: Female, Male Units: Participants | | | |
| Female | 103 | 83 | 186 |
| Male | 75 | 97 | 172 |
| Race/Ethnicity, Customized Units: Subjects | | | |
| White | 118 | 115 | 233 |
| Other Races | 54 | 64 | 118 |
| Not Collected or Reported | 6 | 1 | 7 |
| Ethnicity (NIH/OMB) Units: Subjects | | | |
| Hispanic or Latino | 24 | 20 | 44 |
| Not Hispanic or Latino | 147 | 158 | 305 |
| Unknown or Not Reported | 7 | 2 | 9 |

End points

End points reporting groups

| | |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------|
| Reporting group title | Rituximab + Lenalidomide (R ²) |
| Reporting group description: Participants received rituximab 375 mg/m ² intravenously (IV) every week in Cycle 1 (Days 1, 8, 15 and 22) and on Day 1 of every 28-day cycle from Cycles 2 to 5 plus lenalidomide 20 mg by mouth (PO) once daily on Days 1 to 21 every 28 days up to 12 cycles (21-day treatment and 7-day rest period); if creatinine clearance (CrCl) was ≥ 30 mL/min but < 60 mL/min, participants received lenalidomide 10 mg capsules on days 1 to 21 every 28 days. | |
| Reporting group title | Rituximab + Placebo |
| Reporting group description: Participants received rituximab 375 mg/m ² IV every week in Cycle 1 (Days 1, 8, 15 and 22) and on Day 1 of every 28-day cycle from cycle 2 to 5 plus placebo (identically matched capsule) once daily on Days 1 to 21 of every 28-day cycle up to 12 cycles. | |
| Reporting group title | Rituximab + Lenalidomide (R ²) |
| Reporting group description: Participants received rituximab 375 mg/m ² intravenously (IV) every week in Cycle 1 (Days 1, 8, 15 and 22) and on Day 1 of every 28-day cycle from Cycles 2 to 5 plus lenalidomide 20 mg by mouth (PO) once daily on Days 1 to 21 every 28 days up to 12 cycles (21-day treatment and 7-day rest period); if creatinine clearance (CrCl) was ≥ 30 mL/min but < 60 mL/min, participants received lenalidomide 10 mg capsules on days 1 to 21 every 28 days. | |
| Reporting group title | Rituximab + Placebo |
| Reporting group description: Participants received rituximab 375 mg/m ² IV every week in Cycle 1 (Days 1, 8, 15 and 22) and on Day 1 of every 28-day cycle from cycle 2 to 5 plus placebo (identically matched capsule) once daily on Days 1 to 21 of every 28-day cycle up to 12 cycles. | |

Primary: Kaplan Meier Estimate of Progression Free Survival Assessed by the Independent Review Committee (IRC) According to the 2007 International Working Group Response Criteria (IWGRC)

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|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| End point title | Kaplan Meier Estimate of Progression Free Survival Assessed by the Independent Review Committee (IRC) According to the 2007 International Working Group Response Criteria (IWGRC) |
| End point description: Progression-free survival (PFS) was defined as the time from date of randomization into the study to the first observation of documented disease progression or death due to any cause, whichever occurred first. PFS was based on the data from the IRC review using the modified 2007 International Working Group Response Criteria (IWGRC) using FDA censoring rules. 99999=NA; not enough events had occurred at the time of the data cut-off date | |
| End point type | Primary |
| End point timeframe: From randomization of study drug up to disease progression or death, which occurred first; up to the data cut-off date of 22 June 2018; overall median follow-up time for all participants was 28.30 months (range: 0.1 to 51.3 months). | |

| End point values | Rituximab + Lenalidomide (R ²) | Rituximab + Placebo | | |
|----------------------------------|--------------------------------------------|---------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 178 | 180 | | |
| Units: months | | | | |
| median (confidence interval 95%) | 39.4 (22.9 to 99999) | 14.1 (11.4 to 16.7) | | |

Statistical analyses

| Statistical analysis title | Hazard Ratio |
|-----------------------------------------|------------------------------------------------------------------|
| Comparison groups | Rituximab + Lenalidomide (R ²) v Rituximab + Placebo |
| Number of subjects included in analysis | 358 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | < 0.0001 |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.46 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.34 |
| upper limit | 0.62 |

Secondary: Durable Complete Response Rate (DCCR) as Assessed by the IRC According to the 2007 IWGRC

| | |
|------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| End point title | Durable Complete Response Rate (DCCR) as Assessed by the IRC According to the 2007 IWGRC |
| End point description: | DCCR was defined as the percentage of participants with a best response of complete response (CR) that lasted no less than one year (≥ 48 weeks) during the study prior to administration of new anti-lymphoma therapy. A CR is defined as a complete disappearance of any disease-related symptoms and normalization of biochemical abnormalities. |
| End point type | Secondary |
| End point timeframe: | From first dose of investigational product (IP) to data cut-off date of 22 June 2018; the median treatment duration was 11.19 months in the rituximab/lenalidomide arm and 11.04 months in the rituximab/placebo arm |

| End point values | Rituximab + Lenalidomide (R ²) | Rituximab + Placebo | | |
|-----------------------------------|--------------------------------------------|---------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 178 | 180 | | |
| Units: Percentage of Participants | | | | |
| number (confidence interval 95%) | 25.3 (19.1 to 32.3) | 11.1 (6.9 to 16.6) | | |

Statistical analyses

| Statistical analysis title | P-Value |
|-----------------------------------------|------------------------------------------------------------------|
| Comparison groups | Rituximab + Lenalidomide (R ²) v Rituximab + Placebo |
| Number of subjects included in analysis | 358 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.0006 |
| Method | Cochran-Mantel-Haenszel |

Secondary: Kaplan-Meier Estimate of Overall Survival (OS)

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|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------|
| End point title | Kaplan-Meier Estimate of Overall Survival (OS) |
| End point description: | |
| Overall survival was defined as the time from randomization to death from any cause. Overall survival was censored at the last date that the participant was known to be alive for participants who were alive at the time of analysis and for participants who were lost to follow-up before death was documented. 99999=NA; insufficient number of participants with events. | |
| End point type | Secondary |
| End point timeframe: | |
| From date of randomization to death due to any cause (Average of 55.71 months and a maximum up to 95.2 months) | |

| End point values | Rituximab + Lenalidomide (R ²) | Rituximab + Placebo | | |
|----------------------------------|--------------------------------------------|------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 178 | 180 | | |
| Units: Months | | | | |
| median (confidence interval 95%) | 99999 (99999 to 99999) | 99999 (99999 to 99999) | | |

Statistical analyses

| Statistical analysis title | Hazard Ratio (HR) |
|----------------------------------------------------------------------------------------------------------------|-------------------|
| Statistical analysis description: | |
| Stratified by 3 factors: previous rituximab treatment, time since last antilymphoma therapy (≤ 2 , > 2 | |

years), and disease histology (FL, MZL).

| | |
|-----------------------------------------|------------------------------------------------------------------|
| Comparison groups | Rituximab + Lenalidomide (R ²) v Rituximab + Placebo |
| Number of subjects included in analysis | 358 |
| Analysis specification | Pre-specified |
| Analysis type | |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.59 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.37 |
| upper limit | 0.95 |

Secondary: Percentage of Participants with an Objective Response as Assessed by the IRC According to the 2007 IWGRC

| | |
|-----------------|----------------------------------------------------------------------------------------------------------|
| End point title | Percentage of Participants with an Objective Response as Assessed by the IRC According to the 2007 IWGRC |
|-----------------|----------------------------------------------------------------------------------------------------------|

End point description:

Percentage of participants with an objective response is defined as having a response of at least a PR during the study without administration of new anti-lymphoma therapy. A complete response = a complete disappearance of all detectable clinical and radiographic evidence of disease, disappearance of any disease-related symptoms, and normalization of biochemical abnormalities; a partial response (PR) = 50% decrease in SPD of the 6 largest dominant nodes or nodal masses. No increase in the size of other nodes, liver, or spleen. Splenic and hepatic nodules must regress by at least 50% in the SPD.

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

End point timeframe:

From date of first dose to data cut-off date of 22 June 2018; the median treatment duration was 11.19 months in the rituximab/lenalidomide arm and 11.04 months in the rituximab/placebo arm

| End point values | Rituximab + Lenalidomide (R ²) | Rituximab + Placebo | | |
|-----------------------------------|--------------------------------------------|---------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 178 | 180 | | |
| Units: Percentage of Participants | | | | |
| number (confidence interval 95%) | 77.5 (70.7 to 83.4) | 53.3 (45.8 to 60.8) | | |

Statistical analyses

| | |
|----------------------------|------------------------------------------------------------------|
| Statistical analysis title | P-value |
| Comparison groups | Rituximab + Lenalidomide (R ²) v Rituximab + Placebo |

| | |
|-----------------------------------------|-------------------------|
| Number of subjects included in analysis | 358 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | < 0.0001 |
| Method | Cochran-Mantel-Haenszel |

Secondary: Percentage of Participants with a Best Response of Complete Response as Assessed by the IRC According to the 2007 IWGRC

| | |
|-----------------|-------------------------------------------------------------------------------------------------------------------------|
| End point title | Percentage of Participants with a Best Response of Complete Response as Assessed by the IRC According to the 2007 IWGRC |
|-----------------|-------------------------------------------------------------------------------------------------------------------------|

End point description:

Percentage of participants with a best response of at CR during the study without administration of new anti-lymphoma therapy. A CR = Complete disappearance of all detectable clinical and radiographic evidence of disease, disappearance of any disease-related symptoms, and normalization of biochemical abnormalities.

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

End point timeframe:

From date of first dose up to data cut-off date of 22 June 2018; the median treatment duration was 11.19 months in the rituximab/lenalidomide arm and 11.04 months in the rituximab/placebo arm

| End point values | Rituximab + Lenalidomide (R ²) | Rituximab + Placebo | | |
|-----------------------------------|--------------------------------------------|---------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 178 | 180 | | |
| Units: Percentage of Participants | | | | |
| number (confidence interval 95%) | 33.7 (26.8 to 41.2) | 18.3 (13.0 to 24.8) | | |

Statistical analyses

| | |
|-----------------------------------------|------------------------------------------------------------------|
| Statistical analysis title | P-value |
| Comparison groups | Rituximab + Lenalidomide (R ²) v Rituximab + Placebo |
| Number of subjects included in analysis | 358 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.001 |
| Method | Cochran-Mantel-Haenszel |

Secondary: Kaplan-Meier Estimate of Duration of Objective Response as Assessed by the IRC According to the 2007 IWGRC

| | |
|-----------------|------------------------------------------------------------------------------------------------------------|
| End point title | Kaplan-Meier Estimate of Duration of Objective Response as Assessed by the IRC According to the 2007 IWGRC |
|-----------------|------------------------------------------------------------------------------------------------------------|

End point description:

Duration of response (DOR) was defined as the time from initial response (at least PR) until documented progressive disease (PD) or death. Participants who had not progressed at the time of analysis were censored at the last assessment date that the participant was known to be progression free. Participants who received a new treatment without documented progression were censored at the last assessment date that the participants was known to be progression free.

99999=NA; Not estimable as not enough events had occurred at the time of the data cut-off date

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

End point timeframe:

From randomization up to data cut-off date of 22 June 2018; overall median follow-up time for all participants was 28.30 months (range: 0.1 to 51.3 months).

| End point values | Rituximab + Lenalidomide (R ²) | Rituximab + Placebo | | |
|----------------------------------|--------------------------------------------|---------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 138 | 96 | | |
| Units: months | | | | |
| median (confidence interval 95%) | 36.6 (22.9 to 99999) | 21.7 (12.8 to 27.6) | | |

Statistical analyses

| Statistical analysis title | Hazard Ratio (HR) |
|-----------------------------------------|------------------------------------------------------------------|
| Comparison groups | Rituximab + Lenalidomide (R ²) v Rituximab + Placebo |
| Number of subjects included in analysis | 234 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.0015 |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.53 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.36 |
| upper limit | 0.79 |

Secondary: Kaplan-Meier Estimate of Duration of Complete Response (DOCR) as Assessed by the IRC According to the 2007 IWGRC

| | |
|-----------------|------------------------------------------------------------------------------------------------------------------|
| End point title | Kaplan-Meier Estimate of Duration of Complete Response (DOCR) as Assessed by the IRC According to the 2007 IWGRC |
|-----------------|------------------------------------------------------------------------------------------------------------------|

End point description:

DOCR was defined as the time from initial CR until documented PD or death. Participants who had not progressed at the time of analysis were censored at the last assessment date that the participant was known to be progression free. Participants who received a new treatment without documented progression were censored at the last assessment date that the participants was known to be progression free.

99999=NA; Not enough events had occurred at the time of the data cut-off date

| | |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| From randomization up to data cut-off date of 22 June 2018; overall median follow-up time for all participants was 28.30 months (range: 0.1 to 51.3 months). | |

| End point values | Rituximab + Lenalidomide (R ²) | Rituximab + Placebo | | |
|----------------------------------|--------------------------------------------|-----------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 60 | 33 | | |
| Units: months | | | | |
| median (confidence interval 95%) | 99999 (25.3 to 99999) | 99999 (13.8 to 99999) | | |

Statistical analyses

| | |
|-----------------------------------------|------------------------------------------------------------------|
| Statistical analysis title | Hazard Ratio (HR) |
| Comparison groups | Rituximab + Lenalidomide (R ²) v Rituximab + Placebo |
| Number of subjects included in analysis | 93 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.2993 |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.68 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.32 |
| upper limit | 1.43 |

Secondary: Kaplan Meier Estimate of Event Free Survival as Assessed by the IRC According to the 2007 IWGRC

| | |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------|
| End point title | Kaplan Meier Estimate of Event Free Survival as Assessed by the IRC According to the 2007 IWGRC |
| End point description: | |
| Event-free survival (EFS) was defined as the time from date of randomization to date of first documented progression, relapse, institution of new anti-lymphoma treatment (chemotherapy, radiotherapy or immunotherapy) or death from any cause. Responding participants and those who were lost to follow up were censored at their last tumor assessment date. | |
| 99999=NA; Not enough events had occurred at the time of the data cut-off date | |
| End point type | Secondary |
| End point timeframe: | |
| From date of randomization to data cut-off date of 22 June 2018; overall median follow-up time for all participants was 28.30 months (range: 0.1 to 51.3 months). | |

| End point values | Rituximab + Lenalidomide (R ²) | Rituximab + Placebo | | |
|----------------------------------|--------------------------------------------|---------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 178 | 180 | | |
| Units: months | | | | |
| median (confidence interval 95%) | 27.6 (22.1 to 99999) | 13.9 (11.4 to 16.7) | | |

Statistical analyses

| Statistical analysis title | Hazard Ratio (HR) |
|-----------------------------------------|------------------------------------------------------------------|
| Comparison groups | Rituximab + Lenalidomide (R ²) v Rituximab + Placebo |
| Number of subjects included in analysis | 358 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | < 0.0001 |
| Method | Stratified Log-Rank Test |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.51 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.38 |
| upper limit | 0.67 |

Secondary: Kaplan Meier Estimate of Time to Next Anti-Lymphoma Treatment (TTNLT)

| | |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------|
| End point title | Kaplan Meier Estimate of Time to Next Anti-Lymphoma Treatment (TTNLT) |
| End point description: | |
| Time to next anti-lymphoma treatment (TTNLT) was defined as the time from date of randomization to date of first documented administration of a new anti-lymphoma treatment (including chemotherapy, radiotherapy, radioimmunotherapy or immunotherapy). The time to the next anti-lymphoma treatment was of special interest to the study. | |
| 99999=NA; upper limit not available due to insufficient number of participants with events | |
| End point type | Secondary |
| End point timeframe: | |
| From date of randomization to date of first documented administration of a new anti-lymphoma treatment (Average of 55.71 months and a maximum up to 95.2 months) | |

| End point values | Rituximab + Lenalidomide (R ²) | Rituximab + Placebo | | |
|----------------------------------|--------------------------------------------|---------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 178 | 180 | | |
| Units: Months | | | | |
| median (confidence interval 95%) | 73.1 (43.0 to 99999) | 31.8 (22.2 to 39.4) | | |

Statistical analyses

| Statistical analysis title | Hazard Ratio (HR) |
|-----------------------------------------|------------------------------------------------------------------|
| Comparison groups | Rituximab + Lenalidomide (R ²) v Rituximab + Placebo |
| Number of subjects included in analysis | 358 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | < 0.0001 |
| Method | Stratified Log Rank Test |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.53 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.39 |
| upper limit | 0.71 |

Secondary: Number of Participants with Treatment Emergent Adverse Events (TEAEs)

| | |
|-----------------|-----------------------------------------------------------------------|
| End point title | Number of Participants with Treatment Emergent Adverse Events (TEAEs) |
|-----------------|-----------------------------------------------------------------------|

End point description:

TEAEs include AEs that started or worsened between the date of the first dose and 28 days after the date of the last dose. A serious adverse event (SAE) is any: • Death; • Life-threatening event; • Any inpatient hospitalization or prolongation of existing hospitalization; • Persistent or significant disability or incapacity; • Congenital anomaly or birth defect; • Any other important medical event. The investigator determined the relationship of an AE to study drug based on the timing of the AE relative to drug administration and whether or not other drugs, therapeutic interventions, or underlying conditions could provide a sufficient explanation for the event. The severity of an AE was evaluated by the investigator according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) (Version 4.03) where Grade 1 = Mild, Grade 2 = Moderate, Grade 3 = Severe, Grade 4 = Life-threatening and Grade 5 = Death

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

End point timeframe:

From first dose to 28 days post last dose (Average of 55.71 months and a maximum up to 95.2 months)

| End point values | Rituximab + Lenalidomide (R^2) | Rituximab + Placebo | | |
|-------------------------------------------------------|--------------------------------------|------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 176 | 180 | | |
| Units: Participants | | | | |
| Any TEAE | 174 | 173 | | |
| Any TEAE Related to Lenalidomide/Placebo (LEN/PBO) | 159 | 118 | | |
| Any TEAE Related to Rituximab (RIT) | 134 | 105 | | |
| Any Serious TEAE | 45 | 25 | | |
| Any Serious TEAE Related to LEN/PBO | 23 | 8 | | |
| Any Serious TEAE Related to RIT | 13 | 4 | | |
| Any CTCAE Grade (GR) 3/4 TEAE | 121 | 58 | | |
| Any CTCAE GR 3/4 TEAE Related to LEN/PBO | 101 | 38 | | |
| Any CTCAE GR 3/4 TEAE Related to RIT | 57 | 20 | | |
| Any GR 5 TEAE | 2 | 2 | | |
| Any TEAE Leading to Dose Reduction LEN/PBO | 46 | 6 | | |
| Any TEAE Leading to Dose Interruption LEN/PBO | 113 | 47 | | |
| Any TEAE Leading to Dose Interruption RIT | 59 | 38 | | |
| Any TEAE Leading to Discontinuation of LEN/PBO | 15 | 9 | | |
| Any TEAE Leading to Discontinuation of RIT | 6 | 2 | | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

SAEs and NSAEs are collected from first dose to 28 days post last dose (Average of 55.71 months and a maximum of 95.2 months). Deaths (All-causes) was assessed from date of randomization to study completion (Up to approximately 100 months).

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

Dictionary used

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

| | |
|--------------------|------|
| Dictionary version | 24.1 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|---------------------|
| Reporting group title | Rituximab + Placebo |
|-----------------------|---------------------|

Reporting group description:

Participants received rituximab 375 mg/m² IV every week in Cycle 1 (Days 1, 8, 15 and 22) and on Day 1 of every 28-day cycle from cycle 2 to 5 plus placebo (identically matched capsule) once daily on Days 1 to 21 of every 28-day cycle up to 12 cycles.

| | |
|-----------------------|--------------------------------------------|
| Reporting group title | Rituximab + Lenalidomide (R ²) |
|-----------------------|--------------------------------------------|

Reporting group description:

Participants received rituximab 375 mg/m² intravenously (IV) every week in Cycle 1 (Days 1, 8, 15 and 22) and on Day 1 of every 28-day cycle from Cycles 2 to 5 plus lenalidomide 20 mg by mouth (PO) once daily on Days 1 to 21 every 28 days up to 12 cycles (21-day treatment and 7-day rest period); if creatinine clearance (CrCl) was ≥ 30 mL/min but < 60 mL/min, participants received lenalidomide 10 mg capsules on days 1 to 21 every 28 days.

| Serious adverse events | Rituximab + Placebo | Rituximab + Lenalidomide (R ²) | |
|---------------------------------------------------------------------|---------------------|--------------------------------------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 25 / 180 (13.89%) | 45 / 176 (25.57%) | |
| number of deaths (all causes) | 47 | 26 | |
| number of deaths resulting from adverse events | | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Basal cell carcinoma | | | |
| subjects affected / exposed | 1 / 180 (0.56%) | 0 / 176 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Invasive ductal breast carcinoma | | | |
| subjects affected / exposed | 1 / 180 (0.56%) | 0 / 176 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Malignant melanoma | | | |

| | | | |
|-------------------------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 180 (0.56%) | 0 / 176 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Squamous cell carcinoma of skin | | | |
| subjects affected / exposed | 0 / 180 (0.00%) | 2 / 176 (1.14%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Transitional cell cancer of the renal pelvis and ureter localised | | | |
| subjects affected / exposed | 1 / 180 (0.56%) | 0 / 176 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Tumour flare | | | |
| subjects affected / exposed | 0 / 180 (0.00%) | 1 / 176 (0.57%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vascular disorders | | | |
| Deep vein thrombosis | | | |
| subjects affected / exposed | 0 / 180 (0.00%) | 1 / 176 (0.57%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lymphoedema | | | |
| subjects affected / exposed | 0 / 180 (0.00%) | 1 / 176 (0.57%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Peripheral arterial occlusive disease | | | |
| subjects affected / exposed | 1 / 180 (0.56%) | 0 / 176 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| General disorders and administration site conditions | | | |
| Asthenia | | | |
| subjects affected / exposed | 1 / 180 (0.56%) | 0 / 176 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|-------------------------------------------------|-----------------|-----------------|--|
| Fatigue | | | |
| subjects affected / exposed | 1 / 180 (0.56%) | 0 / 176 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| General physical health deterioration | | | |
| subjects affected / exposed | 1 / 180 (0.56%) | 2 / 176 (1.14%) | |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 3 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Localised oedema | | | |
| subjects affected / exposed | 1 / 180 (0.56%) | 0 / 176 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Oedema peripheral | | | |
| subjects affected / exposed | 1 / 180 (0.56%) | 1 / 176 (0.57%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pyrexia | | | |
| subjects affected / exposed | 0 / 180 (0.00%) | 3 / 176 (1.70%) | |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Immune system disorders | | | |
| Anaphylactic shock | | | |
| subjects affected / exposed | 0 / 180 (0.00%) | 1 / 176 (0.57%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infusion related hypersensitivity reaction | | | |
| subjects affected / exposed | 0 / 180 (0.00%) | 1 / 176 (0.57%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Reproductive system and breast disorders | | | |
| Adnexal torsion | | | |

| | | | |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 180 (0.56%) | 0 / 176 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Asthmatic crisis | | | |
| subjects affected / exposed | 0 / 180 (0.00%) | 1 / 176 (0.57%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Chronic obstructive pulmonary disease | | | |
| subjects affected / exposed | 0 / 180 (0.00%) | 1 / 176 (0.57%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dyspnoea | | | |
| subjects affected / exposed | 1 / 180 (0.56%) | 1 / 176 (0.57%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pleural effusion | | | |
| subjects affected / exposed | 3 / 180 (1.67%) | 1 / 176 (0.57%) | |
| occurrences causally related to treatment / all | 1 / 3 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pulmonary embolism | | | |
| subjects affected / exposed | 1 / 180 (0.56%) | 4 / 176 (2.27%) | |
| occurrences causally related to treatment / all | 1 / 1 | 4 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pulmonary toxicity | | | |
| subjects affected / exposed | 0 / 180 (0.00%) | 1 / 176 (0.57%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory failure | | | |
| subjects affected / exposed | 0 / 180 (0.00%) | 2 / 176 (1.14%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Injury, poisoning and procedural | | | |

| | | | |
|-------------------------------------------------|-----------------|-----------------|--|
| complications | | | |
| Fall | | | |
| subjects affected / exposed | 0 / 180 (0.00%) | 1 / 176 (0.57%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Femur fracture | | | |
| subjects affected / exposed | 0 / 180 (0.00%) | 1 / 176 (0.57%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infusion related reaction | | | |
| subjects affected / exposed | 0 / 180 (0.00%) | 1 / 176 (0.57%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lower limb fracture | | | |
| subjects affected / exposed | 0 / 180 (0.00%) | 1 / 176 (0.57%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Rib fracture | | | |
| subjects affected / exposed | 0 / 180 (0.00%) | 1 / 176 (0.57%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Spinal compression fracture | | | |
| subjects affected / exposed | 0 / 180 (0.00%) | 1 / 176 (0.57%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Traumatic fracture | | | |
| subjects affected / exposed | 1 / 180 (0.56%) | 0 / 176 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac disorders | | | |
| Angina pectoris | | | |
| subjects affected / exposed | 0 / 180 (0.00%) | 1 / 176 (0.57%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|-------------------------------------------------|-----------------|-----------------|--|
| Arrhythmia | | | |
| subjects affected / exposed | 0 / 180 (0.00%) | 1 / 176 (0.57%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 1 / 1 | |
| Atrial fibrillation | | | |
| subjects affected / exposed | 2 / 180 (1.11%) | 1 / 176 (0.57%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Atrial flutter | | | |
| subjects affected / exposed | 1 / 180 (0.56%) | 0 / 176 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiopulmonary failure | | | |
| subjects affected / exposed | 0 / 180 (0.00%) | 1 / 176 (0.57%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Myocardial infarction | | | |
| subjects affected / exposed | 1 / 180 (0.56%) | 0 / 176 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Supraventricular tachycardia | | | |
| subjects affected / exposed | 0 / 180 (0.00%) | 2 / 176 (1.14%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nervous system disorders | | | |
| Cerebrovascular accident | | | |
| subjects affected / exposed | 1 / 180 (0.56%) | 1 / 176 (0.57%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Syncope | | | |
| subjects affected / exposed | 2 / 180 (1.11%) | 0 / 176 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Transient ischaemic attack | | | |

| | | | |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed | 2 / 180 (1.11%) | 0 / 176 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Blood and lymphatic system disorders | | | |
| Febrile neutropenia | | | |
| subjects affected / exposed | 0 / 180 (0.00%) | 5 / 176 (2.84%) | |
| occurrences causally related to treatment / all | 0 / 0 | 5 / 5 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Anaemia | | | |
| subjects affected / exposed | 0 / 180 (0.00%) | 2 / 176 (1.14%) | |
| occurrences causally related to treatment / all | 0 / 0 | 3 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Neutropenia | | | |
| subjects affected / exposed | 0 / 180 (0.00%) | 3 / 176 (1.70%) | |
| occurrences causally related to treatment / all | 0 / 0 | 4 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Leukopenia | | | |
| subjects affected / exposed | 0 / 180 (0.00%) | 1 / 176 (0.57%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pancytopenia | | | |
| subjects affected / exposed | 0 / 180 (0.00%) | 1 / 176 (0.57%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ear and labyrinth disorders | | | |
| Vertigo | | | |
| subjects affected / exposed | 0 / 180 (0.00%) | 1 / 176 (0.57%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Eye disorders | | | |
| Retinal detachment | | | |
| subjects affected / exposed | 1 / 180 (0.56%) | 0 / 176 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|-------------------------------------------------|-----------------|-----------------|--|
| Gastrointestinal disorders | | | |
| Diarrhoea | | | |
| subjects affected / exposed | 0 / 180 (0.00%) | 1 / 176 (0.57%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Faecaloma | | | |
| subjects affected / exposed | 0 / 180 (0.00%) | 1 / 176 (0.57%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Haemorrhagic erosive gastritis | | | |
| subjects affected / exposed | 1 / 180 (0.56%) | 0 / 176 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Haemorrhoids | | | |
| subjects affected / exposed | 1 / 180 (0.56%) | 0 / 176 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Volvulus | | | |
| subjects affected / exposed | 0 / 180 (0.00%) | 1 / 176 (0.57%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatobiliary disorders | | | |
| Cholecystitis | | | |
| subjects affected / exposed | 0 / 180 (0.00%) | 1 / 176 (0.57%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cholelithiasis | | | |
| subjects affected / exposed | 1 / 180 (0.56%) | 0 / 176 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Skin and subcutaneous tissue disorders | | | |
| Pruritus | | | |

| | | | |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 180 (0.00%) | 1 / 176 (0.57%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Rash maculo-papular | | | |
| subjects affected / exposed | 0 / 180 (0.00%) | 1 / 176 (0.57%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal and urinary disorders | | | |
| Acute kidney injury | | | |
| subjects affected / exposed | 0 / 180 (0.00%) | 2 / 176 (1.14%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Haematuria | | | |
| subjects affected / exposed | 1 / 180 (0.56%) | 0 / 176 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal colic | | | |
| subjects affected / exposed | 1 / 180 (0.56%) | 0 / 176 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Musculoskeletal and connective tissue disorders | | | |
| Pain in extremity | | | |
| subjects affected / exposed | 0 / 180 (0.00%) | 1 / 176 (0.57%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Seronegative arthritis | | | |
| subjects affected / exposed | 0 / 180 (0.00%) | 1 / 176 (0.57%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Spinal pain | | | |
| subjects affected / exposed | 0 / 180 (0.00%) | 1 / 176 (0.57%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------|-----------------------------------|--|
| Infections and infestations Appendicitis subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 1 / 180 (0.56%) 0 / 1 0 / 0 | 1 / 176 (0.57%) 0 / 1 0 / 0 | |
| Cellulitis subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 0 / 180 (0.00%) 0 / 0 0 / 0 | 1 / 176 (0.57%) 1 / 1 0 / 0 | |
| Diverticulitis subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 0 / 180 (0.00%) 0 / 0 0 / 0 | 1 / 176 (0.57%) 1 / 2 0 / 0 | |
| Gastroenteritis subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 0 / 180 (0.00%) 0 / 0 0 / 0 | 1 / 176 (0.57%) 0 / 1 0 / 0 | |
| Herpes zoster subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 1 / 180 (0.56%) 1 / 1 0 / 0 | 0 / 176 (0.00%) 0 / 0 0 / 0 | |
| Neurosyphilis subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 0 / 180 (0.00%) 0 / 0 0 / 0 | 1 / 176 (0.57%) 0 / 1 0 / 0 | |
| Pneumonia subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 6 / 180 (3.33%) 2 / 7 1 / 1 | 6 / 176 (3.41%) 5 / 8 0 / 0 | |
| Pneumonia influenzal subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 0 / 180 (0.00%) 0 / 0 0 / 0 | 1 / 176 (0.57%) 1 / 1 0 / 0 | |
| Pyelonephritis | | | |

| | | | |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 180 (0.00%) | 1 / 176 (0.57%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pyelonephritis acute | | | |
| subjects affected / exposed | 0 / 180 (0.00%) | 1 / 176 (0.57%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory tract infection | | | |
| subjects affected / exposed | 0 / 180 (0.00%) | 1 / 176 (0.57%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Sepsis | | | |
| subjects affected / exposed | 2 / 180 (1.11%) | 3 / 176 (1.70%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Septic shock | | | |
| subjects affected / exposed | 1 / 180 (0.56%) | 0 / 176 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Sialoadenitis | | | |
| subjects affected / exposed | 0 / 180 (0.00%) | 1 / 176 (0.57%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 2 / 180 (1.11%) | 0 / 176 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Urinary tract infection | | | |
| subjects affected / exposed | 1 / 180 (0.56%) | 1 / 176 (0.57%) | |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metabolism and nutrition disorders | | | |
| Dehydration | | | |

| | | | |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 180 (0.56%) | 0 / 176 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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

| Non-serious adverse events | Rituximab + Placebo | Rituximab + Lenalidomide (R ²) | |
|---------------------------------------------------------------------|---------------------|--------------------------------------------|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 158 / 180 (87.78%) | 170 / 176 (96.59%) | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Tumour flare | | | |
| subjects affected / exposed | 1 / 180 (0.56%) | 18 / 176 (10.23%) | |
| occurrences (all) | 1 | 18 | |
| Vascular disorders | | | |
| Hypertension | | | |
| subjects affected / exposed | 11 / 180 (6.11%) | 6 / 176 (3.41%) | |
| occurrences (all) | 14 | 7 | |
| Hypotension | | | |
| subjects affected / exposed | 1 / 180 (0.56%) | 9 / 176 (5.11%) | |
| occurrences (all) | 4 | 10 | |
| General disorders and administration site conditions | | | |
| Asthenia | | | |
| subjects affected / exposed | 18 / 180 (10.00%) | 24 / 176 (13.64%) | |
| occurrences (all) | 22 | 28 | |
| Chills | | | |
| subjects affected / exposed | 8 / 180 (4.44%) | 14 / 176 (7.95%) | |
| occurrences (all) | 8 | 19 | |
| Fatigue | | | |
| subjects affected / exposed | 33 / 180 (18.33%) | 38 / 176 (21.59%) | |
| occurrences (all) | 42 | 46 | |
| Influenza like illness | | | |
| subjects affected / exposed | 7 / 180 (3.89%) | 9 / 176 (5.11%) | |
| occurrences (all) | 7 | 10 | |
| Malaise | | | |

| | | | |
|----------------------------------------------------------------------------------------|-------------------------|-------------------------|--|
| subjects affected / exposed occurrences (all) | 10 / 180 (5.56%) 10 | 13 / 176 (7.39%) 14 | |
| Oedema peripheral subjects affected / exposed occurrences (all) | 15 / 180 (8.33%) 20 | 24 / 176 (13.64%) 28 | |
| Pyrexia subjects affected / exposed occurrences (all) | 27 / 180 (15.00%) 35 | 35 / 176 (19.89%) 46 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough subjects affected / exposed occurrences (all) | 31 / 180 (17.22%) 43 | 40 / 176 (22.73%) 54 | |
| Dyspnoea subjects affected / exposed occurrences (all) | 7 / 180 (3.89%) 7 | 18 / 176 (10.23%) 24 | |
| Oropharyngeal pain subjects affected / exposed occurrences (all) | 9 / 180 (5.00%) 11 | 10 / 176 (5.68%) 14 | |
| Productive cough subjects affected / exposed occurrences (all) | 8 / 180 (4.44%) 9 | 12 / 176 (6.82%) 17 | |
| Psychiatric disorders | | | |
| Insomnia subjects affected / exposed occurrences (all) | 11 / 180 (6.11%) 11 | 14 / 176 (7.95%) 22 | |
| Investigations | | | |
| Alanine aminotransferase increased subjects affected / exposed occurrences (all) | 15 / 180 (8.33%) 23 | 18 / 176 (10.23%) 31 | |
| Lymphocyte count decreased subjects affected / exposed occurrences (all) | 13 / 180 (7.22%) 25 | 12 / 176 (6.82%) 29 | |
| Blood bilirubin increased subjects affected / exposed occurrences (all) | 0 / 180 (0.00%) 0 | 11 / 176 (6.25%) 25 | |
| Aspartate aminotransferase increased | | | |

| | | | |
|---------------------------------------------------------------------------------------------------------------------------------|-------------------------|---------------------------|--|
| subjects affected / exposed occurrences (all) | 9 / 180 (5.00%) 14 | 10 / 176 (5.68%) 18 | |
| White blood cell count decreased subjects affected / exposed occurrences (all) | 14 / 180 (7.78%) 34 | 17 / 176 (9.66%) 52 | |
| Weight decreased subjects affected / exposed occurrences (all) | 2 / 180 (1.11%) 2 | 14 / 176 (7.95%) 15 | |
| Injury, poisoning and procedural complications Infusion related reaction subjects affected / exposed occurrences (all) | 24 / 180 (13.33%) 36 | 24 / 176 (13.64%) 28 | |
| Nervous system disorders Headache subjects affected / exposed occurrences (all) | 17 / 180 (9.44%) 29 | 26 / 176 (14.77%) 38 | |
| Dizziness subjects affected / exposed occurrences (all) | 9 / 180 (5.00%) 11 | 15 / 176 (8.52%) 18 | |
| Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all) | 8 / 180 (4.44%) 12 | 28 / 176 (15.91%) 48 | |
| Lymphopenia subjects affected / exposed occurrences (all) | 14 / 180 (7.78%) 21 | 8 / 176 (4.55%) 26 | |
| Leukopenia subjects affected / exposed occurrences (all) | 18 / 180 (10.00%) 25 | 37 / 176 (21.02%) 140 | |
| Neutropenia subjects affected / exposed occurrences (all) | 40 / 180 (22.22%) 81 | 103 / 176 (58.52%) 355 | |
| Thrombocytopenia subjects affected / exposed occurrences (all) | 9 / 180 (5.00%) 23 | 26 / 176 (14.77%) 75 | |
| Gastrointestinal disorders | | | |

| | | | |
|----------------------------------------|-------------------|-------------------|--|
| Constipation | | | |
| subjects affected / exposed | 25 / 180 (13.89%) | 46 / 176 (26.14%) | |
| occurrences (all) | 34 | 71 | |
| Abdominal pain | | | |
| subjects affected / exposed | 16 / 180 (8.89%) | 22 / 176 (12.50%) | |
| occurrences (all) | 19 | 28 | |
| Abdominal pain upper | | | |
| subjects affected / exposed | 7 / 180 (3.89%) | 11 / 176 (6.25%) | |
| occurrences (all) | 7 | 14 | |
| Diarrhoea | | | |
| subjects affected / exposed | 42 / 180 (23.33%) | 55 / 176 (31.25%) | |
| occurrences (all) | 52 | 111 | |
| Dyspepsia | | | |
| subjects affected / exposed | 5 / 180 (2.78%) | 16 / 176 (9.09%) | |
| occurrences (all) | 5 | 20 | |
| Nausea | | | |
| subjects affected / exposed | 23 / 180 (12.78%) | 21 / 176 (11.93%) | |
| occurrences (all) | 28 | 33 | |
| Stomatitis | | | |
| subjects affected / exposed | 7 / 180 (3.89%) | 9 / 176 (5.11%) | |
| occurrences (all) | 10 | 11 | |
| Vomiting | | | |
| subjects affected / exposed | 13 / 180 (7.22%) | 18 / 176 (10.23%) | |
| occurrences (all) | 16 | 20 | |
| Skin and subcutaneous tissue disorders | | | |
| Dry skin | | | |
| subjects affected / exposed | 6 / 180 (3.33%) | 9 / 176 (5.11%) | |
| occurrences (all) | 6 | 9 | |
| Pruritus | | | |
| subjects affected / exposed | 8 / 180 (4.44%) | 33 / 176 (18.75%) | |
| occurrences (all) | 12 | 44 | |
| Rash | | | |
| subjects affected / exposed | 9 / 180 (5.00%) | 20 / 176 (11.36%) | |
| occurrences (all) | 10 | 28 | |
| Rash maculo-papular | | | |

| | | | |
|--------------------------------------------------|----------------------|------------------------|--|
| subjects affected / exposed occurrences (all) | 4 / 180 (2.22%) 4 | 14 / 176 (7.95%) 15 | |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia | | | |
| subjects affected / exposed | 17 / 180 (9.44%) | 19 / 176 (10.80%) | |
| occurrences (all) | 23 | 25 | |
| Back pain | | | |
| subjects affected / exposed | 18 / 180 (10.00%) | 14 / 176 (7.95%) | |
| occurrences (all) | 24 | 17 | |
| Muscle spasms | | | |
| subjects affected / exposed | 9 / 180 (5.00%) | 23 / 176 (13.07%) | |
| occurrences (all) | 15 | 28 | |
| Myalgia | | | |
| subjects affected / exposed | 12 / 180 (6.67%) | 10 / 176 (5.68%) | |
| occurrences (all) | 12 | 14 | |
| Infections and infestations | | | |
| Influenza | | | |
| subjects affected / exposed | 8 / 180 (4.44%) | 17 / 176 (9.66%) | |
| occurrences (all) | 10 | 17 | |
| Pneumonia | | | |
| subjects affected / exposed | 7 / 180 (3.89%) | 14 / 176 (7.95%) | |
| occurrences (all) | 8 | 16 | |
| Nasopharyngitis | | | |
| subjects affected / exposed | 18 / 180 (10.00%) | 13 / 176 (7.39%) | |
| occurrences (all) | 24 | 22 | |
| Sinusitis | | | |
| subjects affected / exposed | 5 / 180 (2.78%) | 13 / 176 (7.39%) | |
| occurrences (all) | 5 | 13 | |
| Urinary tract infection | | | |
| subjects affected / exposed | 7 / 180 (3.89%) | 12 / 176 (6.82%) | |
| occurrences (all) | 9 | 16 | |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 23 / 180 (12.78%) | 33 / 176 (18.75%) | |
| occurrences (all) | 28 | 48 | |
| Metabolism and nutrition disorders | | | |

| | | | |
|------------------------------------------------------------------------|------------------------|-------------------------|--|
| Decreased appetite subjects affected / exposed occurrences (all) | 11 / 180 (6.11%) 12 | 23 / 176 (13.07%) 27 | |
| Hyperglycaemia subjects affected / exposed occurrences (all) | 11 / 180 (6.11%) 16 | 12 / 176 (6.82%) 20 | |
| Hyperuricaemia subjects affected / exposed occurrences (all) | 8 / 180 (4.44%) 15 | 10 / 176 (5.68%) 13 | |
| Hypokalaemia subjects affected / exposed occurrences (all) | 5 / 180 (2.78%) 5 | 15 / 176 (8.52%) 27 | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|---------------------------------------------------------------------------------------------------------------------------|
| 17 July 2013 | Update inclusion criteria and exploratory endpoints |
| 22 May 2014 | Update exclusion and inclusion criteria. Clarify treatment continuation rules and other minor clarifications/corrections. |
| 21 October 2015 | Modified inclusion criteria and revised exclusion criteria. |
| 13 December 2018 | Updated contact information. Updated follow-up frequency. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported