



## Clinical trial results:

### A Phase IIa, International, Multicenter, Open-label, Uncontrolled Study to Evaluate the Safety and Pharmacokinetics of 4x375 mg/m<sup>2</sup> Intravenous Rituximab in Pediatric Patients with Granulomatosis with Polyangiitis (Wegener's) or Microscopic Polyangiitis

#### Summary

|                          |                |
|--------------------------|----------------|
| EudraCT number           | 2012-002062-13 |
| Trial protocol           | GB DE IT       |
| Global end of trial date | 10 May 2018    |

#### Results information

|                                |                  |
|--------------------------------|------------------|
| Result version number          | v2 (current)     |
| This version publication date  | 02 May 2019      |
| First version publication date | 24 November 2018 |
| Version creation reason        |                  |

#### Trial information

##### Trial identification

|                       |         |
|-----------------------|---------|
| Sponsor protocol code | WA25615 |
|-----------------------|---------|

##### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT01750697 |
| WHO universal trial number (UTN)   | -           |

Notes:

#### Sponsors

|                              |   |
|------------------------------|---|
| Sponsor organisation name    | F. Hoffmann-La Roche AG   |
| Sponsor organisation address | Grenzacherstrasse 124, Basel, Switzerland, CH-4070  |
| Public contact               | Roche Trial Information Hotline, F. Hoffmann-La Roche AG, +41 616878333, global.trial_information@roche.com |
| Scientific contact           | Roche Trial Information Hotline, 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)       | Yes                 |
| EMA paediatric investigation plan number(s)                          | EMA-000308-PIP02-01 |
| 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? | Yes                 |

Notes:

## Results analysis stage

|  |              |
|--|--------------|
| Analysis stage                                       | Final        |
| Date of interim/final analysis                       | 05 July 2018 |
| Is this the analysis of the primary completion data? | No           |
| Global end of trial reached?                         | Yes          |
| Global end of trial date                             | 10 May 2018  |
| Was the trial ended prematurely?                     | No           |

Notes:

## General information about the trial

Main objective of the trial:

The main objectives of this study were to evaluate the safety, tolerability, and pharmacokinetic (PK) parameters of rituximab in paediatric subjects with severe granulomatosis with polyangiitis (GPA) or microscopic polyangiitis (MPA).

Protection of trial subjects:

All study subjects, parent or legal guardian were required to read and sign an Informed Consent Form. An Internal Monitoring Committee (IMC) composed of a Clinical Scientist, a Statistician, a Statistical Programmer Analyst, and a safety representative reviewed safety data from subjects participating in this study on a regular basis. The IMC was responsible for monitoring the overall safety of the subjects in this study to help to minimize subject exposure to unacceptable risk.

Background therapy:

Subjects must have received three daily doses of 30 milligrams per kilogram (mg/kg) of methylprednisolone (up to 1 g/day) or the equivalent dose of other glucocorticoids by intravenous (IV) infusion, which could occur at any time, up to and including Day 1. If clinically indicated, and at the discretion of the investigator, additional doses (up to three) of methylprednisolone (30 mg/kg, up to 1 g/day, or equivalent) could be given by IV infusion. No more than six doses of methylprednisolone in total could be given. All methylprednisolone doses must have been completed prior to the first rituximab infusion.

On Day 1 and following completion of IV glucocorticoids, all subjects received concomitant oral prednisolone or prednisone (1 mg/kg/day or up to 60 mg/day or equivalent, whichever was lower), the dose of which was tapered to a minimum of 0.2 mg/kg/day (or 10 mg/day, whichever was the lowest) no later than Month 6.

Prophylactic treatment for *Pneumocystis jiroveci* was in accordance with local, routine clinical practise. Treatment of granulomatosis with polyangiitis (GPA) or microscopic polyangiitis (MPA) after Month 6: subjects who had failed to achieve clinical remission or who exhibited progressive disease or flare that could not be controlled by glucocorticoids alone were to receive treatment for their GPA or MPA in accordance with local standard of care, which could include rituximab and/or other therapies, at the discretion of the investigator and were to remain in the study.

Repeat treatment with rituximab was given at the discretion of the investigator, per their clinical judgement (including dose and treatment regimen) based on disease activity, previous response to treatment, and the investigator's assessment of the benefit/risk of additional rituximab treatment.

Evidence for comparator: -

|   |             |
|---|-------------|
| Actual start date of recruitment                          | 23 May 2013 |
| Long term follow-up planned                               | Yes         |
| Long term follow-up rationale                             | Safety      |
| Long term follow-up duration                              | 54 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 | United Kingdom: 13 |
| Country: Number of subjects enrolled | Italy: 1           |
| Country: Number of subjects enrolled | Serbia: 1          |
| Country: Number of subjects enrolled | Turkey: 2          |
| Country: Number of subjects enrolled | Canada: 4          |
| Country: Number of subjects enrolled | United States: 4   |
| Worldwide total number of subjects   | 25                 |
| EEA total number of subjects         | 14                 |

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)                     | 6  |
| Adolescents (12-17 years)                 | 19 |
| Adults (18-64 years)                      | 0  |
| From 65 to 84 years                       | 0  |
| 85 years and over                         | 0  |

## Subject disposition

### Recruitment

Recruitment details:

A total of 25 subjects were enrolled in the study over a 3.5 year period from 11 sites across the United Kingdom, Italy, Serbia, Turkey, Canada, and the United States.

### Pre-assignment

Screening details:

The screening visit occurred up to 28 days prior to the Day 1 baseline visit. Following successful screening, eligible subjects entered the 6 month Remission Induction Phase of the study.

### Period 1

|                              |  |
|------------------------------|--|
| Period 1 title               | Remission Induction Phase (up to 6 mos.) |
| Is this the baseline period? | Yes                                      |
| Allocation method            | Not applicable                           |
| Blinding used                | Not blinded                              |

### Arms

|           |           |
|-----------|-----------|
| Arm title | Rituximab |
|-----------|-----------|

Arm description:

Subjects received rituximab as an intravenous (IV) infusion of 375 milligrams per metre squared (mg/m<sup>2</sup>) once a week on Days 1, 8, 15, and 22 during Remission Induction Phase (Day 1 (baseline) to Month 6).

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

Dosage and administration details:

Rituximab was administered as an IV infusion of 375 mg/m<sup>2</sup> once a week for 4 consecutive weeks, starting at the baseline visit.

|                                       |           |
|---------------------------------------|-----------|
| <b>Number of subjects in period 1</b> | Rituximab |
| Started                               | 25        |
| Completed                             | 25        |

### Period 2

|                              |   |
|------------------------------|---|
| Period 2 title               | Overall Follow-up Phase (up to 4.5 yrs) |
| Is this the baseline period? | No                                      |
| Allocation method            | Not applicable                          |
| Blinding used                | Not blinded                             |

## Arms

|           |           |
|-----------|-----------|
| Arm title | Rituximab |
|-----------|-----------|

### Arm description:

Subjects who received rituximab during 6-month Remission Induction Phase were followed for 12 months during the Follow-up Phase ((Month 6 to Month 18)) and then an Extended Follow-up Phase (Month 18 to Common-closeout (CCO)).

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

### Dosage and administration details:

Subjects received additional rituximab infusions (dose and treatment regimen per Investigator's clinical judgement) post Remission Induction Phase (Month 6) up to 4.5 years during the overall Follow-up Phase until the CCO.

| Number of subjects in period 2              | Rituximab |
|---|-----------|
| Started                                     | 25        |
| Follow-up Phase (Month 6 to Month 18)       | 24        |
| Completed                                   | 16        |
| Not completed                               | 9         |
| Subject Transferring Back To Local Hospital | 1         |
| Transferred to Adult Services               | 5         |
| Physician decision                          | 1         |
| Withdrawal by Subject                       | 1         |
| Physician and Family Decision               | 1         |

## Baseline characteristics

### Reporting groups

|                       |           |
|-----------------------|-----------|
| Reporting group title | Rituximab |
|-----------------------|-----------|

Reporting group description:

Subjects received rituximab as an intravenous (IV) infusion of 375 milligrams per metre squared (mg/m<sup>2</sup>) once a week on Days 1, 8, 15, and 22 during Remission Induction Phase (Day 1 (baseline) to Month 6).

| Reporting group values  | Rituximab     | Total |  |
|---|---------------|-------|--|
| Number of subjects  | 25            | 25    |  |
| Age Categorical<br>Units: Subjects                                      |               |       |  |
| Age Continuous<br>Units: years<br>arithmetic mean<br>standard deviation | 13.4<br>± 2.9 | -     |  |
| Gender Categorical<br>Units: Subjects                                   |               |       |  |
| Female  | 20            | 20    |  |
| Male  | 5             | 5     |  |

## End points

### End points reporting groups

|   |                    |
|---|--------------------|
| Reporting group title   | Rituximab          |
| Reporting group description:<br>Subjects received rituximab as an intravenous (IV) infusion of 375 milligrams per metre squared (mg/m <sup>2</sup> ) once a week on Days 1, 8, 15, and 22 during Remission Induction Phase (Day 1 (baseline) to Month 6).         |                    |
| Reporting group title   | Rituximab          |
| Reporting group description:<br>Subjects who received rituximab during 6-month Remission Induction Phase were followed for 12 months during the Follow-up Phase ((Month 6 to Month 18)) and then an Extended Follow-up Phase (Month 18 to Common-closeout (CCO)). |                    |
| Subject analysis set title  | Overall: Rituximab |
| Subject analysis set type   | Safety analysis    |
| Subject analysis set description:<br>Subjects received rituximab as an IV infusion of 375 mg/m <sup>2</sup> once a week on Days 1, 8, 15, and 22.   |                    |

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

|  |  |
|--|--|
| End point title  | Percentage of Subjects With Adverse Events (AEs) and Serious AEs (SAEs) <sup>[1]</sup> |
| End point description:<br>An AE is any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a study drug, whether or not considered related to the study drug. A SAE is any experience that: results in death, is life-threatening, requires in-patient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability/incapacity, is a congenital anomaly/birth defect, or is medically significant. The safety population included all subjects who received at least part of one infusion of rituximab. |  |
| End point type   | Primary  |
| End point timeframe:<br>Up to approximately 5 years  |  |

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: Only descriptive statistics was planned to be reported in the endpoint.

| End point values                 | Rituximab       | Rituximab       |  |  |
|----------------------------------|-----------------|-----------------|--|--|
| Subject group type               | Reporting group | Reporting group |  |  |
| Number of subjects analysed      | 25              | 25              |  |  |
| Units: percentage of subjects    |                 |                 |  |  |
| number (not applicable)          |                 |                 |  |  |
| Percentage of subjects with AEs  | 100.0           | 100.0           |  |  |
| Percentage of subjects with SAEs | 28.0            | 48.0            |  |  |

### Statistical analyses

No statistical analyses for this end point

### Primary: Pharmacokinetics (PK) Parameter: Rituximab Clearance (CL)

|                 |  |
|-----------------|--|
| End point title | Pharmacokinetics (PK) Parameter: Rituximab Clearance (CL) <sup>[2]</sup> |
|-----------------|--|

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**End point description:**

CL is a quantitative measure of the rate at which a drug substance is removed from the body. The following allometric scaling equation was used for the estimation of CL in children:

$$CL = qCL \times (BSA/1.9)^{0.92} \times 1.31^{ADA}$$

where qCL is a typical value of clearance in millilitres per day (mL/day) for a typical patient (i.e., Body Surface Area (BSA) of 1.9 m<sup>2</sup> and absence of anti-rituximab antibodies (ADA)) and is equal to 258 mL/day; BSA is in m<sup>2</sup> and ADA is 1 when anti-rituximab antibodies are present (0 otherwise). The allometric scaling factor was 0.92. CL was calculated in millilitres per day (mL/day).

The PK analysis population included all subjects in the safety population who provided at least one evaluable PK sample.

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

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**End point timeframe:**

Pre-dose (0 hour) on Days 1, 8, 15, 22; 30 minutes post infusion on Days 1 and 22 and then on Day 29, Months 2, 4, 6, 9, 18, thereafter every 6 months up to approximately 5 years

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**Notes:**

[2] - 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: Only descriptive statistics was planned to be reported in the endpoint.

|   |                       |  |  |  |
|---|-----------------------|--|--|--|
| <b>End point values</b>                             | Overall:<br>Rituximab |  |  |  |
| Subject group type                                  | Subject analysis set  |  |  |  |
| Number of subjects analysed                         | 25                    |  |  |  |
| Units: mL/day                                       |                       |  |  |  |
| geometric mean (geometric coefficient of variation) | 204 (± 0.414)         |  |  |  |

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**Statistical analyses**

No statistical analyses for this end point

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**Primary: PK Parameter: Volume of Distribution (Vd) of Rituximab**

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|                 |   |
|-----------------|---|
| End point title | PK Parameter: Volume of Distribution (Vd) of Rituximab <sup>[3]</sup> |
|-----------------|---|

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**End point description:**

Vd is defined as the theoretical central volume in which the total amount of drug would need to be uniformly distributed to produce the desired plasma concentration of a drug. Vd was calculated in millilitres (mL). The PK analysis population included all subjects in the safety population who provided at least one evaluable PK sample.

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

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**End point timeframe:**

Pre-dose (0 hour) on Days 1, 8, 15, 22; 30 minutes post infusion on Days 1 and 22 and then on Day 29, Months 2, 4, 6, 9, 18, thereafter every 6 months up to approximately 5 years

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**Notes:**

[3] - 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: Only descriptive statistics was planned to be reported in the endpoint.



|   |                       |  |  |  |
|---|-----------------------|--|--|--|
| <b>End point values</b>                             | Overall:<br>Rituximab |  |  |  |
| Subject group type                                  | Subject analysis set  |  |  |  |
| Number of subjects analysed                         | 25                    |  |  |  |
| Units: mL   |                       |  |  |  |
| geometric mean (geometric coefficient of variation) | 2220 ( $\pm$ 0.212)   |  |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: PK Parameter: Area Under the Concentration-Time Curve From Time 0 to 180 Days (AUC0-180) of Rituximab

|                 |   |
|-----------------|---|
| End point title | PK Parameter: Area Under the Concentration-Time Curve From Time 0 to 180 Days (AUC0-180) of Rituximab |
|-----------------|---|

End point description:

The AUC0-180 is a measure of the plasma concentration of rituximab over time. The AUC0-180 was calculated in micrograms per millilitres times day (mcg/mL\*day). The PK analysis population included all subjects in the safety population who provided at least one evaluable PK sample.

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

End point timeframe:

Pre-dose (0 hour) on Days 1, 8, 15, 22; 30 minutes post infusion on Days 1 and 22 and then on Day 29, Months 2, 4, 6, 9, 18, thereafter every 6 months up to approximately 5 years

|   |                       |  |  |  |
|---|-----------------------|--|--|--|
| <b>End point values</b>                             | Overall:<br>Rituximab |  |  |  |
| Subject group type                                  | Subject analysis set  |  |  |  |
| Number of subjects analysed                         | 25                    |  |  |  |
| Units: mcg/mL*day                                   |                       |  |  |  |
| geometric mean (geometric coefficient of variation) | 10120 ( $\pm$ 0.42)   |  |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: PK Parameter: Maximum Plasma Concentration (Cmax) of Rituximab

|                 |  |
|-----------------|--|
| End point title | PK Parameter: Maximum Plasma Concentration (Cmax) of Rituximab |
|-----------------|--|

End point description:

Cmax is the maximum observed plasma rituximab concentration. Cmax was assessed at each visit following 1st, 2nd, 3rd, and 4th IV dose of rituximab 375 mg/m<sup>2</sup> on Days 1, 8, 15, and 22. Cmax was calculated in micrograms per millilitre (mcg/mL). The PK analysis population included all subjects in the safety population who provided at least one evaluable PK sample.

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

End point timeframe:

Pre-dose (0 hour) on Days 1, 8, 15, 22; 30 minutes post infusion on Days 1 and 22 and then on Day 29,

|   |                       |  |  |  |
|---|-----------------------|--|--|--|
| <b>End point values</b>                             | Overall:<br>Rituximab |  |  |  |
| Subject group type                                  | Subject analysis set  |  |  |  |
| Number of subjects analysed                         | 25                    |  |  |  |
| Units: mcg/mL                                       |                       |  |  |  |
| geometric mean (geometric coefficient of variation) |                       |  |  |  |
| 1st dose  | 230 ( $\pm$ 0.166)    |  |  |  |
| 2nd dose  | 305 ( $\pm$ 0.181)    |  |  |  |
| 3rd dose  | 353 ( $\pm$ 0.183)    |  |  |  |
| 4th dose  | 378 ( $\pm$ 0.174)    |  |  |  |

### Statistical analyses

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No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Up to approximately 5 years

Adverse event reporting additional description:

The safety population included all subjects who received at least part of one infusion of rituximab.

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

### Dictionary used

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

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

### Reporting groups

|                       |                                      |
|-----------------------|--------------------------------------|
| Reporting group title | Remission Induction Phase: Rituximab |
|-----------------------|--------------------------------------|

Reporting group description:

Subjects received rituximab as an IV infusion of 375 mg/m<sup>2</sup> once a week on Days 1, 8, 15, and 22 during Remission Induction Phase (Day 1 (baseline) to Month 6).

|                       |                                    |
|-----------------------|------------------------------------|
| Reporting group title | Overall Follow-up Phase: Rituximab |
|-----------------------|------------------------------------|

Reporting group description:

Subjects who received rituximab during the remission induction phase were followed for a minimum of 18 months during the follow-up phase and could receive additional rituximab or other treatments for GPA/MPA (Day 1 (baseline) up to 4.5 yrs).

| Serious adverse events                            | Remission Induction Phase: Rituximab | Overall Follow-up Phase: Rituximab |  |
|---|--------------------------------------|------------------------------------|--|
| Total subjects affected by serious adverse events |                                      |                                    |  |
| subjects affected / exposed                       | 7 / 25 (28.00%)                      | 12 / 25 (48.00%)                   |  |
| number of deaths (all causes)                     | 0                                    | 0                                  |  |
| number of deaths resulting from adverse events    | 0                                    | 0                                  |  |
| Injury, poisoning and procedural complications    |                                      |                                    |  |
| Infusion related reaction                         |                                      |                                    |  |
| subjects affected / exposed                       | 1 / 25 (4.00%)                       | 1 / 25 (4.00%)                     |  |
| occurrences causally related to treatment / all   | 0 / 1                                | 0 / 1                              |  |
| deaths causally related to treatment / all        | 0 / 0                                | 0 / 0                              |  |
| Vascular disorders                                |                                      |                                    |  |
| Granulomatosis with polyangiitis                  |                                      |                                    |  |
| subjects affected / exposed                       | 2 / 25 (8.00%)                       | 4 / 25 (16.00%)                    |  |
| occurrences causally related to treatment / all   | 0 / 3                                | 0 / 6                              |  |
| deaths causally related to treatment / all        | 0 / 0                                | 0 / 0                              |  |
| Vasculitis  |                                      |                                    |  |

|  |                |                |  |
|--|----------------|----------------|--|
| subjects affected / exposed                              | 1 / 25 (4.00%) | 1 / 25 (4.00%) |  |
| occurrences causally related to treatment / all          | 0 / 1          | 0 / 1          |  |
| deaths causally related to treatment / all               | 0 / 0          | 0 / 0          |  |
| Congenital, familial and genetic disorders               |                |                |  |
| Sickle cell anaemia                                      |                |                |  |
| subjects affected / exposed                              | 0 / 25 (0.00%) | 1 / 25 (4.00%) |  |
| occurrences causally related to treatment / all          | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all               | 0 / 0          | 0 / 0          |  |
| Nervous system disorders                                 |                |                |  |
| Seizure  |                |                |  |
| subjects affected / exposed                              | 0 / 25 (0.00%) | 1 / 25 (4.00%) |  |
| occurrences causally related to treatment / all          | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all               | 0 / 0          | 0 / 0          |  |
| Blood and lymphatic system disorders                     |                |                |  |
| Sickle cell anaemia with crisis                          |                |                |  |
| subjects affected / exposed                              | 0 / 25 (0.00%) | 1 / 25 (4.00%) |  |
| occurrences causally related to treatment / all          | 0 / 0          | 0 / 2          |  |
| deaths causally related to treatment / all               | 0 / 0          | 0 / 0          |  |
| Immune system disorders                                  |                |                |  |
| Anti-neutrophil cytoplasmic antibody positive vasculitis |                |                |  |
| subjects affected / exposed                              | 0 / 25 (0.00%) | 1 / 25 (4.00%) |  |
| occurrences causally related to treatment / all          | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all               | 0 / 0          | 0 / 0          |  |
| Gastrointestinal disorders                               |                |                |  |
| Pancreatitis   |                |                |  |
| subjects affected / exposed                              | 0 / 25 (0.00%) | 1 / 25 (4.00%) |  |
| occurrences causally related to treatment / all          | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all               | 0 / 0          | 0 / 0          |  |
| Respiratory, thoracic and mediastinal disorders          |                |                |  |
| Bronchostenosis  |                |                |  |
| subjects affected / exposed                              | 1 / 25 (4.00%) | 1 / 25 (4.00%) |  |
| occurrences causally related to treatment / all          | 0 / 1          | 0 / 1          |  |
| deaths causally related to treatment / all               | 0 / 0          | 0 / 0          |  |
| Laryngeal obstruction                                    |                |                |  |

|   |                |                |  |
|---|----------------|----------------|--|
| subjects affected / exposed                     | 0 / 25 (0.00%) | 1 / 25 (4.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Psychiatric disorders                           |                |                |  |
| Suicidal ideation                               |                |                |  |
| subjects affected / exposed                     | 0 / 25 (0.00%) | 1 / 25 (4.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Musculoskeletal and connective tissue disorders |                |                |  |
| Myopathy  |                |                |  |
| subjects affected / exposed                     | 1 / 25 (4.00%) | 1 / 25 (4.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Infections and infestations                     |                |                |  |
| Influenza                                       |                |                |  |
| subjects affected / exposed                     | 1 / 25 (4.00%) | 2 / 25 (8.00%) |  |
| occurrences causally related to treatment / all | 1 / 1          | 1 / 2          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Lower respiratory tract infection               |                |                |  |
| subjects affected / exposed                     | 1 / 25 (4.00%) | 2 / 25 (8.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 2          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Gastroenteritis viral                           |                |                |  |
| subjects affected / exposed                     | 1 / 25 (4.00%) | 1 / 25 (4.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Device related sepsis                           |                |                |  |
| subjects affected / exposed                     | 0 / 25 (0.00%) | 1 / 25 (4.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Eye infection bacterial                         |                |                |  |
| subjects affected / exposed                     | 0 / 25 (0.00%) | 1 / 25 (4.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |

|   |                |                |  |
|---|----------------|----------------|--|
| Gastroenteritis norovirus                       |                |                |  |
| subjects affected / exposed                     | 0 / 25 (0.00%) | 1 / 25 (4.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Sinusitis                                       |                |                |  |
| subjects affected / exposed                     | 0 / 25 (0.00%) | 1 / 25 (4.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |

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

| <b>Non-serious adverse events</b>                     | Remission Induction Phase: Rituximab | Overall Follow-up Phase: Rituximab |  |
|---|--------------------------------------|------------------------------------|--|
| Total subjects affected by non-serious adverse events |                                      |                                    |  |
| subjects affected / exposed                           | 22 / 25 (88.00%)                     | 24 / 25 (96.00%)                   |  |
| Vascular disorders                                    |                                      |                                    |  |
| Hypertension  |                                      |                                    |  |
| subjects affected / exposed                           | 2 / 25 (8.00%)                       | 3 / 25 (12.00%)                    |  |
| occurrences (all)                                     | 2                                    | 3                                  |  |
| Granulomatosis with polyangiitis                      |                                      |                                    |  |
| subjects affected / exposed                           | 0 / 25 (0.00%)                       | 2 / 25 (8.00%)                     |  |
| occurrences (all)                                     | 0                                    | 2                                  |  |
| General disorders and administration site conditions  |                                      |                                    |  |
| Chest pain  |                                      |                                    |  |
| subjects affected / exposed                           | 2 / 25 (8.00%)                       | 3 / 25 (12.00%)                    |  |
| occurrences (all)                                     | 3                                    | 4                                  |  |
| Non-cardiac chest pain                                |                                      |                                    |  |
| subjects affected / exposed                           | 0 / 25 (0.00%)                       | 2 / 25 (8.00%)                     |  |
| occurrences (all)                                     | 0                                    | 2                                  |  |
| Immune system disorders                               |                                      |                                    |  |
| Hypogammaglobulinaemia                                |                                      |                                    |  |
| subjects affected / exposed                           | 0 / 25 (0.00%)                       | 3 / 25 (12.00%)                    |  |
| occurrences (all)                                     | 0                                    | 3                                  |  |
| Reproductive system and breast disorders              |                                      |                                    |  |
| Amenorrhoea   |                                      |                                    |  |

|  |                     |                     |  |
|--|---------------------|---------------------|--|
| subjects affected / exposed<br>occurrences (all) | 2 / 25 (8.00%)<br>2 | 2 / 25 (8.00%)<br>2 |  |
| Respiratory, thoracic and mediastinal disorders  |                     |                     |  |
| Epistaxis  |                     |                     |  |
| subjects affected / exposed                      | 3 / 25 (12.00%)     | 7 / 25 (28.00%)     |  |
| occurrences (all)                                | 3                   | 8                   |  |
| Cough  |                     |                     |  |
| subjects affected / exposed                      | 3 / 25 (12.00%)     | 6 / 25 (24.00%)     |  |
| occurrences (all)                                | 3                   | 9                   |  |
| Dyspnoea   |                     |                     |  |
| subjects affected / exposed                      | 0 / 25 (0.00%)      | 2 / 25 (8.00%)      |  |
| occurrences (all)                                | 0                   | 2                   |  |
| Oropharyngeal pain                               |                     |                     |  |
| subjects affected / exposed                      | 0 / 25 (0.00%)      | 2 / 25 (8.00%)      |  |
| occurrences (all)                                | 0                   | 2                   |  |
| Psychiatric disorders                            |                     |                     |  |
| Depression                                       |                     |                     |  |
| subjects affected / exposed                      | 0 / 25 (0.00%)      | 2 / 25 (8.00%)      |  |
| occurrences (all)                                | 0                   | 2                   |  |
| Insomnia   |                     |                     |  |
| subjects affected / exposed                      | 0 / 25 (0.00%)      | 2 / 25 (8.00%)      |  |
| occurrences (all)                                | 0                   | 2                   |  |
| Investigations                                   |                     |                     |  |
| Blood immunoglobulin G decreased                 |                     |                     |  |
| subjects affected / exposed                      | 2 / 25 (8.00%)      | 2 / 25 (8.00%)      |  |
| occurrences (all)                                | 2                   | 2                   |  |
| C-reactive protein increased                     |                     |                     |  |
| subjects affected / exposed                      | 0 / 25 (0.00%)      | 2 / 25 (8.00%)      |  |
| occurrences (all)                                | 0                   | 2                   |  |
| Serum ferritin decreased                         |                     |                     |  |
| subjects affected / exposed                      | 0 / 25 (0.00%)      | 2 / 25 (8.00%)      |  |
| occurrences (all)                                | 0                   | 2                   |  |
| Injury, poisoning and procedural complications   |                     |                     |  |
| Infusion related reaction                        |                     |                     |  |
| subjects affected / exposed                      | 14 / 25 (56.00%)    | 16 / 25 (64.00%)    |  |
| occurrences (all)                                | 28                  | 48                  |  |

|   |                      |                       |  |
|---|----------------------|-----------------------|--|
| Fall<br>subjects affected / exposed<br>occurrences (all)  | 0 / 25 (0.00%)<br>0  | 2 / 25 (8.00%)<br>3   |  |
| Skin abrasion<br>subjects affected / exposed<br>occurrences (all)                                       | 0 / 25 (0.00%)<br>0  | 2 / 25 (8.00%)<br>2   |  |
| Nervous system disorders<br>Headache<br>subjects affected / exposed<br>occurrences (all)                | 4 / 25 (16.00%)<br>4 | 9 / 25 (36.00%)<br>9  |  |
| Migraine<br>subjects affected / exposed<br>occurrences (all)  | 0 / 25 (0.00%)<br>0  | 3 / 25 (12.00%)<br>4  |  |
| Tremor<br>subjects affected / exposed<br>occurrences (all)  | 2 / 25 (8.00%)<br>3  | 2 / 25 (8.00%)<br>3   |  |
| Blood and lymphatic system disorders<br>Neutropenia<br>subjects affected / exposed<br>occurrences (all) | 0 / 25 (0.00%)<br>0  | 2 / 25 (8.00%)<br>2   |  |
| Ear and labyrinth disorders<br>Deafness unilateral<br>subjects affected / exposed<br>occurrences (all)  | 0 / 25 (0.00%)<br>0  | 2 / 25 (8.00%)<br>3   |  |
| Gastrointestinal disorders<br>Diarrhoea<br>subjects affected / exposed<br>occurrences (all)             | 0 / 25 (0.00%)<br>0  | 7 / 25 (28.00%)<br>7  |  |
| Nausea<br>subjects affected / exposed<br>occurrences (all)  | 4 / 25 (16.00%)<br>5 | 5 / 25 (20.00%)<br>10 |  |
| Abdominal pain upper<br>subjects affected / exposed<br>occurrences (all)                                | 3 / 25 (12.00%)<br>3 | 4 / 25 (16.00%)<br>4  |  |
| Vomiting<br>subjects affected / exposed<br>occurrences (all)  | 2 / 25 (8.00%)<br>3  | 4 / 25 (16.00%)<br>6  |  |



|   |                      |                      |  |
|---|----------------------|----------------------|--|
| Abdominal pain<br>subjects affected / exposed<br>occurrences (all)    | 2 / 25 (8.00%)<br>2  | 3 / 25 (12.00%)<br>3 |  |
| Constipation<br>subjects affected / exposed<br>occurrences (all)      | 3 / 25 (12.00%)<br>3 | 3 / 25 (12.00%)<br>8 |  |
| Gastritis<br>subjects affected / exposed<br>occurrences (all)         | 0 / 25 (0.00%)<br>0  | 2 / 25 (8.00%)<br>2  |  |
| Skin and subcutaneous tissue disorders                                |                      |                      |  |
| Erythema<br>subjects affected / exposed<br>occurrences (all)          | 0 / 25 (0.00%)<br>0  | 3 / 25 (12.00%)<br>3 |  |
| Pruritus<br>subjects affected / exposed<br>occurrences (all)          | 2 / 25 (8.00%)<br>2  | 2 / 25 (8.00%)<br>2  |  |
| Purpura<br>subjects affected / exposed<br>occurrences (all)           | 0 / 25 (0.00%)<br>0  | 2 / 25 (8.00%)<br>2  |  |
| Rash<br>subjects affected / exposed<br>occurrences (all)              | 0 / 25 (0.00%)<br>0  | 2 / 25 (8.00%)<br>2  |  |
| Rash erythematous<br>subjects affected / exposed<br>occurrences (all) | 2 / 25 (8.00%)<br>2  | 2 / 25 (8.00%)<br>2  |  |
| Skin striae<br>subjects affected / exposed<br>occurrences (all)       | 2 / 25 (8.00%)<br>2  | 2 / 25 (8.00%)<br>2  |  |
| Musculoskeletal and connective tissue disorders                       |                      |                      |  |
| Arthralgia<br>subjects affected / exposed<br>occurrences (all)        | 3 / 25 (12.00%)<br>3 | 5 / 25 (20.00%)<br>6 |  |
| Back pain<br>subjects affected / exposed<br>occurrences (all)         | 3 / 25 (12.00%)<br>3 | 5 / 25 (20.00%)<br>6 |  |
| Pain in extremity   |                      |                      |  |

|   |                 |                  |  |
|---|-----------------|------------------|--|
| subjects affected / exposed             | 2 / 25 (8.00%)  | 4 / 25 (16.00%)  |  |
| occurrences (all)                       | 2               | 4                |  |
| Musculoskeletal chest pain              |                 |                  |  |
| subjects affected / exposed             | 0 / 25 (0.00%)  | 2 / 25 (8.00%)   |  |
| occurrences (all)                       | 0               | 2                |  |
| Infections and infestations             |                 |                  |  |
| Upper respiratory tract infection       |                 |                  |  |
| subjects affected / exposed             | 4 / 25 (16.00%) | 12 / 25 (48.00%) |  |
| occurrences (all)                       | 4               | 21               |  |
| Conjunctivitis                          |                 |                  |  |
| subjects affected / exposed             | 2 / 25 (8.00%)  | 5 / 25 (20.00%)  |  |
| occurrences (all)                       | 2               | 6                |  |
| Nasopharyngitis                         |                 |                  |  |
| subjects affected / exposed             | 2 / 25 (8.00%)  | 5 / 25 (20.00%)  |  |
| occurrences (all)                       | 3               | 10               |  |
| Influenza                               |                 |                  |  |
| subjects affected / exposed             | 0 / 25 (0.00%)  | 4 / 25 (16.00%)  |  |
| occurrences (all)                       | 0               | 4                |  |
| Viral upper respiratory tract infection |                 |                  |  |
| subjects affected / exposed             | 2 / 25 (8.00%)  | 4 / 25 (16.00%)  |  |
| occurrences (all)                       | 2               | 4                |  |
| Ear infection                           |                 |                  |  |
| subjects affected / exposed             | 0 / 25 (0.00%)  | 3 / 25 (12.00%)  |  |
| occurrences (all)                       | 0               | 3                |  |
| Gastroenteritis                         |                 |                  |  |
| subjects affected / exposed             | 2 / 25 (8.00%)  | 3 / 25 (12.00%)  |  |
| occurrences (all)                       | 2               | 3                |  |
| Lower respiratory tract infection       |                 |                  |  |
| subjects affected / exposed             | 0 / 25 (0.00%)  | 3 / 25 (12.00%)  |  |
| occurrences (all)                       | 0               | 3                |  |
| Pharyngitis                             |                 |                  |  |
| subjects affected / exposed             | 0 / 25 (0.00%)  | 3 / 25 (12.00%)  |  |
| occurrences (all)                       | 0               | 7                |  |
| Sinusitis                               |                 |                  |  |
| subjects affected / exposed             | 0 / 25 (0.00%)  | 3 / 25 (12.00%)  |  |
| occurrences (all)                       | 0               | 3                |  |

|   |                     |                      |  |
|---|---------------------|----------------------|--|
| Urinary tract infection<br>subjects affected / exposed<br>occurrences (all)                               | 0 / 25 (0.00%)<br>0 | 3 / 25 (12.00%)<br>3 |  |
| Fungal skin infection<br>subjects affected / exposed<br>occurrences (all)                                 | 0 / 25 (0.00%)<br>0 | 2 / 25 (8.00%)<br>2  |  |
| Herpes zoster<br>subjects affected / exposed<br>occurrences (all)   | 0 / 25 (0.00%)<br>0 | 2 / 25 (8.00%)<br>2  |  |
| Oral herpes<br>subjects affected / exposed<br>occurrences (all)   | 2 / 25 (8.00%)<br>2 | 2 / 25 (8.00%)<br>2  |  |
| Pneumonia<br>subjects affected / exposed<br>occurrences (all)   | 0 / 25 (0.00%)<br>0 | 2 / 25 (8.00%)<br>2  |  |
| Tooth infection<br>subjects affected / exposed<br>occurrences (all)                                       | 0 / 25 (0.00%)<br>0 | 2 / 25 (8.00%)<br>2  |  |
| Metabolism and nutrition disorders<br>Iron deficiency<br>subjects affected / exposed<br>occurrences (all) | 0 / 25 (0.00%)<br>0 | 2 / 25 (8.00%)<br>2  |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date            | Amendment  |
|-----------------|--|
| 13 October 2012 | Changed the tool used for the exploratory endpoint of the measurement of childhood primary vasculitis from the Vasculitis Damage Index (VDI) to the Paediatric Vasculitis Damage Index (PVDI). Added the quality of life (QOL) instrument the Child Health Questionnaire (CHQ) to the exploratory outcome measures. Changed procedure for rituximab administration. Reduced duration of fasting when glycosylated haemoglobin (HbA1c) measurements are required, from 8 hours to at least 4 hours. Amended criterion related to low immunoglobulin levels. Added criterion based on tuberculosis. Provided absolute contraindications to all infusions subsequent to the first infusion and to retreatment infusions. Included definition of treatment failure. Amended the condition for immunisation with any live or attenuated vaccine to also include corticosteroid taper to 0 prior to immunisation with any live or attenuated vaccine. Replaced the term "courses" with "doses." Added oral prednisolone as an option along with oral prednisone. Deleted lateral chest x-rays. Clarified that the screening period was 28 days. Replaced the terms "IVRS" and "IWRS" with the term "IxRS" (interactive voice/web-based response system).   |
| 31 May 2013     | Provided new safety information on severe skin reactions. Increased the exclusion limit of alanine aminotransferase (ALT) or aspartate aminotransferase (AST) levels. Provided definitions of progressive disease, disease relapse/flare, and major and minor items for Birmingham Vasculitis Activity Score (BVAS) for Wegener's granulomatosis (WG) BVAS/WG and Paediatric Vasculitis Activity Score (PVAS). Accordingly, additional exploratory efficacy outcome measures/endpoints were included and clarifications provided. Removed fasting for laboratory assessment of glycosylated haemoglobin (HbA1c). Provided flexibility to the investigator on the use of a corticosteroid premedication subject at his/her discretion. Provided recommendations on non-mandatory treatment for major and minor relapses after Month 6. Added a new section providing information on monitoring of the overall safety of subjects in this study by an Internal Monitoring Committee. Clarified that plasmapheresis was permitted during the study, if absolutely necessary in the opinion of the investigator to treat the subject. Clarified that Pharmacokinetics (PK) samples would be collected from the opposite arm to that into which the rituximab infusion was administered when collected on days of rituximab infusion. Provided clarity about the washout of agents such as mycophenolate mofetil (MMF). Clarified that prophylactic treatment for Pneumocystis jirovecii should be in accordance with local, routine clinical practise. Clarified that the dose of rituximab and the frequency of retreatment for the maintenance of remission will be at the discretion of the investigator, if subjects required retreatment with rituximab after Month 6. Clarified that rituximab is to be diluted to a final concentration of 1–4 mg/mL into an infusion bag containing 0.9% sodium chloride USP or British Pharmacopoeia. |
| 31 May 2013     | Clarified that subjects who receive any protocol-defined prohibited therapy, granulomatosis with polyangiitis (GPA) or microscopic polyangiitis (MPA) treatment other than protocol-defined glucocorticoids, would remain in the study for follow-up, and that they would be included as failing the protocol remission endpoints according to the protocol-defined criteria thereafter (i.e., at timepoints after the receipt of any GPA or MPA treatment other than protocol-defined glucocorticoids), irrespective of BVAS/WG and PVAS scores. Merged the section on "Immunisation" with the "Vaccinations" section.  |

|               |   |
|---------------|---|
| 26 April 2016 | <p>Modified the exclusion criteria related to general health, prior medications and laboratory findings.</p> <p>These changes were made in order to extend the possibility of entry into this clinical study to a wider range of suitable GPA and MPA patients, who would otherwise have limited treatment options in this potentially life-threatening and organ-threatening disease.</p> <p>Exclusions Related to General Health:<br/>Current active infection was an exclusion criterion, a statement was added to clarify that entry into this study may be reconsidered once any known active infection had fully resolved.</p> <p>Exclusions Related to Medications:<br/>Criteria was amended to permit prior treatment with rituximab and/or other B cell-depleting therapies, provided last dose was more than 6 months before the baseline visit.</p> <p>Exclusions Related to Laboratory Findings:<br/>The laboratory exclusion level of serum immunoglobulin G (IgG) was amended from the central laboratory LLN, which varied according to age, to an absolute exclusionary value of below 5.65 mg/mL. This proposed IgG threshold was used as exclusion criteria in rheumatoid arthritis (RA) global clinical trials for rituximab, where adult patients were observed up to 11 years.</p> |
|---------------|---|

Notes:

## Interruptions (globally)

Were there any global interruptions to the trial? No

## Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

After Month 6, subjects could receive treatment for GPA/MPA in accordance with local standard of care, and this could include additional rituximab infusions and/or other immunosuppressive therapies. Low subject numbers (e.g., 1 subject = 4%).

Notes: