Clinical trial results:
A Phase IIa, International, Multicenter, Open-label, Uncontrolled Study to Evaluate the Safety and Pharmacokinetics of 4×375 mg/m2 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	v1
This version publication date	24 November 2018
First version publication date	24 November 2018

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)	EMEA-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:

Population of trial subjects

Subjects enrolled per country

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:

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)	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^2) 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^2 once a week for 4 consecutive weeks, starting at the baseline visit.

Number of subjects in period 1	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	24
Completed	10
Not completed	15
Entered Extended Safety Follow-up	6
Physician decision	1
Subject Transferring Back To Local Hospital	1
Transferred to Adult Services	5
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^2) 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 Units: Subjects			
Age Continuous Units: years			
arithmetic mean	13.4		
standard deviation	± 2.9	-	
Gender Categorical Units: Subjects			
Female	20	20	
Male	5	5	

End points

End points 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^2) 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:

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:

Subjects received rituximab as an IV infusion of 375 mg/m^2 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)[1]

End point description:

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:

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)[2]

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 X (BSA/1.9) 0.92 X 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^2 and absence of anti-rituximab antibodies (ADA)) and is equal to 258 mL/day; BSA is in m^2 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.

End point type	Primary

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

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.

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

Statistical analyses

No statistical analyses for this end point

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

End point title	PK Parameter: Volume of Distribution (Vd) of Rituximab[3]

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.

End point type	Primary

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

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.

End point values	Overall: Rituximab			
Subject group type	Subject analysis set			
Number of subjects analysed	25			
Units: mL				
geometric mean (geometric coefficient of variation)	2220 (± 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

End point values	Overall: Rituximab			
Subject group type	Subject analysis set			
Number of subjects analysed	25			
Units: mcg/mL*day				
geometric mean (geometric coefficient of variation)	10120 (± 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^2 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,

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

Statistical analyses

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	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).

Reporting group title	Remission Induction Phase: Rituximab

Reporting group description:

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

Serious adverse events	Overall Follow-up Phase: Rituximab	Remission Induction Phase: Rituximab	
Total subjects affected by serious adverse events			
subjects affected / exposed	12 / 25 (48.00%)	7 / 25 (28.00%)	
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	4 / 25 (16.00%)	2 / 25 (8.00%)	
occurrences causally related to treatment / all	0 / 6	0 / 3	
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	1 / 25 (4.00%)	0 / 25 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Seizure			
subjects affected / exposed	1 / 25 (4.00%)	0 / 25 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Sickle cell anaemia with crisis			
subjects affected / exposed	1 / 25 (4.00%)	0 / 25 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Anti-neutrophil cytoplasmic antibody positive vasculitis			
subjects affected / exposed	1 / 25 (4.00%)	0 / 25 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Pancreatitis			
subjects affected / exposed	1 / 25 (4.00%)	0 / 25 (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			
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	1 / 25 (4.00%)	0 / 25 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Suicidal ideation			
subjects affected / exposed	1 / 25 (4.00%)	0 / 25 (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			
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	2 / 25 (8.00%)	1 / 25 (4.00%)	
occurrences causally related to treatment / all	1 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			
subjects affected / exposed	2 / 25 (8.00%)	1 / 25 (4.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
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	1 / 25 (4.00%)	0 / 25 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye infection bacterial			
subjects affected / exposed	1 / 25 (4.00%)	0 / 25 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Gastroenteritis norovirus			
subjects affected / exposed	1 / 25 (4.00%)	0 / 25 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinusitis			
subjects affected / exposed	1 / 25 (4.00%)	0 / 25 (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	Overall Follow-up Phase: Rituximab	Remission Induction Phase: Rituximab	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	24 / 25 (96.00%)	22 / 25 (88.00%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	3 / 25 (12.00%)	2 / 25 (8.00%)	
occurrences (all)	3	2	
Granulomatosis with polyangiitis			
subjects affected / exposed	2 / 25 (8.00%)	0 / 25 (0.00%)	
occurrences (all)	2	0	
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	3 / 25 (12.00%)	2 / 25 (8.00%)	
occurrences (all)	4	3	
Non-cardiac chest pain			
subjects affected / exposed	2 / 25 (8.00%)	0 / 25 (0.00%)	
occurrences (all)	2	0	
Immune system disorders			
Hypogammaglobulinaemia			
subjects affected / exposed	3 / 25 (12.00%)	0 / 25 (0.00%)	
occurrences (all)	3	0	
Reproductive system and breast disorders			
Amenorrhoea			

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

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

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

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

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

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 Pneumocystic jiroveci 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	Modified the exclusion criteria related to general health, prior medications and laboratory findings. 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. Exclusions Related to General Health: 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. Exclusions Related to Medications: 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. Exclusions Related to Laboratory Findings: 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.

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: