Clinical trial results:
A Phase 3, Multi-Centre, Multinational, Randomized, Double-Blind, Study to Evaluate the Efficacy and Safety of Belimumab (HGS1006) in Combination with Azathioprine for the Maintenance of Remission in Wegener's Granulomatosis and Microscopic Polyangiitis.

Summary

EudraCT number	2011-004569-33
Trial protocol	GB DE CZ BE ES IE SE HU IT PL
Global end of trial date	06 February 2017

Results information

Result version number	v2 (current)
This version publication date	21 March 2018
First version publication date	14 February 2018
Version creation reason	

Trial information

Trial identification

Sponsor protocol code	115466

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	GlaxoSmithKline
Sponsor organisation address	980 Great West Road, Brentford, Middlesex, United Kingdom,
Public contact	GSK Response Center, GlaxoSmithKline, 1 866-435-7343,
Scientific contact	GSK Response Center, GlaxoSmithKline, 1 866-435-7343,

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	18 May 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	06 February 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

-To evaluate the efficacy of belimumab in the maintenance of remission following a standard induction regimen in subjects with Wegener’s granulomatosis (WG) or microscopic polyangiitis (MPA).
-To evaluate the safety of belimumab in subjects with WG or MPA

Protection of trial subjects:

N/A

Background therapy:

N/A

Evidence for comparator:

N/A

Actual start date of recruitment	20 March 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	Australia: 1
Country: Number of subjects enrolled	Belgium: 11
Country: Number of subjects enrolled	Canada: 4
Country: Number of subjects enrolled	Czech Republic: 3
Country: Number of subjects enrolled	Germany: 10
Country: Number of subjects enrolled	Ireland: 5
Country: Number of subjects enrolled	Italy: 8
Country: Number of subjects enrolled	Mexico: 2
Country: Number of subjects enrolled	Peru: 10
Country: Number of subjects enrolled	Poland: 3
Country: Number of subjects enrolled	Russian Federation: 31
Country: Number of subjects enrolled	Spain: 1
Country: Number of subjects enrolled	Switzerland: 4
Country: Number of subjects enrolled	United Kingdom: 5
Country: Number of subjects enrolled	United States: 8
Worldwide total number of subjects	106
EEA total number of subjects	46

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)	79
From 65 to 84 years	27
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants with diagnosis of Granulomatosis with polyangiitis (GPA) or microscopic polyangiitis (MPA) were randomized in this study. The study was conducted at 37 centers in 15 countries in North America, Central America, South America, Western Europe, Eastern Europe, and Australia during 20 March 2013 - 06 February 2017.

Pre-assignment

Screening details:

A total of 164 participants were screened and 106 were enrolled and randomized in a 1:1 ratio to receive placebo or belimumab 10 milligram per kilogram (mg/kg). Of which, 105 received at least 1 dose of study agent and one participant was randomized in error.

Period 1

Period 1 title	Overall Study (overall period)
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	Placebo

Arm description:

Participants were administered induction therapy (corticosteroids and either cyclophosphamide or rituximab) in the 6 months leading up to randomization. After randomization, participants were administered matching placebo intravenously over 1 hour, at Day 0, 14, 28 and every 28 days thereafter until 12 months after the last subject was randomized. All participants received oral azathioprine at a target dose of 2 milligram per kilogram per day (mg/kg/day). In Belgium-only open-label extension, all participants received belimumab 10mg/day every 28 days until Week 24, with a final evaluation at Week 28.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Placebo was administered intravenously over 1 hour, at Day 0, 14, 28 and every 28 days

Arm title	Belimumab 10 mg/kg

Arm description:

Participants were administered induction therapy (corticosteroids and either cyclophosphamide or rituximab) in the 6 months leading up to randomization. After randomization, participants were administered belimumab 10 mg/kg intravenously over 1 hour, at Day 0, 14, 28 and every 28 days thereafter until 12 months after the last subject was randomized. All participants received oral azathioprine at a target dose of 2 mg/kg/day. In Belgium-only open-label extension, all participants received belimumab 10 mg/kg every 28 days until Week 24, with a final evaluation at Week 28.

Arm type	Experimental
Investigational medicinal product name	Belimumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Belimumab was administered intravenously over 1 hour, at Day 0, 14, 28 and every 28 days

Number of subjects in period 1[1]	Placebo	Belimumab 10 mg/kg
Started	52	53
Completed	40	33
Not completed	12	20
Physician decision	1	4
Consent withdrawn by subject	2	1
Adverse event, non-fatal	3	7
Other-Study closed/terminated	1	1
Lack of efficacy	5	6
Protocol deviation	-	1

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: A total of 164 participants were screened and 106 were enrolled and randomized in a 1:1 ratio to receive placebo or belimumab 10 mg/kg. Of which, 105 received at least 1 dose of study agent and one participant was randomized in error.

Baseline characteristics

Reporting groups	
Reporting group title	Placebo

Reporting group description:

Participants were administered induction therapy (corticosteroids and either cyclophosphamide or rituximab) in the 6 months leading up to randomization. After randomization, participants were administered matching placebo intravenously over 1 hour, at Day 0, 14, 28 and every 28 days thereafter until 12 months after the last subject was randomized. All participants received oral azathioprine at a target dose of 2 milligram per kilogram per day (mg/kg/day). In Belgium-only open-label extension, all participants received belimumab 10mg/day every 28 days until Week 24, with a final evaluation at Week 28.

Reporting group title	Belimumab 10 mg/kg

Reporting group description:

Participants were administered induction therapy (corticosteroids and either cyclophosphamide or rituximab) in the 6 months leading up to randomization. After randomization, participants were administered belimumab 10 mg/kg intravenously over 1 hour, at Day 0, 14, 28 and every 28 days thereafter until 12 months after the last subject was randomized. All participants received oral azathioprine at a target dose of 2 mg/kg/day. In Belgium-only open-label extension, all participants received belimumab 10 mg/kg every 28 days until Week 24, with a final evaluation at Week 28.

Reporting group values	Placebo	Belimumab 10 mg/kg	Total
Number of subjects	52	53	105
Age categorical Units: Subjects			
Age continuous Units: years arithmetic mean standard deviation	 53.5 ± 13.56	 56.2 ± 13.59	 -
Gender categorical Units: Subjects			
Female	25	26	51
Male	27	27	54
Race/Ethnicity, Customized Units: Subjects			
African American/African Heritage	1	1	2
American Indian or Alaskan Native	5	6	11
Central/South Asian Heritage	2	0	2
White	44	46	90

End points

End points reporting groups

Reporting group title	Placebo

Reporting group description:

Participants were administered induction therapy (corticosteroids and either cyclophosphamide or rituximab) in the 6 months leading up to randomization. After randomization, participants were administered matching placebo intravenously over 1 hour, at Day 0, 14, 28 and every 28 days thereafter until 12 months after the last subject was randomized. All participants received oral azathioprine at a target dose of 2 milligram per kilogram per day (mg/kg/day). In Belgium-only open-label extension, all participants received belimumab 10mg/day every 28 days until Week 24, with a final evaluation at Week 28.

Reporting group title	Belimumab 10 mg/kg

Reporting group description:

Participants were administered induction therapy (corticosteroids and either cyclophosphamide or rituximab) in the 6 months leading up to randomization. After randomization, participants were administered belimumab 10 mg/kg intravenously over 1 hour, at Day 0, 14, 28 and every 28 days thereafter until 12 months after the last subject was randomized. All participants received oral azathioprine at a target dose of 2 mg/kg/day. In Belgium-only open-label extension, all participants received belimumab 10 mg/kg every 28 days until Week 24, with a final evaluation at Week 28.

Primary: Time to First Relapse

End point title	Time to First Relapse

End point description:

Time to relapse is defined as the number of days from Day 0 until the participant experienced a relapse (relapse date – treatment start date +1). Only post-baseline relapses were considered in these analyses. Only relapses occurring up to and including the last visit date in the double-blind treatment period were considered in these analyses. Intent-to-treat population comprised of all randomized participants who received at least one dose of study agent (belimumab or placebo). "99999" indicates that the data was not available as Kaplan Meier statistics could not be estimated where the number of events is too low to estimate the value. Median and Inter-quartile range were presented and were based on Kaplan Meier estimates.

End point type	Primary

End point timeframe:

Approximately up to 4 years

End point values	Placebo	Belimumab 10 mg/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	52[1]	53[2]		
Units: Days				
median (inter-quartile range (Q1-Q3))				
Days	99999 (789.0 to 99999)	99999 (99999 to 99999)		

Notes:

[1] - Intent-to-treat population

[2] - Intent-to-treat population

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

Analysis performed using a Cox Proportional Hazards model with covariates treatment group, Actual ANCA type, Actual disease stage at induction and Actual induction regimen.

Comparison groups	Placebo v Belimumab 10 mg/kg
Number of subjects included in analysis	105
Analysis specification	Pre-specified
Analysis type	other[3]
P-value	= 0.884 [4]
Method	Cox Proportional Hazards model
Parameter estimate	Hazard ratio (HR)
Point estimate	1.07
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.44
upper limit	2.59

Notes:

[3] - Analysis was adjusted for ANCA type, disease stage at induction and induction regimen

[4] - Cox proportional Hazards (Wald Chi Square)

Secondary: Number of participants with major relapse during the double-bind phase of the study

End point title	Number of participants with major relapse during the double-bind phase of the study

End point description:

Data for number of participants with major relapse [defined as experiencing at least 1 major Birmingham Vasculitis Activity Score (BVAS) item] during the double-bind phase of the study was reported. Analysis was performed using a Cox proportional hazard model.

End point type	Secondary

End point timeframe:

Approximately up to 4 years

End point values	Placebo	Belimumab 10 mg/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	52[5]	53[6]		
Units: Participants				
Participants	0	1		

Notes:

[5] - Intent-to-treat population

[6] - Intent-to-treat population

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events (AE) were collected from the start of study agent administration (Day 0) through 8 weeks following administration of the last dose of study agent (approximately up to 4 years).

Adverse event reporting additional description:

Intent to treat population. Participants who discontinued treatment, all AE were collected through 8 weeks following the last dose of study agent. All SAEs were collected until relapse or the study was analyzed for the primary endpoint and study sites are informed that SAE data collection can cease, whichever occurs first.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19.1

Reporting groups

Reporting group title	Placebo

Reporting group description:

Participants were administered induction therapy (corticosteroids and either cyclophosphamide or rituximab) in the 6 months leading up to randomization. After randomization, participants were administered matching placebo intravenously over 1 hour, at Day 0, 14, 28 and every 28 days thereafter until 12 months after the last subject was randomized. All participants received oral azathioprine at a target dose of 2 milligram per kilogram per day (mg/kg/day). In Belgium-only open-label extension, all participants received belimumab 10mg/day every 28 days until Week 24, with a final evaluation at Week 28.

Reporting group title	Belimumab 10 mg/kg

Reporting group description:

Participants were administered induction therapy (corticosteroids and either cyclophosphamide or rituximab) in the 6 months leading up to randomization. After randomization, participants were administered belimumab 10 milligram per kilogram (mg/kg) intravenously over 1 hour, at Day 0, 14, 28 and every 28 days thereafter until 12 months after the last subject was randomized. All participants received oral azathioprine at a target dose of 2 mg/kg/day. In Belgium-only open-label extension, all participants received belimumab 10 mg/kg every 28 days until Week 24, with a final evaluation at Week 28.

Serious adverse events	Placebo	Belimumab 10 mg/kg	
Total subjects affected by serious adverse events			
subjects affected / exposed	16 / 52 (30.77%)	18 / 53 (33.96%)	
number of deaths (all causes)	0	1	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Anal cancer			
subjects affected / exposed	0 / 52 (0.00%)	1 / 53 (1.89%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Basal cell carcinoma			

subjects affected / exposed	0 / 52 (0.00%)	1 / 53 (1.89%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Plasma cell myeloma			
subjects affected / exposed	0 / 52 (0.00%)	1 / 53 (1.89%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Vasculitis			
subjects affected / exposed	1 / 52 (1.92%)	0 / 53 (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			
Pyrexia			
subjects affected / exposed	2 / 52 (3.85%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical health deterioration			
subjects affected / exposed	0 / 52 (0.00%)	1 / 53 (1.89%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	0 / 52 (0.00%)	2 / 53 (3.77%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anaphylactic reaction			
subjects affected / exposed	0 / 52 (0.00%)	1 / 53 (1.89%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			

subjects affected / exposed	1 / 52 (1.92%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleuritic pain			
subjects affected / exposed	1 / 52 (1.92%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumomediastinum			
subjects affected / exposed	0 / 52 (0.00%)	1 / 53 (1.89%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Liver function test increased			
subjects affected / exposed	1 / 52 (1.92%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Hip fracture			
subjects affected / exposed	0 / 52 (0.00%)	1 / 53 (1.89%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax traumatic			
subjects affected / exposed	0 / 52 (0.00%)	1 / 53 (1.89%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural discharge			
subjects affected / exposed	0 / 52 (0.00%)	1 / 53 (1.89%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tendon rupture			
subjects affected / exposed	1 / 52 (1.92%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Cardiac disorders			
Sinus bradycardia			
subjects affected / exposed	1 / 52 (1.92%)	0 / 53 (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			
Haemorrhagic stroke			
subjects affected / exposed	0 / 52 (0.00%)	1 / 53 (1.89%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic stroke			
subjects affected / exposed	0 / 52 (0.00%)	1 / 53 (1.89%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 52 (1.92%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	0 / 52 (0.00%)	1 / 53 (1.89%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancytopenia			
subjects affected / exposed	1 / 52 (1.92%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	0 / 52 (0.00%)	1 / 53 (1.89%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Idiopathic orbital inflammation			

subjects affected / exposed	1 / 52 (1.92%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Chronic gastritis			
subjects affected / exposed	0 / 52 (0.00%)	1 / 53 (1.89%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis ulcerative			
subjects affected / exposed	1 / 52 (1.92%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholangitis			
subjects affected / exposed	0 / 52 (0.00%)	1 / 53 (1.89%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Drug-induced liver injury			
subjects affected / exposed	1 / 52 (1.92%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 52 (0.00%)	1 / 53 (1.89%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 52 (0.00%)	1 / 53 (1.89%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscle contracture			

subjects affected / exposed	1 / 52 (1.92%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Bronchitis			
subjects affected / exposed	1 / 52 (1.92%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	0 / 52 (0.00%)	1 / 53 (1.89%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			
subjects affected / exposed	0 / 52 (0.00%)	1 / 53 (1.89%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			
subjects affected / exposed	0 / 52 (0.00%)	1 / 53 (1.89%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenic sepsis			
subjects affected / exposed	0 / 52 (0.00%)	1 / 53 (1.89%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis acute			
subjects affected / exposed	1 / 52 (1.92%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Salmonellosis			
subjects affected / exposed	1 / 52 (1.92%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tuberculosis			

subjects affected / exposed	1 / 52 (1.92%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hypercalcaemia			
subjects affected / exposed	0 / 52 (0.00%)	1 / 53 (1.89%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Placebo	Belimumab 10 mg/kg	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	33 / 52 (63.46%)	32 / 53 (60.38%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	4 / 52 (7.69%)	3 / 53 (5.66%)	
occurrences (all)	4	3	
Nervous system disorders			
Headache			
subjects affected / exposed	7 / 52 (13.46%)	5 / 53 (9.43%)	
occurrences (all)	7	5	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	7 / 52 (13.46%)	7 / 53 (13.21%)	
occurrences (all)	9	8	
Pyrexia			
subjects affected / exposed	2 / 52 (3.85%)	6 / 53 (11.32%)	
occurrences (all)	4	7	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	2 / 52 (3.85%)	7 / 53 (13.21%)	
occurrences (all)	2	9	
Diarrhoea			
subjects affected / exposed	3 / 52 (5.77%)	5 / 53 (9.43%)	
occurrences (all)	4	6	

Abdominal pain upper			
subjects affected / exposed	4 / 52 (7.69%)	3 / 53 (5.66%)	
occurrences (all)	4	3	
Vomiting			
subjects affected / exposed	1 / 52 (1.92%)	5 / 53 (9.43%)	
occurrences (all)	1	5	
Abdominal pain			
subjects affected / exposed	3 / 52 (5.77%)	1 / 53 (1.89%)	
occurrences (all)	6	1	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	8 / 52 (15.38%)	10 / 53 (18.87%)	
occurrences (all)	10	14	
Epistaxis			
subjects affected / exposed	3 / 52 (5.77%)	5 / 53 (9.43%)	
occurrences (all)	3	20	
Oropharyngeal pain			
subjects affected / exposed	2 / 52 (3.85%)	4 / 53 (7.55%)	
occurrences (all)	2	5	
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	3 / 52 (5.77%)	5 / 53 (9.43%)	
occurrences (all)	3	5	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	6 / 52 (11.54%)	6 / 53 (11.32%)	
occurrences (all)	6	6	
Back pain			
subjects affected / exposed	4 / 52 (7.69%)	3 / 53 (5.66%)	
occurrences (all)	6	4	
Bursitis			
subjects affected / exposed	3 / 52 (5.77%)	2 / 53 (3.77%)	
occurrences (all)	3	2	
Infections and infestations			
Nasopharyngitis			

subjects affected / exposed	10 / 52 (19.23%)	6 / 53 (11.32%)	
occurrences (all)	15	9	
Upper respiratory tract infection			
subjects affected / exposed	8 / 52 (15.38%)	7 / 53 (13.21%)	
occurrences (all)	10	11	
Urinary tract infection			
subjects affected / exposed	4 / 52 (7.69%)	5 / 53 (9.43%)	
occurrences (all)	7	5	
Bronchitis			
subjects affected / exposed	6 / 52 (11.54%)	1 / 53 (1.89%)	
occurrences (all)	6	1	
Influenza			
subjects affected / exposed	1 / 52 (1.92%)	5 / 53 (9.43%)	
occurrences (all)	1	5	
Gastroenteritis			
subjects affected / exposed	3 / 52 (5.77%)	0 / 53 (0.00%)	
occurrences (all)	3	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
22 June 2012	Amendment 01: The protocol was modified to further define allowable or prohibited doses of corticosteroids that could be given for vasculitis and for reasons other than vasculitis, A statement was added to clarify that the protocol-defined induction regimens for cyclophosphamide were given as treatment targets but that they could be adjusted to account for renal insufficiency or reduced white blood cell counts as dictated by local standard of care practices, A subgroup analysis by duration of Intravenous (IV) corticosteroid pulse used for induction (1 day versus. >1 day) was added, The language regarding the recommended High dose corticosteroids (HDCS) tapering to reach the entry criteria of <10 mg/day was corrected from the previously written <10 mg/kg, The dose of Methotrexate (MTX) to be used in case of Azathioprine (AZA) toxicity was clarified to be a target dose, to allow for flexibility in individual practice. A minimum dose of MTX (no less than 10 mg/week) was also specified, to ensure participants were receiving a sufficient and relatively consistent therapy. This change also ensured the guidance given for MTX was consistent with that given for AZA
25 April 2013	Amendment 02: The protocol was modified to include testing at Screening for human immunodeficiency virus (HIV) antibody, to expand Hepatitis B serology testing, and to exclude participants who tested positive according to the criteria specified, an alternative test, Hepatitis C virus (HCV) ribonucleic acid (RNA)-polymerase chain reaction (PCR) assay, was used to detect the presence of viral RNA, and hence confirm a current infection, The protocol was modified to exclude participants at baseline with abnormal liver function according to the criteria specified, A new section was added to clarify how participants care should be managed if a patient had a liver chemistry event during the study, Measurement of vital signs (temperature, sitting blood pressure [systolic and diastolic], and heart rate) were added to the procedures for all scheduled study visits and a 12 lead electrocardiogram (ECG) was added to the procedures for the Day 0 visit, Text was added to clarify that study agents were to be provided by the sponsor during the double-blind treatment phase, Within the definition of postmenopausal in Inclusion Criterion, "1 year without menses" was changed to "12 consecutive months with no menses without an alternative medical cause, Steroid use for vasculitis was modified to restrict the use of corticosteroids up to a maximum of 20 mg/day of prednisone (or equivalent) for a maximum of 1 week within the first 2 months of the double-blind treatment period, and at other times, to <10 mg/day, The investigator evaluation of Adverse events regarding causality was modified from a multi-choice assessment, Two new appendices were added to provide the questionnaires for the possible suicidality related history questionnaire (PSRHQ), The protocol was modified to include a Benefit and Risk Assessment, The Chapel Hill Consensus Conference (CHCC) definitions for Wegener's granulomatosis and microscopic polyangiitis were updated.

04 February 2014	Amendment 03: The protocol was modified to provide flexibility in timing of initiation of AZA maintenance therapy.The protocol was modified to allow alternative unlicensed RTX dose for induction (1 g every 2 weeks) in addition to the licensed dosing regimen (375 mg/m2/wk for 4 doses, The protocol was modified to provide flexibility in timing of baseline Birmingham Vasculitis Activity Score (BVAS) assessments – allowing 2 baseline assessments separated by at least 14 days, The absolute requirement to randomize within 14 days of confirmation of remission was removed and clarification was added that subjects could not be randomized until at least 6 weeks after initiation of induction therapy, Clarification was added regarding HDCS for induction and text provided guidance but allowed locally accepted practice. No subject should have received <10 mg for induction, The protocol was modified to allow some flexibility to Cyclophosphamide dosing regimens, The protocol was modified to allow the option to use MTX from the outset, as an alternative to AZA, if subject was a priori known to be AZA intolerant or had low/absent thiopurine methyltransferase (TPMT) activity. Exclusion of subjects with intolerance or contraindications to MTX (where this was being considered as an alternative to AZA), The protocol was modified to allow equal to/less than 10 mg prednisone daily during maintenance, Progressive multifocal leukoencephalopathy (PML) text was updated based on new information, The Benefit and Risk Assessment section was updated to reflect new and/or amended information in the protocol body.
26 February 2015	Amendment 04: Protocol was modified to reflect a change by the sponsor to the strategic objectives for the evaluation of belimumab in ANCA-associated vasculitis (AAV). It was proposed that trial be changed from a Phase 3 to allow for an exploratory evaluation of belimumab in AAV only. The study design and schedule was modified in to clarify that the study would no longer be driven by the requirement to achieve at least 66 relapse events. The study was to complete and the primary analysis to be undertaken once 12 months had elapsed following enrolment of the last subject. The protocol was modified throughout such that (with exception of Belgium) participants completing the study no longer had the option to participate in a 6-month open-label extension following completion of the double-blind treatment phase, In the statistical sections of the protocol, the sample size considerations were modified to reflect the fact that approximately 100 participants were to be recruited, In the section "Dose, route of administration and schedule", it was clarified that administration of belimumab or placebo should be over 1 hour, but not less than 1 hour for reasons of safety, The section on liver chemistry stopping and follow-up criteria, which described how participant care should be managed if a liver event occurred during the study, was updated with the most recent GSK-specified protocol for managing these events, The text on Progressive multifocal PML was updated to provide further guidance, The section "Reporting a pregnancy" was modified to provide scope for following up outcomes of a pregnancy as well as the status of mother and child, The section "Randomization procedure and assignment to treatment requirements" was modified to remove the requirement for participants to be randomized within 2 weeks of achieving remission, Protocol Appendix 12 was updated to reflect the change in study status to an exploratory trial and to reflect the changes in the main protocol.

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.

The sample size was small as it was truncated from approximately 300 to 100 participants, largely owing to a change in standard of care.

Notes: