Clinical trial results:
A randomized, double blind (sponsor open), comparative, multicenter study to evaluate the safety and efficacy of subcutaneous belimumab (GSK1550188) and intravenous rituximab coadministration in subjects with primary Sjögren's syndrome

Summary

EudraCT number	2015-000400-26
Trial protocol	SE NO DE ES NL GB FR IT
Global end of trial date	23 June 2020

Results information

Result version number	v1 (current)
This version publication date	29 May 2021
First version publication date	29 May 2021

Trial information

Trial identification

Sponsor protocol code	201842

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 8664357343, GSKClinicalSupportHD@gsk.com
Scientific contact	GSK Response Center, GlaxoSmithKline, 1 8664357343, GSKClinicalSupportHD@gsk.com

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	14 October 2020
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	23 June 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Safety and tolerability of anti- B lymphocyte stimulator (anti-BLyS)/ anti-cluster of differentiation 20 (anti-CD 20) co-administration therapy and anti-BLyS and anti-CD 20 monotherapies.

Protection of trial subjects:

Not Applicable

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	17 February 2016
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	Argentina: 2
Country: Number of subjects enrolled	Canada: 8
Country: Number of subjects enrolled	France: 24
Country: Number of subjects enrolled	Germany: 12
Country: Number of subjects enrolled	Italy: 11
Country: Number of subjects enrolled	Netherlands: 4
Country: Number of subjects enrolled	Norway: 5
Country: Number of subjects enrolled	Spain: 6
Country: Number of subjects enrolled	Sweden: 4
Country: Number of subjects enrolled	United Kingdom: 10
Worldwide total number of subjects	86
EEA total number of subjects	66

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	0

months)	
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	71
From 65 to 84 years	15
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This study was conducted in 10 countries across 31 centers. Participants were randomized to receive one of the four treatments; Placebo, Belimumab + Rituximab Co-administration therapy, Belimumab Monotherapy or Rituximab Monotherapy.

Pre-assignment

Screening details:

A total of 162 participants were screened of which 76 were screen failures. A total of 86 participants were enrolled in this study.

Period 1

Period 1 title	Treatment Period (Up to Week 52)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Participants received belimumab matching placebo weekly subcutaneous injections up to Week 52 and rituximab matching placebo infusions at Weeks 8 and 10 in the treatment period. Participants then entered in a 16-week no-treatment General Follow-Up (GFU) period.

Arm type	Placebo
Investigational medicinal product name	Rituximab placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Participants received rituximab placebo infusions at Weeks 8 and 10.

Investigational medicinal product name	Belimumab placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Participants received belimumab placebo weekly subcutaneous injections up to Week 52.

Arm title	Belimumab + Rituximab Co-administration therapy

Arm description:

Participants received belimumab 200 milligrams (mg) weekly subcutaneous injections for 24 weeks followed by belimumab matching placebo injections weekly up to Week 52; along with rituximab 1000 mg intravenous infusions at Weeks 8 and 10 in the treatment period. Participants then entered in a 16-week no-treatment GFU period.

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

Dosage and administration details:	
Participants received belimumab 200 milligrams (mg) weekly subcutaneous injections up to Week 52.	
Investigational medicinal product name	Belimumab placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use
Dosage and administration details:	
Participants received belimumab placebo weekly subcutaneous injections up to Week 52.	
Investigational medicinal product name	Rituximab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use
Dosage and administration details:	
Participants received rituximab 1000 mg intravenous (IV) infusions at Weeks 8 and 10.	
Arm title	Belimumab Monotherapy
Arm description:	
Participants received 200 mg weekly subcutaneous injections of belimumab up to Week 52 and rituximab matching placebo infusions at Weeks 8 and 10 in the treatment period. Participants then entered in a 16-week no-treatment GFU period.	
Arm type	Experimental
Investigational medicinal product name	Belimumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use
Dosage and administration details:	
Participants received belimumab 200 milligrams (mg) weekly subcutaneous injections up to Week 52.	
Investigational medicinal product name	Rituximab placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use
Dosage and administration details:	
Participants received rituximab placebo infusions at Weeks 8 and 10.	
Arm title	Rituximab Monotherapy
Arm description:	
Participants received 1000 mg intravenous rituximab infusions at Weeks 8 and 10 and weekly subcutaneous injections of belimumab matching placebo up to Week 52 in the treatment period. Participants then entered in a 16-week no-treatment GFU period.	
Arm type	Active comparator
Investigational medicinal product name	Rituximab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use
Dosage and administration details:	
Participants received rituximab 1000 mg intravenous (IV) infusions at Weeks 8 and 10.	
Investigational medicinal product name	Belimumab placebo
Investigational medicinal product code	
Other name	

Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Participants received belimumab placebo weekly subcutaneous injections up to Week 52.

Number of subjects in period 1	Placebo	Belimumab + Rituximab Co-administration therapy	Belimumab Monotherapy
Started	13	24	24
Completed	9	17	19
Not completed	4	7	5
Adverse event, serious fatal	-	1	-
Consent withdrawn by subject	1	1	2
Physician decision	1	-	-
Adverse event, non-fatal	1	4	2
Reached stopping criteria	-	-	1
Lack of efficacy	1	1	-

Number of subjects in period 1	Rituximab Monotherapy
Started	25
Completed	17
Not completed	8
Adverse event, serious fatal	-
Consent withdrawn by subject	5
Physician decision	1
Adverse event, non-fatal	2
Reached stopping criteria	-
Lack of efficacy	-

Period 2

Period 2 title	General follow-up (GFU) (Up to Week 68)
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes

Arm title	Placebo

Arm description:

Participants received belimumab matching placebo weekly subcutaneous injections up to Week 52 and rituximab matching placebo infusions at Weeks 8 and 10 in the treatment period. Participants then entered in a 16-week no-treatment General Follow-Up (GFU) period.

Arm type	Placebo
Investigational medicinal product name	Rituximab placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Participants received rituximab placebo infusions at Weeks 8 and 10.

Investigational medicinal product name	Belimumab placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Participants received belimumab placebo weekly subcutaneous injections up to Week 52.

Arm title	Belimumab + Rituximab Co-administration therapy

Arm description:

Participants received belimumab 200 milligrams (mg) weekly subcutaneous injections for 24 weeks followed by belimumab matching placebo injections weekly up to Week 52; along with rituximab 1000 mg intravenous infusions at Weeks 8 and 10 in the treatment period. Participants then entered in a 16-week no-treatment GFU period.

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

Dosage and administration details:

Participants received belimumab 200 milligrams (mg) weekly subcutaneous injections up to Week 52.

Investigational medicinal product name	Belimumab placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Participants received belimumab placebo weekly subcutaneous injections up to Week 52.

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

Dosage and administration details:

Participants received rituximab 1000 mg intravenous (IV) infusions at Weeks 8 and 10.

Arm title	Belimumab Monotherapy

Arm description:

Participants received 200 mg weekly subcutaneous injections of belimumab up to Week 52 and rituximab matching placebo infusions at Weeks 8 and 10 in the treatment period. Participants then entered in a 16-week no-treatment GFU period.

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

Dosage and administration details:

Participants received belimumab 200 milligrams (mg) weekly subcutaneous injections up to Week 52.

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

Dosage and administration details:

Participants received rituximab placebo infusions at Weeks 8 and 10.

Arm title	Rituximab Monotherapy

Arm description:

Participants received 1000 mg intravenous rituximab infusions at Weeks 8 and 10 and weekly subcutaneous injections of belimumab matching placebo up to Week 52 in the treatment period. Participants then entered in a 16-week no-treatment GFU period.

Arm type	Active comparator
Investigational medicinal product name	Rituximab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Participants received rituximab 1000 mg intravenous (IV) infusions at Weeks 8 and 10.

Investigational medicinal product name	Belimumab placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Participants received belimumab placebo weekly subcutaneous injections up to Week 52.

Number of subjects in period 2	Placebo	Belimumab + Rituximab Co-administration therapy	Belimumab Monotherapy
Started	9	17	19
Completed	8	17	19
Not completed	1	0	0
Lost to follow-up	1	-	-

Number of subjects in period 2	Rituximab Monotherapy
Started	17
Completed	16
Not completed	1

Lost to follow-up	1

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Participants received belimumab matching placebo weekly subcutaneous injections up to Week 52 and rituximab matching placebo infusions at Weeks 8 and 10 in the treatment period. Participants then entered in a 16-week no-treatment General Follow-Up (GFU) period.	
Reporting group title	Belimumab + Rituximab Co-administration therapy
Reporting group description:	
Participants received belimumab 200 milligrams (mg) weekly subcutaneous injections for 24 weeks followed by belimumab matching placebo injections weekly up to Week 52; along with rituximab 1000 mg intravenous infusions at Weeks 8 and 10 in the treatment period. Participants then entered in a 16-week no-treatment GFU period.	
Reporting group title	Belimumab Monotherapy
Reporting group description:	
Participants received 200 mg weekly subcutaneous injections of belimumab up to Week 52 and rituximab matching placebo infusions at Weeks 8 and 10 in the treatment period. Participants then entered in a 16-week no-treatment GFU period.	
Reporting group title	Rituximab Monotherapy
Reporting group description:	
Participants received 1000 mg intravenous rituximab infusions at Weeks 8 and 10 and weekly subcutaneous injections of belimumab matching placebo up to Week 52 in the treatment period. Participants then entered in a 16-week no-treatment GFU period.	

Reporting group values	Placebo	Belimumab + Rituximab Co-administration therapy	Belimumab Monotherapy
Number of subjects	13	24	24
Age categorical Units: Subjects			
All participants	13	24	24
Age Continuous Units: Years			
arithmetic mean	52.7	45.1	52.0
standard deviation	± 12.67	± 10.93	± 11.49
Sex: Female, Male Units: Participants			
Female	13	22	22
Male	0	2	2
Race/Ethnicity, Customized Units: Subjects			
African American/African Heritage	1	2	2
American Indian or Alaskan Native	0	0	0
Asian - East Asian Heritage	0	1	1
White - Arabic/North African Heritage	0	2	3
White-White/Caucasian/European Heritage	12	18	18
African American/African and Asian Heritage	0	1	0

Reporting group values	Rituximab Monotherapy	Total	
Number of subjects	25	86	
Age categorical Units: Subjects			
All participants	25	86	
Age Continuous Units: Years			
arithmetic mean	55.2		
standard deviation	± 15.07	-	
Sex: Female, Male Units: Participants			
Female	23	80	
Male	2	6	
Race/Ethnicity, Customized Units: Subjects			
African American/African Heritage	1	6	
American Indian or Alaskan Native	1	1	
Asian - East Asian Heritage	2	4	
White - Arabic/North African Heritage	0	5	
White-White/Caucasian/European Heritage	21	69	
African American/African and Asian Heritage	0	1	

End points

End points reporting groups

Reporting group title	Placebo

Reporting group description:

Participants received belimumab matching placebo weekly subcutaneous injections up to Week 52 and rituximab matching placebo infusions at Weeks 8 and 10 in the treatment period. Participants then entered in a 16-week no-treatment General Follow-Up (GFU) period.

Reporting group title	Belimumab + Rituximab Co-administration therapy

Reporting group description:

Participants received belimumab 200 milligrams (mg) weekly subcutaneous injections for 24 weeks followed by belimumab matching placebo injections weekly up to Week 52; along with rituximab 1000 mg intravenous infusions at Weeks 8 and 10 in the treatment period. Participants then entered in a 16-week no-treatment GFU period.

Reporting group title	Belimumab Monotherapy

Reporting group description:

Participants received 200 mg weekly subcutaneous injections of belimumab up to Week 52 and rituximab matching placebo infusions at Weeks 8 and 10 in the treatment period. Participants then entered in a 16-week no-treatment GFU period.

Reporting group title	Rituximab Monotherapy

Reporting group description:

Participants received 1000 mg intravenous rituximab infusions at Weeks 8 and 10 and weekly subcutaneous injections of belimumab matching placebo up to Week 52 in the treatment period. Participants then entered in a 16-week no-treatment GFU period.

Reporting group title	Placebo

Reporting group description:

Participants received belimumab matching placebo weekly subcutaneous injections up to Week 52 and rituximab matching placebo infusions at Weeks 8 and 10 in the treatment period. Participants then entered in a 16-week no-treatment General Follow-Up (GFU) period.

Reporting group title	Belimumab + Rituximab Co-administration therapy

Reporting group description:

Participants received belimumab 200 milligrams (mg) weekly subcutaneous injections for 24 weeks followed by belimumab matching placebo injections weekly up to Week 52; along with rituximab 1000 mg intravenous infusions at Weeks 8 and 10 in the treatment period. Participants then entered in a 16-week no-treatment GFU period.

Reporting group title	Belimumab Monotherapy

Reporting group description:

Participants received 200 mg weekly subcutaneous injections of belimumab up to Week 52 and rituximab matching placebo infusions at Weeks 8 and 10 in the treatment period. Participants then entered in a 16-week no-treatment GFU period.

Reporting group title	Rituximab Monotherapy

Reporting group description:

Participants received 1000 mg intravenous rituximab infusions at Weeks 8 and 10 and weekly subcutaneous injections of belimumab matching placebo up to Week 52 in the treatment period. Participants then entered in a 16-week no-treatment GFU period.

Primary: Number of participants with serious adverse events (SAE) and non-serious AEs (non-SAE)

End point title	Number of participants with serious adverse events (SAE) and non-serious AEs (non-SAE)[1]

End point description:

An AE is any untoward medical occurrence in a participant or clinical investigation participant, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. An SAE is any untoward medical occurrence that at any dose results in death, is life-threatening, requires hospitalization or prolongation of existing hospitalization, results in

disability/incapacity, is a congenital anomaly/birth defect, other situations based on medical or scientific judgment and is associated with liver injury and impaired liver function. Data for number of participants with SAE and non-SAE has been summarized. Safety Population comprised of all participants who received at least one dose of study treatment.

End point type	Primary

End point timeframe:

Up to Week 68

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: There are no statistical data to report.

End point values	Placebo	Belimumab + Rituximab Co-administration therapy	Belimumab Monotherapy	Rituximab Monotherapy
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	13[2]	24[3]	24[4]	25[5]
Units: Participants				
Any SAE	0	3	2	4
Any non-SAE	12	24	23	17

Notes:

[2] - Safety Population

[3] - Safety Population

[4] - Safety Population

[5] - Safety Population

Statistical analyses

No statistical analyses for this end point

Primary: Number of participants with adverse event of special interests (AESIs)

End point title	Number of participants with adverse event of special interests (AESIs)[6]

End point description:

An AE is any untoward medical occurrence in a participant or clinical investigation participant, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. AESIs were Malignant Neoplasms, Post-Administration Systemic Reactions (PASR), All Infections of Special Interest (opportunistic infections, herpes zoster, tuberculosis and sepsis), Depression/suicide/self-injury, Deaths and study specific AESI which includes: severe skin reaction per GlaxoSmithKline (GSK) Adjudication, cardiac disorders, Posterior Reversible Encephalopathy Syndrome (PRES) and Progressive multifocal leukoencephalopathy (PML). Data for number of participants with AESI has been summarized.

End point type	Primary

End point timeframe:

Up to Week 68

Notes:

[6] - 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: There are no statistical data to report.

End point values	Placebo	Belimumab + Rituximab Co-administration therapy	Belimumab Monotherapy	Rituximab Monotherapy
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	13[7]	24[8]	24[9]	25[10]
Units: Participants				
Malignant Neoplasms	0	0	0	1
PASR	4	2	3	5
All Infections of Special Interest	2	1	3	2
Depression/Suicide/Self-injury	0	3	5	1
Deaths	0	1	0	0
Severe Skin Reactions	0	0	0	0
Cardiac Disorders	0	1	0	1
PRES	0	0	0	0
PML	0	0	0	0

Notes:

[7] - Safety Population

[8] - Safety Population

[9] - Safety Population

[10] - Safety Population

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in European League Against Rheumatism (EULAR) Sjogren's Syndrome Disease Activity Index (ESSDAI) Total scores over time

End point title	Change from Baseline in European League Against Rheumatism (EULAR) Sjogren's Syndrome Disease Activity Index (ESSDAI) Total scores over time

End point description:

ESSDAI is a disease activity index developed by EULAR consortium consisting of twelve clinically relevant organ specific domains. Each domain has 3 or 4 possible activity levels (i.e., no, low, moderate, high [if available]) using a 4-point scale, ranging from 0 (No activity) to 3 (High activity). Higher score indicates high disease activity. Each domain is assigned a weight between 1 and 6. Total ESSDAI Scores are obtained by multiplying level of activity (domain score) by domain weights, ranges between 0 (no activity) and 123 (highest activity). Higher score indicates more disease activity. Baseline value is screening visit value. Change from Baseline was defined as post-dose visit value minus Baseline value. Completer Population comprised of participants who completed 52 Week treatment visits and general follow up phase of study including visit at Week 68. Only those participants with data available at specified data points were analyzed (represented by n=X in category titles).

End point type	Secondary

End point timeframe:

Baseline (Screening [within 35 days prior to Day 0]), Week 12, Week 24, Week 36, Week 52 and Week 68

End point values	Placebo	Belimumab + Rituximab Co-administration therapy	Belimumab Monotherapy	Rituximab Monotherapy
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	8[11]	17[12]	19[13]	16[14]
Units: Scores on a scale				

least squares mean (standard error)				
Week 12; n=8, 17, 19 ,15	-2.00 (± 1.449)	-4.85 (± 0.996)	-3.87 (± 0.949)	-4.22 (± 1.048)
Week 24; n=8, 17, 19 ,16	-2.87 (± 1.324)	-5.32 (± 0.911)	-3.87 (± 0.869)	-5.25 (± 0.940)
Week 36; n=8, 17, 19 ,16	-3.12 (± 1.520)	-4.09 (± 1.045)	-4.23 (± 0.995)	-4.94 (± 1.079)
Week 52;n=8, 17, 19 ,16	-2.87 (± 1.294)	-5.67 (± 0.890)	-4.76 (± 0.850)	-4.32 (± 0.919)
Week 68;n=8, 17, 19 ,16	-1.75 (± 1.400)	-5.73 (± 0.962)	-3.87 (± 0.918)	-4.38 (± 0.994)

Notes:

[11] - Completer Population

[12] - Completer Population

[13] - Completer Population

[14] - Completer Population

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Week 12. Analysis was performed using mixed effects repeated measures model, with Baseline, treatment, visit and interactions of visit with treatment as fixed effects and participant as a random effect.

Comparison groups	Placebo v Belimumab + Rituximab Co-administration therapy
Number of subjects included in analysis	25
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Least square (LS) mean difference
Point estimate	-2.86
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.38
upper limit	0.67
Variability estimate	Standard error of the mean
Dispersion value	1.758

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

Week 12. Analysis was performed using mixed effects repeated measures model, with Baseline, treatment, visit and interactions of visit with treatment as fixed effects and participant as a random effect.

Comparison groups	Belimumab + Rituximab Co-administration therapy v Belimumab Monotherapy
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	LS mean difference
Point estimate	-0.99

Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.75
upper limit	1.78
Variability estimate	Standard error of the mean
Dispersion value	1.382

Statistical analysis title	Statistical Analysis 3

Statistical analysis description:

Week 12. Analysis was performed using mixed effects repeated measures model, with Baseline, treatment, visit and interactions of visit with treatment as fixed effects and participant as a random effect.

Comparison groups	Belimumab + Rituximab Co-administration therapy v Rituximab Monotherapy
Number of subjects included in analysis	33
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	LS mean difference
Point estimate	-0.63
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.52
upper limit	2.26
Variability estimate	Standard error of the mean
Dispersion value	1.442

Statistical analysis title	Statistical Analysis 4

Statistical analysis description:

Week 12. Analysis was performed using mixed effects repeated measures model, with Baseline, treatment, visit and interactions of visit with treatment as fixed effects and participant as a random effect.

Comparison groups	Placebo v Belimumab Monotherapy
Number of subjects included in analysis	27
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	LS mean difference
Point estimate	-1.87
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.34
upper limit	1.6
Variability estimate	Standard error of the mean
Dispersion value	1.732

Statistical analysis title	Statistical Analysis 5
Statistical analysis description:	
Week 12. Analysis was performed using mixed effects repeated measures model, with Baseline, treatment, visit and interactions of visit with treatment as fixed effects and participant as a random effect.	
Comparison groups	Belimumab Monotherapy v Rituximab Monotherapy
Number of subjects included in analysis	35
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	LS mean difference
Point estimate	0.35
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.5
upper limit	3.2
Variability estimate	Standard error of the mean
Dispersion value	1.422

Statistical analysis title	Statistical Analysis 6
Statistical analysis description:	
Week 24. Analysis was performed using mixed effects repeated measures model, with Baseline, treatment, visit and interactions of visit with treatment as fixed effects and participant as a random effect.	
Comparison groups	Placebo v Belimumab + Rituximab Co-administration therapy
Number of subjects included in analysis	25
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	LS mean difference
Point estimate	-2.45
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.67
upper limit	0.77
Variability estimate	Standard error of the mean
Dispersion value	1.607

Statistical analysis title	Statistical Analysis 7
Statistical analysis description:	
Week 24. Analysis was performed using mixed effects repeated measures model, with Baseline, treatment, visit and interactions of visit with treatment as fixed effects and participant as a random effect.	
Comparison groups	Belimumab + Rituximab Co-administration therapy v Belimumab Monotherapy

Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	LS mean difference
Point estimate	-1.46
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.99
upper limit	1.08
Variability estimate	Standard error of the mean
Dispersion value	1.265

Statistical analysis title	Statistical Analysis 8

Statistical analysis description:

Week 24. Analysis was performed using mixed effects repeated measures model, with Baseline, treatment, visit and interactions of visit with treatment as fixed effects and participant as a random effect.

Comparison groups	Belimumab + Rituximab Co-administration therapy v Rituximab Monotherapy
Number of subjects included in analysis	33
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	LS mean difference
Point estimate	-0.07
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.68
upper limit	2.55
Variability estimate	Standard error of the mean
Dispersion value	1.305

Statistical analysis title	Statistical Analysis 9

Statistical analysis description:

Week 24. Analysis was performed using mixed effects repeated measures model, with Baseline, treatment, visit and interactions of visit with treatment as fixed effects and participant as a random effect.

Comparison groups	Placebo v Belimumab Monotherapy
Number of subjects included in analysis	27
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	LS mean difference
Point estimate	-1

Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.17
upper limit	2.18
Variability estimate	Standard error of the mean
Dispersion value	1.584

Statistical analysis title	Statistical Analysis 10

Statistical analysis description:

Week 24. Analysis was performed using mixed effects repeated measures model, with Baseline, treatment, visit and interactions of visit with treatment as fixed effects and participant as a random effect.

Comparison groups	Belimumab Monotherapy v Rituximab Monotherapy
Number of subjects included in analysis	35
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	LS mean difference
Point estimate	1.39
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.2
upper limit	3.97
Variability estimate	Standard error of the mean
Dispersion value	1.29

Statistical analysis title	Statistical Analysis 11

Statistical analysis description:

Week 36. Analysis was performed using mixed effects repeated measures model, with Baseline, treatment, visit and interactions of visit with treatment as fixed effects and participant as a random effect.

Comparison groups	Placebo v Belimumab + Rituximab Co-administration therapy
Number of subjects included in analysis	25
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	LS mean difference
Point estimate	-0.97
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.66
upper limit	2.73
Variability estimate	Standard error of the mean
Dispersion value	1.845

Statistical analysis title	Statistical Analysis 12

Statistical analysis description:

Week 36. Analysis was performed using mixed effects repeated measures model, with Baseline, treatment, visit and interactions of visit with treatment as fixed effects and participant as a random effect.

Comparison groups	Belimumab + Rituximab Co-administration therapy v Belimumab Monotherapy
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	LS mean difference
Point estimate	0.15
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.76
upper limit	3.05
Variability estimate	Standard error of the mean
Dispersion value	1.449

Statistical analysis title	Statistical Analysis 13

Statistical analysis description:

Week 36. Analysis was performed using mixed effects repeated measures model, with Baseline, treatment, visit and interactions of visit with treatment as fixed effects and participant as a random effect.

Comparison groups	Belimumab + Rituximab Co-administration therapy v Rituximab Monotherapy
Number of subjects included in analysis	33
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	LS mean difference
Point estimate	0.85
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.15
upper limit	3.86
Variability estimate	Standard error of the mean
Dispersion value	1.498

Statistical analysis title	Statistical Analysis 14

Statistical analysis description:

Week 36. Analysis was performed using mixed effects repeated measures model, with Baseline, treatment, visit and interactions of visit with treatment as fixed effects and participant as a random effect.

Comparison groups	Placebo v Belimumab Monotherapy
Number of subjects included in analysis	27
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	LS mean difference
Point estimate	-1.11
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.76
upper limit	2.53
Variability estimate	Standard error of the mean
Dispersion value	1.817

Statistical analysis title	Statistical Analysis 15

Statistical analysis description:

Week 36. Analysis was performed using mixed effects repeated measures model, with Baseline, treatment, visit and interactions of visit with treatment as fixed effects and participant as a random effect.

Comparison groups	Belimumab Monotherapy v Rituximab Monotherapy
Number of subjects included in analysis	35
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	LS mean difference
Point estimate	0.71
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.25
upper limit	3.66
Variability estimate	Standard error of the mean
Dispersion value	1.476

Statistical analysis title	Statistical Analysis 16

Statistical analysis description:

Week 52. Analysis was performed using mixed effects repeated measures model, with Baseline, treatment, visit and interactions of visit with treatment as fixed effects and participant as a random effect.

Comparison groups	Placebo v Belimumab + Rituximab Co-administration therapy
Number of subjects included in analysis	25
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	LS mean difference
Point estimate	-2.8

Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.95
upper limit	0.34
Variability estimate	Standard error of the mean
Dispersion value	1.57

Statistical analysis title	Statistical Analysis 17

Statistical analysis description:

Week 52. Analysis was performed using mixed effects repeated measures model, with Baseline, treatment, visit and interactions of visit with treatment as fixed effects and participant as a random effect.

Comparison groups	Belimumab + Rituximab Co-administration therapy v Belimumab Monotherapy
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	LS mean difference
Point estimate	-0.91
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.39
upper limit	1.56
Variability estimate	Standard error of the mean
Dispersion value	1.237

Statistical analysis title	Statistical Analysis 18

Statistical analysis description:

Week 52. Analysis was performed using mixed effects repeated measures model, with Baseline, treatment, visit and interactions of visit with treatment as fixed effects and participant as a random effect.

Comparison groups	Belimumab + Rituximab Co-administration therapy v Rituximab Monotherapy
Number of subjects included in analysis	33
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	LS mean difference
Point estimate	-1.36
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.91
upper limit	1.2
Variability estimate	Standard error of the mean
Dispersion value	1.275

Statistical analysis title	Statistical Analysis 19
Statistical analysis description:	
Week 52. Analysis was performed using mixed effects repeated measures model, with Baseline, treatment, visit and interactions of visit with treatment as fixed effects and participant as a random effect.	
Comparison groups	Placebo v Belimumab Monotherapy
Number of subjects included in analysis	27
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	LS mean difference
Point estimate	-1.89
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.99
upper limit	1.21
Variability estimate	Standard error of the mean
Dispersion value	1.548

Statistical analysis title	Statistical Analysis 20
Statistical analysis description:	
Week 52. Analysis was performed using mixed effects repeated measures model, with Baseline, treatment, visit and interactions of visit with treatment as fixed effects and participant as a random effect.	
Comparison groups	Belimumab Monotherapy v Rituximab Monotherapy
Number of subjects included in analysis	35
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	LS mean difference
Point estimate	-0.44
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.97
upper limit	2.08
Variability estimate	Standard error of the mean
Dispersion value	1.261

Statistical analysis title	Statistical Analysis 21
Statistical analysis description:	
Week 68. Analysis was performed using mixed effects repeated measures model, with Baseline, treatment, visit and interactions of visit with treatment as fixed effects and participant as a random effect.	
Comparison groups	Placebo v Belimumab + Rituximab Co-administration therapy

Number of subjects included in analysis	25
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	LS mean difference
Point estimate	-3.99
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.39
upper limit	-0.58
Variability estimate	Standard error of the mean
Dispersion value	1.699

Statistical analysis title	Statistical Analysis 22

Statistical analysis description:

Week 68. Analysis was performed using mixed effects repeated measures model, with Baseline, treatment, visit and interactions of visit with treatment as fixed effects and participant as a random effect.

Comparison groups	Belimumab + Rituximab Co-administration therapy v Belimumab Monotherapy
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	LS mean difference
Point estimate	-1.87
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.54
upper limit	0.81
Variability estimate	Standard error of the mean
Dispersion value	1.336

Statistical analysis title	Statistical Analysis 23

Statistical analysis description:

Week 68. Analysis was performed using mixed effects repeated measures model, with Baseline, treatment, visit and interactions of visit with treatment as fixed effects and participant as a random effect.

Comparison groups	Belimumab + Rituximab Co-administration therapy v Rituximab Monotherapy
Number of subjects included in analysis	33
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	LS mean difference
Point estimate	-1.35

Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.12
upper limit	1.41
Variability estimate	Standard error of the mean
Dispersion value	1.379

Statistical analysis title	Statistical Analysis 24

Statistical analysis description:

Week 68. Analysis was performed using mixed effects repeated measures model, with Baseline, treatment, visit and interactions of visit with treatment as fixed effects and participant as a random effect.

Comparison groups	Placebo v Belimumab Monotherapy
Number of subjects included in analysis	27
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	LS mean difference
Point estimate	-2.12
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.47
upper limit	1.23
Variability estimate	Standard error of the mean
Dispersion value	1.674

Statistical analysis title	Statistical Analysis 25

Statistical analysis description:

Week 68. Analysis was performed using mixed effects repeated measures model, with Baseline, treatment, visit and interactions of visit with treatment as fixed effects and participant as a random effect.

Comparison groups	Belimumab Monotherapy v Rituximab Monotherapy
Number of subjects included in analysis	35
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	LS mean difference
Point estimate	0.51
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.21
upper limit	3.24
Variability estimate	Standard error of the mean
Dispersion value	1.362

Secondary: Stimulated salivary flow rate over time

End point title	Stimulated salivary flow rate over time

End point description:

Participants were instructed to chew a piece of paraffin wax for a period of 5 minutes and saliva was collected. The volume of saliva (milliliter) was divided by the duration of the test (minutes) to calculate the stimulated salivary flow rate (milliliter per minute). Baseline value is the screening visit value (within 35 days prior to Day 0). Only those participants with data available at the specified data points were analyzed (represented by n=X in category titles).

End point type	Secondary

End point timeframe:

Baseline (Screening [within 35 days prior to Day 0]), Week 12, Week 24, Week 36, Week 52 and Week 68

End point values	Placebo	Belimumab + Rituximab Co-administration therapy	Belimumab Monotherapy	Rituximab Monotherapy
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	8[15]	17[16]	19[17]	16[18]
Units: Milliliter per minute				
arithmetic mean (standard deviation)				
Baseline (Screening); n=8, 17, 19 ,16	0.470 (± 0.2470)	0.714 (± 0.6294)	0.425 (± 0.3292)	0.618 (± 0.6211)
Week 12; n=8, 17, 19 ,16	0.486 (± 0.2045)	0.754 (± 0.8342)	0.493 (± 0.3733)	0.581 (± 0.5265)
Week 24; n=8, 17, 19 ,16	0.554 (± 0.3054)	0.784 (± 0.7900)	0.454 (± 0.4105)	0.724 (± 0.8901)
Week 36; n=8, 17, 19 ,15	0.404 (± 0.2497)	1.039 (± 1.1027)	0.506 (± 0.4261)	0.689 (± 0.5907)
Week 52; n=8, 17, 19 ,16	0.531 (± 0.3782)	0.999 (± 1.1457)	0.582 (± 0.6084)	0.693 (± 0.7813)
Week 68; n=8, 17, 19 ,15	0.361 (± 0.1628)	0.879 (± 0.8167)	0.517 (± 0.4499)	0.733 (± 0.7850)

Notes:

[15] - Completer Population

[16] - Completer Population

[17] - Completer Population

[18] - Completer Population

Statistical analyses

No statistical analyses for this end point

Secondary: Oral dryness numeric response scale (NRS) over time

End point title	Oral dryness numeric response scale (NRS) over time

End point description:

Oral dryness was reported by participants on a numeric response scale, ranging from 0 (no dryness) to 10 (maximal dryness), higher score indicates worst imaginable dryness. Baseline value is the screening visit value (within 35 days prior to Day 0). Only those participants with data available at the specified data points were analyzed (represented by n=X in category titles).

End point type	Secondary

End point timeframe:

Baseline (Screening [within 35 days prior to Day 0]), Week 12, Week 24, Week 36, Week 52 and Week 68

End point values	Placebo	Belimumab + Rituximab Co-administration therapy	Belimumab Monotherapy	Rituximab Monotherapy
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	8[19]	17[20]	19[21]	16[22]
Units: Scores on a scale				
arithmetic mean (standard deviation)				
Baseline (Screening); n= 8, 17, 19, 16	7.6 (± 1.51)	7.4 (± 1.46)	7.2 (± 2.14)	7.3 (± 1.91)
Week 12; n=8, 17, 19, 16	6.1 (± 2.59)	5.7 (± 1.96)	6.9 (± 2.32)	5.1 (± 2.77)
Week 24; n=8, 17, 19, 15	5.8 (± 2.38)	5.3 (± 1.83)	6.8 (± 2.51)	5.6 (± 2.72)
Week 36; n=8, 17, 19, 16	5.8 (± 2.76)	5.9 (± 2.26)	6.6 (± 2.19)	6.2 (± 2.51)
Week 52; n=8, 17, 19, 16	5.6 (± 2.13)	5.7 (± 1.92)	7.0 (± 2.40)	6.3 (± 2.32)
Week 68; n=8, 17, 19, 16	6.6 (± 2.26)	6.1 (± 2.63)	6.9 (± 2.34)	6.1 (± 2.62)

Notes:

[19] - Completer Population

[20] - Completer Population

[21] - Completer Population

[22] - Completer Population

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute values for B-cells (cluster of differentiation 20 [CD20]) within salivary gland biopsy at Week 24

End point title	Absolute values for B-cells (cluster of differentiation 20 [CD20]) within salivary gland biopsy at Week 24

End point description:

Minor salivary gland biopsies were taken for histological analysis to quantify CD20 B Cells. Only those participants with data available at the specified data points were analyzed.

End point type	Secondary

End point timeframe:

At Week 24

End point values	Placebo	Belimumab + Rituximab Co-administration therapy	Belimumab Monotherapy	Rituximab Monotherapy
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	8[23]	10[24]	15[25]	12[26]
Units: Cells per millimeter square				
arithmetic mean (standard deviation)	380.21719 (± 569.908102)	8.65550 (± 20.199794)	396.86058 (± 781.245844)	650.76069 (± 1311.360352)

Notes:
[23] - Completer Population
[24] - Completer Population
[25] - Completer Population
[26] - Completer Population

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Serious adverse events (SAEs) and non-SAEs were collected up to Week 68.

Adverse event reporting additional description:

Safety Population was used to assess SAEs and non-SAEs which comprised of all participants who received at least one dose of study treatment.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	23.1

Reporting groups

Reporting group title	Placebo

Reporting group description:

Participants received belimumab matching placebo weekly subcutaneous injections up to Week 52 and rituximab matching placebo infusions at Weeks 8 and 10 in the treatment period. Participants then entered in a 16-week no-treatment General Follow-Up (GFU) period.

Reporting group title	Belimumab + Rituximab Co-administration therapy

Reporting group description:

Participants received belimumab 200 milligrams (mg) weekly subcutaneous injections for 24 weeks followed by belimumab matching placebo injections weekly up to Week 52; along with rituximab 1000 mg intravenous infusions at Weeks 8 and 10 in the treatment period. Participants then entered in a 16-week no-treatment GFU period.

Reporting group title	Belimumab Monotherapy

Reporting group description:

Participants received 200 mg weekly subcutaneous injections of belimumab up to Week 52 and rituximab matching placebo infusions at Weeks 8 and 10 in the treatment period. Participants then entered in a 16-week no-treatment GFU period.

Reporting group title	Rituximab Monotherapy

Reporting group description:

Participants received 1000 mg intravenous rituximab infusions at Weeks 8 and 10 and weekly subcutaneous injections of belimumab matching placebo up to Week 52 in the treatment period. Participants then entered in a 16-week no-treatment GFU period.

Serious adverse events	Placebo	Belimumab + Rituximab Co-administration therapy	Belimumab Monotherapy
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 13 (0.00%)	3 / 24 (12.50%)	2 / 24 (8.33%)
number of deaths (all causes)	0	1	0
number of deaths resulting from adverse events			
Injury, poisoning and procedural complications			
Tendon rupture			
subjects affected / exposed	0 / 13 (0.00%)	0 / 24 (0.00%)	0 / 24 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Vascular disorders			
Hypotension			
subjects affected / exposed	0 / 13 (0.00%)	0 / 24 (0.00%)	0 / 24 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Atrial flutter			
subjects affected / exposed	0 / 13 (0.00%)	1 / 24 (4.17%)	0 / 24 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure acute			
subjects affected / exposed	0 / 13 (0.00%)	0 / 24 (0.00%)	0 / 24 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	0 / 13 (0.00%)	0 / 24 (0.00%)	0 / 24 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Aspiration			
subjects affected / exposed	0 / 13 (0.00%)	1 / 24 (4.17%)	0 / 24 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	0 / 13 (0.00%)	0 / 24 (0.00%)	0 / 24 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Sjogren's syndrome			
subjects affected / exposed	0 / 13 (0.00%)	0 / 24 (0.00%)	1 / 24 (4.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			

Bronchitis			
subjects affected / exposed	0 / 13 (0.00%)	0 / 24 (0.00%)	0 / 24 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Enterocolitis infectious			
subjects affected / exposed	0 / 13 (0.00%)	1 / 24 (4.17%)	0 / 24 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ophthalmic herpes zoster			
subjects affected / exposed	0 / 13 (0.00%)	0 / 24 (0.00%)	0 / 24 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	0 / 13 (0.00%)	0 / 24 (0.00%)	1 / 24 (4.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyelonephritis			
subjects affected / exposed	0 / 13 (0.00%)	1 / 24 (4.17%)	0 / 24 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Rituximab Monotherapy		
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 25 (16.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events			
Injury, poisoning and procedural complications			
Tendon rupture			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Hypotension			

subjects affected / exposed	1 / 25 (4.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Atrial flutter			
subjects affected / exposed	0 / 25 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cardiac failure acute			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Aspiration			
subjects affected / exposed	0 / 25 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Sjogren's syndrome			
subjects affected / exposed	0 / 25 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Bronchitis			

subjects affected / exposed	1 / 25 (4.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Enterocolitis infectious			
subjects affected / exposed	0 / 25 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Ophthalmic herpes zoster			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	0 / 25 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pyelonephritis			
subjects affected / exposed	0 / 25 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Placebo	Belimumab + Rituximab Co-administration therapy	Belimumab Monotherapy
Total subjects affected by non-serious adverse events			
subjects affected / exposed	12 / 13 (92.31%)	24 / 24 (100.00%)	23 / 24 (95.83%)
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 13 (0.00%)	1 / 24 (4.17%)	2 / 24 (8.33%)
occurrences (all)	0	1	2
Nervous system disorders			
Headache			
subjects affected / exposed	2 / 13 (15.38%)	5 / 24 (20.83%)	4 / 24 (16.67%)
occurrences (all)	3	7	5
Dizziness			

subjects affected / exposed	0 / 13 (0.00%)	2 / 24 (8.33%)	6 / 24 (25.00%)
occurrences (all)	0	2	9
Migraine			
subjects affected / exposed	0 / 13 (0.00%)	1 / 24 (4.17%)	2 / 24 (8.33%)
occurrences (all)	0	2	2
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	3 / 13 (23.08%)	6 / 24 (25.00%)	2 / 24 (8.33%)
occurrences (all)	5	6	2
Pyrexia			
subjects affected / exposed	4 / 13 (30.77%)	3 / 24 (12.50%)	2 / 24 (8.33%)
occurrences (all)	4	3	2
Asthenia			
subjects affected / exposed	2 / 13 (15.38%)	2 / 24 (8.33%)	1 / 24 (4.17%)
occurrences (all)	4	2	1
Influenza like illness			
subjects affected / exposed	1 / 13 (7.69%)	2 / 24 (8.33%)	2 / 24 (8.33%)
occurrences (all)	1	2	2
Injection site pain			
subjects affected / exposed	1 / 13 (7.69%)	2 / 24 (8.33%)	2 / 24 (8.33%)
occurrences (all)	1	2	2
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	3 / 13 (23.08%)	3 / 24 (12.50%)	3 / 24 (12.50%)
occurrences (all)	3	5	3
Nausea			
subjects affected / exposed	1 / 13 (7.69%)	1 / 24 (4.17%)	3 / 24 (12.50%)
occurrences (all)	2	1	3
Abdominal pain upper			
subjects affected / exposed	1 / 13 (7.69%)	1 / 24 (4.17%)	3 / 24 (12.50%)
occurrences (all)	1	1	4
Parotid gland enlargement			
subjects affected / exposed	1 / 13 (7.69%)	2 / 24 (8.33%)	1 / 24 (4.17%)
occurrences (all)	2	2	2
Respiratory, thoracic and mediastinal disorders			

Cough			
subjects affected / exposed	2 / 13 (15.38%)	1 / 24 (4.17%)	2 / 24 (8.33%)
occurrences (all)	2	1	2
Oropharyngeal pain			
subjects affected / exposed	0 / 13 (0.00%)	0 / 24 (0.00%)	4 / 24 (16.67%)
occurrences (all)	0	0	4
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	3 / 13 (23.08%)	3 / 24 (12.50%)	1 / 24 (4.17%)
occurrences (all)	4	3	1
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	2 / 13 (15.38%)	7 / 24 (29.17%)	7 / 24 (29.17%)
occurrences (all)	2	10	12
Back pain			
subjects affected / exposed	1 / 13 (7.69%)	2 / 24 (8.33%)	5 / 24 (20.83%)
occurrences (all)	3	2	5
Pain in extremity			
subjects affected / exposed	2 / 13 (15.38%)	3 / 24 (12.50%)	1 / 24 (4.17%)
occurrences (all)	2	3	1
Musculoskeletal pain			
subjects affected / exposed	0 / 13 (0.00%)	2 / 24 (8.33%)	2 / 24 (8.33%)
occurrences (all)	0	2	3
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	4 / 13 (30.77%)	8 / 24 (33.33%)	6 / 24 (25.00%)
occurrences (all)	10	11	9
Urinary tract infection			
subjects affected / exposed	3 / 13 (23.08%)	5 / 24 (20.83%)	3 / 24 (12.50%)
occurrences (all)	4	7	9
Upper respiratory tract infection			
subjects affected / exposed	1 / 13 (7.69%)	3 / 24 (12.50%)	2 / 24 (8.33%)
occurrences (all)	3	4	3
Bronchitis			
subjects affected / exposed	1 / 13 (7.69%)	2 / 24 (8.33%)	3 / 24 (12.50%)
occurrences (all)	1	2	3

Influenza			
subjects affected / exposed	3 / 13 (23.08%)	0 / 24 (0.00%)	4 / 24 (16.67%)
occurrences (all)	4	0	4
Oral herpes			
subjects affected / exposed	1 / 13 (7.69%)	2 / 24 (8.33%)	2 / 24 (8.33%)
occurrences (all)	1	2	2
Pneumonia			
subjects affected / exposed	2 / 13 (15.38%)	2 / 24 (8.33%)	1 / 24 (4.17%)
occurrences (all)	2	3	1

Non-serious adverse events	Rituximab Monotherapy		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	17 / 25 (68.00%)		
Vascular disorders			
Hypertension			
subjects affected / exposed	2 / 25 (8.00%)		
occurrences (all)	2		
Nervous system disorders			
Headache			
subjects affected / exposed	6 / 25 (24.00%)		
occurrences (all)	7		
Dizziness			
subjects affected / exposed	2 / 25 (8.00%)		
occurrences (all)	2		
Migraine			
subjects affected / exposed	2 / 25 (8.00%)		
occurrences (all)	2		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	2 / 25 (8.00%)		
occurrences (all)	2		
Pyrexia			
subjects affected / exposed	2 / 25 (8.00%)		
occurrences (all)	2		
Asthenia			

subjects affected / exposed occurrences (all) Influenza like illness subjects affected / exposed occurrences (all) Injection site pain subjects affected / exposed occurrences (all)	1 / 25 (4.00%) 1 0 / 25 (0.00%) 0 0 / 25 (0.00%) 0		
Gastrointestinal disorders Diarrhoea subjects affected / exposed occurrences (all) Nausea subjects affected / exposed occurrences (all) Abdominal pain upper subjects affected / exposed occurrences (all) Parotid gland enlargement subjects affected / exposed occurrences (all)	 1 / 25 (4.00%) 1 3 / 25 (12.00%) 3 0 / 25 (0.00%) 0 1 / 25 (4.00%) 1		
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all) Oropharyngeal pain subjects affected / exposed occurrences (all)	 1 / 25 (4.00%) 1 2 / 25 (8.00%) 2		
Skin and subcutaneous tissue disorders Rash subjects affected / exposed occurrences (all)	 1 / 25 (4.00%) 3		
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all)	 5 / 25 (20.00%) 5		

Back pain subjects affected / exposed occurrences (all) Pain in extremity subjects affected / exposed occurrences (all) Musculoskeletal pain subjects affected / exposed occurrences (all)	 2 / 25 (8.00%) 3 1 / 25 (4.00%) 2 1 / 25 (4.00%) 1		
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all) Urinary tract infection subjects affected / exposed occurrences (all) Upper respiratory tract infection subjects affected / exposed occurrences (all) Bronchitis subjects affected / exposed occurrences (all) Influenza subjects affected / exposed occurrences (all) Oral herpes subjects affected / exposed occurrences (all) Pneumonia subjects affected / exposed occurrences (all)	 3 / 25 (12.00%) 4 2 / 25 (8.00%) 6 5 / 25 (20.00%) 6 2 / 25 (8.00%) 2 1 / 25 (4.00%) 2 3 / 25 (12.00%) 4 1 / 25 (4.00%) 1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
15 October 2015	Amendment 1: Protocol amended in response to comments received from Swedish regulatory authority. This was country-specific and applied to sites in Sweden. Information about the interim analysis was updated to provide clarity on the timing and number of the analysis. A modification to the withdrawal/stopping criteria language was made to specify that participants will be withdrawn from investigational product (IP) in the event of a life-threatening infection. A statement was also added to clarify that regulatory agency approval is required for the protocol and for substantial amendments to the protocol.
20 November 2015	Amendment 2: Protocol amended in response to comments received from Norwegian regulatory authority. This was country-specific and applied to all sites in Norway. The protocol was amended to clarify the number of participants required for the interim analysis and the basis for the sample size recalculation following that analysis. Language was also added to provide guidance regarding tuberculosis assessment during screening.
04 January 2016	Amendment 3: Protocol amended in response to comments received from Italian regulatory authority. This was country-specific and applied to sites in Italy. The protocol was amended to update the list of highly effective methods of contraception and to correct a typographical error regarding the permitted dose of hydroxychloroquine.
13 June 2016	Amendment 4: The primary reason for this amendment was to modify the participant selection criteria (specifically exclusion criterion number 30 pertaining to exclusionary laboratory thresholds) to better align with the intended population characteristics. Other amendments included the following: Greater clarity was provided regarding the committees involved in monitoring participant safety and review of study data as well as the governance of the study. It has been made clear that a single formal interim analysis is planned. The participant withdrawal and study stopping criteria have been modified. Greater detail was provided regarding prohibited and permitted medications. Additional guidance was provided regarding vaccination. Guidance has been provided for tuberculosis assessment during the screening period. The pregnancy section has been modified to clarify the duration of follow up required.
11 May 2018	Amendment 5: The primary reason for this amendment was to clarify the definition of “sponsor open” in Section 6.3, with respect to study blinding. Additional minor clarifications have been made throughout the protocol.
25 June 2019	Amendment 6: The primary reason for this amendment was to clarify the timing of unblinding for GlaxoSmithKline (GSK) staff and site staff. Additional minor updates have been made in several sections of the protocol.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported