Clinical trial results:
A Multicentre, Randomised, Double-blind, Placebo-controlled, Phase 3 Study Evaluating the Efficacy and Safety of Anifrolumab in Adult Subjects with Active Systemic Lupus Erythematosus

Summary

EudraCT number	2014-004632-19
Trial protocol	LT BE ES CZ DE BG
Global end of trial date	06 December 2018

Results information

Result version number	v1 (current)
This version publication date	21 March 2020
First version publication date	21 March 2020

Trial information

Trial identification

Sponsor protocol code	D3461C00004

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02446899
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	AstraZeneca AB
Sponsor organisation address	Forskargatan 18, Sudertalje, Sweden, 151 85
Public contact	Global Clinical Lead, AstraZeneca AB, +46 317761000, ClinicalTrialTransparency@astrazeneca.com
Scientific contact	Global Clinical Lead, AstraZeneca AB, + 46 317761000, ClinicalTrialTransparency@astrazeneca.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	19 August 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	27 September 2018
Global end of trial reached?	Yes
Global end of trial date	06 December 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the study was to evaluate the effect of anifrolumab 300 mg compared to placebo on disease activity as measured by the difference in the proportion of participants who achieved a British Isles Lupus Assessment Group-based Composite Lupus Assessment (BICLA) response at Week 52.

Protection of trial subjects:

The study was performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with ICH/GCP, applicable regulatory requirements and the AstraZeneca policy on Bioethics and Human Biological Samples.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	09 July 2015
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	3 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Japan: 43
Country: Number of subjects enrolled	Korea, Republic of: 10
Country: Number of subjects enrolled	Bulgaria: 8
Country: Number of subjects enrolled	Belgium: 2
Country: Number of subjects enrolled	France: 16
Country: Number of subjects enrolled	Germany: 10
Country: Number of subjects enrolled	Lithuania: 22
Country: Number of subjects enrolled	Russian Federation: 19
Country: Number of subjects enrolled	Spain: 20
Country: Number of subjects enrolled	Argentina: 12
Country: Number of subjects enrolled	Brazil: 23
Country: Number of subjects enrolled	Mexico: 32
Country: Number of subjects enrolled	South Africa: 13
Country: Number of subjects enrolled	Canada: 9
Country: Number of subjects enrolled	United States: 123
Worldwide total number of subjects	362
EEA total number of subjects	78

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)	356
From 65 to 84 years	6
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants took part in the trial at 119 sites in 15 countries worldwide.

Pre-assignment

Screening details:

Participants reported to the clinical study site for screening within 30 days of 1st study drug administration. 649 participants were screened, and 284 participants were screen failures. 365 participants were randomized, with 3 participant not receiving study drug. 362 participants received the study drug and were included in the full analysis set.

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, Carer, Data analyst, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Anifrolumab 300 mg

Arm description:

Anifrolumab (300 mg) administered via an intravenous infusion (IV) every 4 weeks for up to 48 weeks (13 doses).

Arm type	Experimental
Investigational medicinal product name	Anifrolumab
Investigational medicinal product code	MEDI-546
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

300 mg anifrolumab administered via a controlled intravenous infusion (IV) pump into a peripheral vein over at last 30 minutes, every 4 weeks for up to 48 weeks.

Arm title	Placebo

Arm description:

Matching placebo administered via an intravenous infusion (IV) every 4 weeks for up to 48 weeks (13 doses).

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

Dosage and administration details:

Matching placebo administered via a controlled intravenous infusion (IV) pump into a peripheral vein over at least 30 minutes, every 4 weeks for up to 48 weeks.

Number of subjects in period 1	Anifrolumab 300 mg	Placebo
Started	180	182
Completed	156	136
Not completed	24	46
Adverse event, serious fatal	1	-
Severe non-compliance to protocol	-	1
Consent withdrawn by subject	11	19
Adverse event, non-fatal	2	7
Condition under investigation worsened	1	4
Miscellaneous	5	4
Development of study specific withdrawal criteria	1	-
Lost to follow-up	1	3
Lack of efficacy	2	8

Baseline characteristics

Reporting groups	
Reporting group title	Anifrolumab 300 mg
Reporting group description:	
Anifrolumab (300 mg) administered via an intravenous infusion (IV) every 4 weeks for up to 48 weeks (13 doses).	
Reporting group title	Placebo
Reporting group description:	
Matching placebo administered via an intravenous infusion (IV) every 4 weeks for up to 48 weeks (13 doses).	

Reporting group values	Anifrolumab 300 mg	Placebo	Total
Number of subjects	180	182	362
Age Categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	175	181	356
From 65-84 years	5	1	6
85 years and over	0	0	0
Age Continuous Units: years			
arithmetic mean	43.1	41.1	
standard deviation	± 11.95	± 11.47	-
Gender Categorical Units: Subjects			
Female	168	170	338
Male	12	12	24
Race Units: Subjects			
White	110	107	217
Black or African American	17	25	42
Asian	30	30	60
Native Hawaiian or Other Pacific Islander	0	0	0
American Indian or Alaska Native	4	1	5
Other	11	11	22
Missing	8	8	16
Ethnicity Units: Subjects			
Hispanic or Latino	54	54	108
Not Hispanic or Latino	118	120	238
Missing	8	8	16

Geographic region Units: Subjects			
Asia Pacific	27	26	53
Europe	51	46	97
Latin America	35	32	67
United States/Canada	64	68	132
Rest of World (South Africa)	3	10	13

End points

End points reporting groups

Reporting group title	Anifrolumab 300 mg
Reporting group description:	
Anifrolumab (300 mg) administered via an intravenous infusion (IV) every 4 weeks for up to 48 weeks (13 doses).	
Reporting group title	Placebo
Reporting group description:	
Matching placebo administered via an intravenous infusion (IV) every 4 weeks for up to 48 weeks (13 doses).	
Subject analysis set title	Anifrolumab 300 mg High IFN Test Results Subgroup
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Anifrolumab (300 mg) administered via an intravenous infusion (IV) every 4 weeks for up to 48 weeks (13 doses). Participants with high interferon (IFN) test results at baseline.	
Subject analysis set title	Placebo High IFN Test Results Subgroup
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Matching placebo administered via an intravenous infusion (IV) every 4 weeks for up to 48 weeks (13 cycles). Participants with high interferon (IFN) test results at baseline.	
Subject analysis set title	Anifrolumab 300 mg Baseline OCS ≥10 mg/day
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Anifrolumab (300 mg) administered via an intravenous infusion (IV) every 4 weeks for up to 48 weeks (13 doses). Participants with a baseline oral corticosteroid (OCS) dose of ≥10 mg/day.	
Subject analysis set title	Placebo Baseline OCS ≥10 mg/day
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Matching placebo administered via an intravenous infusion (IV) every 4 weeks for up to 48 weeks (13 doses). Participants with a baseline oral corticosteroid (OCS) dose of ≥10 mg/day.	
Subject analysis set title	Anifrolumab 300 mg CLASI Activity Score ≥10
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Anifrolumab (300 mg) administered via an intravenous infusion (IV) every 4 weeks for up to 48 weeks (13 doses). Participants with Cutaneous Lupus Erythematosus Disease Area and Severity Index (CLASI) activity score of ≥10 at baseline.	
Subject analysis set title	Placebo CLASI Activity Score ≥10
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Matching placebo administered via an intravenous infusion (IV) every 4 weeks for up to 48 weeks (13 doses). Participants with a Cutaneous Lupus Erythematosus Disease Area and Severity Index (CLASI) Activity Score ≥10 at baseline.	
Subject analysis set title	Anifrolumab 300 mg ≥6 Swollen and ≥6 Tender Joints at Baseline
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Anifrolumab (300 mg) administered via an intravenous infusion (IV) every 4 weeks for up to 48 weeks (13 doses). Participants with 6 or more swollen joints and 6 or more tender joints at baseline.	
Subject analysis set title	Placebo ≥6 Swollen and ≥6 Tender Joints at Baseline
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Matching placebo administered via an intravenous infusion (IV) every 4 weeks for up to 48 weeks (13 doses). Participants with 6 or more swollen joints and 6 or more tender joints at baseline.	

Primary: Number of Participants Who Achieved the British Isles Lupus Assessment Group Based Composite Lupus Assessment (BICLA) Response at Week 52

End point title	Number of Participants Who Achieved the British Isles Lupus Assessment Group Based Composite Lupus Assessment (BICLA) Response at Week 52

End point description:

Composite endpoint BICLA, was defined by meeting all of the following criteria:

• Reduction of all baseline British Isles Lupus Assessment Group (BILAG)-2004 A to B/C/D and baseline BILAG-2004 B to C/D, and no BILAG-2004 worsening in other organ systems, as defined by ≥1 new BILAG-2004 A or ≥2 new BILAG-2004 B
• No worsening from baseline in Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K), where worsening is defined as an increase from baseline of >0 points in SLEDAI-2K
• No worsening from baseline in participants' lupus disease activity, where worsening is defined by an increase ≥0.30 points on a 3-point Physician's Global Assessment (PGA) visual analogue scale (VAS)
• No discontinuation of investigational product
• No use of restricted medications beyond the protocol allowed threshold before assessment

End point type	Primary

End point timeframe:

Baseline; Week 52

End point values	Anifrolumab 300 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	180[1]	182[2]		
Units: Participants	86	57		

Notes:

[1] - Full analysis set: Participants who were randomized and received at least 1 dose of study drug.

[2] - Full analysis set: Participants who were randomized and received at least 1 dose of study drug.

Statistical analyses

Statistical analysis title	Anifrolumab 300 mg vs Placebo

Statistical analysis description:

The difference in estimates and associated 95% CI are weighted and are calculated using a stratified Cochran-Mantel-Haenszel (CMH) approach, with stratification factors (SLEDAI-2K score at screening [<10 points vs >= 10 points], Week 0 OCS dose [<10 mg/day vs >=10 mg/day prednisone or equivalent] and type I IFN gene signature test result at screening [high vs low]).

Comparison groups	Anifrolumab 300 mg v Placebo
Number of subjects included in analysis	362
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0013
Method	Cochran-Mantel-Haenszel
Parameter estimate	Mean difference (final values)
Point estimate	16.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	6.3
upper limit	26.3

Secondary: Number of Participants Who Achieved the British Isles Lupus Assessment Group Based Composite Lupus Assessment (BICLA) Response at Week 52 in the IFN Test-High Sub-group

End point title	Number of Participants Who Achieved the British Isles Lupus Assessment Group Based Composite Lupus Assessment (BICLA) Response at Week 52 in the IFN Test-High Sub-group

End point description:

Composite endpoint BICLA, was defined by meeting all of the following criteria:

• Reduction of all baseline British Isles Lupus Assessment Group (BILAG)-2004 A to B/C/D and baseline BILAG-2004 B to C/D, and no BILAG-2004 worsening in other organ systems, as defined by ≥1 new BILAG-2004 A or ≥2 new BILAG-2004 B
• No worsening from baseline in Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K), where worsening is defined as an increase from baseline to >0 points in SLEDAI-2K
• No worsening from baseline in participants' lupus disease activity, where worsening is defined by an increase ≥0.30 points on a 3-point Physician's Global Assessment (PGA) visual analogue scale (VAS)
• No discontinuation of investigational product
• No use of restricted medications beyond the protocol allowed threshold before assessment

End point type	Secondary

End point timeframe:

Baseline; Week 52

End point values	Anifrolumab 300 mg High IFN Test Results Subgroup	Placebo High IFN Test Results Subgroup		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	150[3]	151[4]		
Units: Participants	72	46		

Notes:

[3] - Full analysis set: Participants who were randomized and received at least 1 dose of study drug.

[4] - Full analysis set: Participants who were randomized and received at least 1 dose of study drug.

Statistical analyses

Statistical analysis title	Anifrolumab 300 mg vs Placebo

Statistical analysis description:

The difference in estimates and associated 95% CI are weighted and are calculated using a stratified Cochran-Mantel-Haenszel (CMH) approach, with stratification factors (SLEDAI-2K score at screening [<10 points vs >= 10 points], Week 0 OCS dose [<10 mg/day vs >=10 mg/day prednisone or equivalent] and type I IFN gene signature test result at screening [high vs low]).

Comparison groups	Anifrolumab 300 mg High IFN Test Results Subgroup v Placebo High IFN Test Results Subgroup
Number of subjects included in analysis	301
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0022 [5]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Mean difference (final values)
Point estimate	17.3

Confidence interval	
level	95 %
sides	2-sided
lower limit	6.5
upper limit	28.2

Notes:

[5] - Adjusted p-value.

Secondary: Number of Participants Who Achieve an Oral Corticosteroids (OCS) Dose of ≤7.5 mg/day at Week 40, Which is Maintained Through to Week 52 in the Sub-Group of Participants With Baseline OCS ≥10 mg/day

End point title	Number of Participants Who Achieve an Oral Corticosteroids (OCS) Dose of ≤7.5 mg/day at Week 40, Which is Maintained Through to Week 52 in the Sub-Group of Participants With Baseline OCS ≥10 mg/day

End point description:

Maintained OCS reduction was defined by meeting all of the following criteria:

- Achieve an OCS dose of ≤7.5 mg/day prednisone or equivalent by Week 40
- Maintain an OCS dose ≤7.5 mg/day prednisone or equivalent from Week 40 to Week 52
- No discontinuation of investigational product
- No use of restricted medications beyond the protocol allowed threshold before assessment

End point type	Secondary

End point timeframe:

Week 40; Week 52

End point values	Anifrolumab 300 mg Baseline OCS ≥10 mg/day	Placebo Baseline OCS ≥10 mg/day		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	87[6]	83[7]		
Units: Participants	45	25		

Notes:

[6] - Full analysis set: Participants who were randomized and received at least 1 dose of study drug.

[7] - Full analysis set: Participants who were randomized and received at least 1 dose of study drug.

Statistical analyses

Statistical analysis title	Anifrolumab 300 mg vs Placebo

Statistical analysis description:

The difference in estimates and associated 95% CI are weighted and are calculated using a stratified Cochran-Mantel-Haenszel (CMH) approach, with stratification factors (SLEDAI-2K score at screening [<10 points vs >= 10 points], Week 0 OCS dose [<10 mg/day vs >=10 mg/day prednisone or equivalent] and type I IFN gene signature test result at screening [high vs low]).

Comparison groups	Anifrolumab 300 mg Baseline OCS ≥10 mg/day v Placebo Baseline OCS ≥10 mg/day

Number of subjects included in analysis	170
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0135 [8]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Mean difference (final values)
Point estimate	21.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	6.8
upper limit	35.7

Notes:

[8] - Adjusted p-value.

Secondary: Number of Participants With a ≥50% Reduction in Cutaneous Lupus Erythematosus Disease Area and Severity Index (CLASI) Activity Score at Week 12 in The Sub-Group of Participants With Baseline CLASI Activity Score of ≥10

End point title	Number of Participants With a ≥50% Reduction in Cutaneous Lupus Erythematosus Disease Area and Severity Index (CLASI) Activity Score at Week 12 in The Sub-Group of Participants With Baseline CLASI Activity Score of ≥10

End point description:

50% reduction in CLASI activity score compared to baseline was defined by meeting all of the following criteria:

- Achieve ≥50% reduction of CLASI activity score at Week 12 compared to baseline
- No discontinuation of investigational product
- No use of restricted medications beyond the protocol allowed threshold before assessment

End point type	Secondary

End point timeframe:

Baseline; Week 12

End point values	Anifrolumab 300 mg CLASI Activity Score ≥10	Placebo CLASI Activity Score ≥10		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	49[9]	40[10]		
Units: Participants	24	10		

Notes:

[9] - Full analysis set: Participants who were randomized and received at least 1 dose of study drug.

[10] - Full analysis set: Participants who were randomized and received at least 1 dose of study drug.

Statistical analyses

Statistical analysis title	Anifrolumab 300 mg vs Placebo

Statistical analysis description:

The difference in estimates and associated 95% CI are weighted and are calculated using a stratified Cochran-Mantel-Haenszel (CMH) approach, with stratification factors (SLEDAI-2K score at screening [<10 points vs >= 10 points], Week 0 OCS dose [<10 mg/day vs >=10 mg/day prednisone or equivalent] and type I IFN gene signature test result at screening [high vs low]).

Comparison groups	Anifrolumab 300 mg CLASI Activity Score ≥10 v Placebo CLASI

	Activity Score ≥10
Number of subjects included in analysis	89
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0392 [11]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Mean difference (final values)
Point estimate	24
Confidence interval	
level	95 %
sides	2-sided
lower limit	4.3
upper limit	43.6

Notes:

[11] - Adjusted p-value.

Secondary: Number of Participants With ≥50% Reduction in Joint Count at Week 52 in The Sub-group of Participants With ≥6 Swollen and ≥6 Tender Joints at Baseline

End point title	Number of Participants With ≥50% Reduction in Joint Count at Week 52 in The Sub-group of Participants With ≥6 Swollen and ≥6 Tender Joints at Baseline

End point description:

50% reduction in the number of swollen and tender joints compared to baseline was defined by meeting all of the following criteria:

- Achieve ≥50% reduction in the number of swollen and tender joints, separately
- No discontinuation of investigational product
- No use of restricted medications beyond the protocol allowed threshold before assessment

End point type	Secondary

End point timeframe:

Baseline; Week 52

End point values	Anifrolumab 300 mg ≥6 Swollen and ≥6 Tender Joints at Baseline	Placebo ≥6 Swollen and ≥6 Tender Joints at Baseline		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	71[12]	90[13]		
Units: Participants	30	34		

Notes:

[12] - Full analysis set: Participants who were randomized and received at least 1 dose of study drug.

[13] - Full analysis set: Participants who were randomized and received at least 1 dose of study drug.

Statistical analyses

Statistical analysis title	Anifrolumab 300 mg vs Placebo

Statistical analysis description:

The difference in estimates and associated 95% CI are weighted and are calculated using a stratified Cochran-Mantel-Haenszel (CMH) approach, with stratification factors (SLEDAI-2K score at screening [<10 points vs >= 10 points], Week 0 OCS dose [<10 mg/day vs >=10 mg/day prednisone or equivalent] and type I IFN gene signature test result at screening [high vs low]).

Comparison groups	Anifrolumab 300 mg ≥6 Swollen and ≥6 Tender Joints at Baseline v Placebo ≥6 Swollen and ≥6 Tender Joints at Baseline
Number of subjects included in analysis	161
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5469 [14]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Mean difference (final values)
Point estimate	4.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-10.6
upper limit	20

Notes:

[14] - Adjusted p-value.

Secondary: Annualised Flare Rate Through 52 Weeks

End point title	Annualised Flare Rate Through 52 Weeks

End point description:

Annualised flare rate was defined as either 1 or more new British Isle Lupus Assessment Group (BILAG) 2004 A or 2 or more new BILAG 2004 B items compared to the previous visit.

End point type	Secondary

End point timeframe:

Baseline to Week 52

End point values	Anifrolumab 300 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	180[15]	182[16]		
Units: Annualized flare rate ratio				
number (confidence interval 95%)	0.43 (0.31 to 0.59)	0.64 (0.47 to 0.86)		

Notes:

[15] - Full analysis set: Participants who were randomized and received at least 1 dose of study drug.

[16] - Full analysis set: Participants who were randomized and received at least 1 dose of study drug.

Statistical analyses

Statistical analysis title	Anifrolumab 300 mg vs Placebo

Statistical analysis description:

Analysed using a negative binomial regression model. The response variable in the model is the number of flares over the 52-week treatment period. The model includes covariates of treatment group, and the stratification factors (SLEDAI-2K score at screening [<10 points vs >=10 points], Week 0 OCS dose [<10 mg/day vs >=10 mg/day prednisone or equivalent] and type I IFN gene signature test result at screening [high vs low]). The logarithm of the follow-up time is used as an offset variable.

Comparison groups	Anifrolumab 300 mg v Placebo

Number of subjects included in analysis	362
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0809 [17]
Method	Negative binomial regression
Parameter estimate	Rate Ratio
Point estimate	0.67
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.48
upper limit	0.94

Notes:

[17] - Adjusted p-value.

Secondary: Number of Participants With One or More Adverse Events (AEs)

End point title	Number of Participants With One or More Adverse Events (AEs)

End point description:

An AE is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition following or during exposure to a pharmaceutical product, whether or not considered causally related to the product. AEs were collected throughout the duration of the study, from baseline until end of follow-up (a maximum of 12 weeks post last dose [Week 48]), or until Week 52 for participants who enrolled onto the long term extension (LTE). The reported value is inclusive of serious and non-serious AEs.

End point type	Secondary

End point timeframe:

Baseline to end of trial (Maximum of 60 weeks)

End point values	Anifrolumab 300 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	180[18]	182[19]		
Units: Participants	162	154		

Notes:

[18] - Full analysis set: Participants who were randomized and received at least 1 dose of study drug.

[19] - Full analysis set: Participants who were randomized and received at least 1 dose of study drug.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With One or More Adverse Events of Special Interest (AESIs)

End point title	Number of Participants With One or More Adverse Events of Special Interest (AESIs)

End point description:

An AESI is an adverse event (AE) of scientific and medical concern specific to understanding biologics. An AESI may be serious or non-serious. AESI are serious infections, including non-opportunistic serious infections, opportunistic infections, anaphylaxis, malignancy, herpes zoster, tuberculosis (TB) (including latent TB), influenza, vasculitis (non-systemic lupus erythematosus [SLE]), and major adverse cardiovascular events (MACE) (including stroke, myocardial infarction [MI], or cardiovascular death).

AESIs were collected throughout the study, from baseline until end of follow-up (a maximum of 12 weeks post last dose [Week 48]), or until Week 52 for participants who enrolled onto the long term extension (LTE).

End point type	Secondary

End point timeframe:

Baseline to end of trial (Maximum of 60 weeks)

End point values	Anifrolumab 300 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	180[20]	182[21]		
Units: Participants	29	20		

Notes:

[20] - Full analysis set: Participants who were randomized and received at least 1 dose of study drug.

[21] - Full analysis set: Participants who were randomized and received at least 1 dose of study drug.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with a Potentially Clinically Important Change from Baseline in Vital Sign Measurements

End point title	Number of Participants with a Potentially Clinically Important Change from Baseline in Vital Sign Measurements

End point description:

Vital sign measurements included oral temperature, blood pressure (BP), pulse rate, and respiratory rate.

Vital signs were collected throughout the duration of the study, from baseline until end of follow-up (a maximum of 12 weeks post last dose [Week 48]), or until Week 52 for participants who enrolled onto the long term extension (LTE).

End point type	Secondary

End point timeframe:

Baseline to end of study (Maximum of 60 weeks)

End point values	Anifrolumab 300 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	180[22]	182[23]		
Units: Participants	45	45		

Notes:

[22] - Full analysis set: Participants who were randomized and received at least 1 dose of study drug.

[23] - Full analysis set: Participants who were randomized and received at least 1 dose of study drug.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with a Potentially Clinically Important Change from Baseline in Clinical Laboratory Tests

End point title	Number of Participants with a Potentially Clinically Important Change from Baseline in Clinical Laboratory Tests

End point description:

Clinical laboratory tests were analyzed in a central clinical laboratory and included hematology, serum chemistry and urinalysis tests.

Laboratory values were collected throughout the duration of the study, from baseline until end of follow-up (a maximum of 12 weeks post last dose [Week 48]), or until Week 52 for participants who enrolled onto the long term extension (LTE).

End point type	Secondary

End point timeframe:

Baseline to end of study (Maximum of 60 weeks)

End point values	Anifrolumab 300 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	180[24]	182[25]		
Units: Participants	72	87		

Notes:

[24] - Full analysis set: Participants who were randomized and received at least 1 dose of study drug.

[25] - Full analysis set: Participants who were randomized and received at least 1 dose of study drug.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Day 1 to end of study (Maximum of 60 weeks)

Adverse event reporting additional description:

TEAEs were either spontaneously reported by the participant or reported in response to open questions, revealed by observation, or were changes from baseline/deterioration in tests and vital signs that met SAE criteria or led to study drug discontinuation.

Full analysis set: All participants who had received at least one dose of study drug.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	21.0

Reporting groups

Reporting group title	Anifrolumab 300 mg

Reporting group description:

Anifrolumab (300 mg) administered via an intravenous infusion (IV) every 4 weeks for up to 48 weeks (13 doses).

Reporting group title	Placebo

Reporting group description:

Matching placebo administered via an intravenous infusion (IV) every 4 weeks for up to 48 weeks (13 doses).

Serious adverse events	Anifrolumab 300 mg	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	16 / 180 (8.89%)	34 / 182 (18.68%)	
number of deaths (all causes)	1	0	
number of deaths resulting from adverse events	1	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Lip squamous cell carcinoma			
subjects affected / exposed	1 / 180 (0.56%)	0 / 182 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Uterine cancer			
subjects affected / exposed	0 / 180 (0.00%)	1 / 182 (0.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Haematoma			

subjects affected / exposed	0 / 180 (0.00%)	1 / 182 (0.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
subjects affected / exposed	0 / 180 (0.00%)	1 / 182 (0.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Influenza like illness			
subjects affected / exposed	0 / 180 (0.00%)	1 / 182 (0.55%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	1 / 180 (0.56%)	0 / 182 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Cervical dysplasia			
subjects affected / exposed	1 / 180 (0.56%)	0 / 182 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vaginal ulceration			
subjects affected / exposed	0 / 180 (0.00%)	1 / 182 (0.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	0 / 180 (0.00%)	1 / 182 (0.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary alveolar haemorrhage			

subjects affected / exposed	0 / 180 (0.00%)	1 / 182 (0.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Panic attack			
subjects affected / exposed	0 / 180 (0.00%)	1 / 182 (0.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychotic disorder			
subjects affected / exposed	0 / 180 (0.00%)	1 / 182 (0.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Blood creatinine increased			
subjects affected / exposed	1 / 180 (0.56%)	0 / 182 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
International normalised ratio increased			
subjects affected / exposed	0 / 180 (0.00%)	1 / 182 (0.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Liver function test increased			
subjects affected / exposed	0 / 180 (0.00%)	1 / 182 (0.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Ankle fracture			
subjects affected / exposed	0 / 180 (0.00%)	1 / 182 (0.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fall			

subjects affected / exposed	1 / 180 (0.56%)	0 / 182 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Radius fracture			
subjects affected / exposed	0 / 180 (0.00%)	2 / 182 (1.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Traumatic fracture			
subjects affected / exposed	1 / 180 (0.56%)	0 / 182 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Atrial flutter			
subjects affected / exposed	0 / 180 (0.00%)	1 / 182 (0.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure congestive			
subjects affected / exposed	0 / 180 (0.00%)	1 / 182 (0.55%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute coronary syndrome			
subjects affected / exposed	1 / 180 (0.56%)	0 / 182 (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			
Hypoaesthesia			
subjects affected / exposed	1 / 180 (0.56%)	0 / 182 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 180 (0.00%)	1 / 182 (0.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Gastrointestinal disorders			
Chilaiditi's syndrome			
subjects affected / exposed	1 / 180 (0.56%)	0 / 182 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematemesis			
subjects affected / exposed	0 / 180 (0.00%)	1 / 182 (0.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intra-abdominal haematoma			
subjects affected / exposed	0 / 180 (0.00%)	1 / 182 (0.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal stenosis			
subjects affected / exposed	0 / 180 (0.00%)	1 / 182 (0.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	0 / 180 (0.00%)	1 / 182 (0.55%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Angioedema			
subjects affected / exposed	1 / 180 (0.56%)	0 / 182 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Drug eruption			
subjects affected / exposed	0 / 180 (0.00%)	1 / 182 (0.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			

subjects affected / exposed	0 / 180 (0.00%)	1 / 182 (0.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lupus nephritis			
subjects affected / exposed	0 / 180 (0.00%)	1 / 182 (0.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephrolithiasis			
subjects affected / exposed	1 / 180 (0.56%)	0 / 182 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Osteonecrosis			
subjects affected / exposed	1 / 180 (0.56%)	1 / 182 (0.55%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Systemic lupus erythematosus			
subjects affected / exposed	1 / 180 (0.56%)	6 / 182 (3.30%)	
occurrences causally related to treatment / all	0 / 1	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Abscess			
subjects affected / exposed	0 / 180 (0.00%)	1 / 182 (0.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis			
subjects affected / exposed	1 / 180 (0.56%)	0 / 182 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulitis			
subjects affected / exposed	1 / 180 (0.56%)	0 / 182 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Gastroenteritis			
subjects affected / exposed	0 / 180 (0.00%)	1 / 182 (0.55%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis viral			
subjects affected / exposed	2 / 180 (1.11%)	0 / 182 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes zoster			
subjects affected / exposed	1 / 180 (0.56%)	0 / 182 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			
subjects affected / exposed	0 / 180 (0.00%)	1 / 182 (0.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Periodontitis			
subjects affected / exposed	0 / 180 (0.00%)	1 / 182 (0.55%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	3 / 180 (1.67%)	7 / 182 (3.85%)	
occurrences causally related to treatment / all	3 / 3	7 / 7	
deaths causally related to treatment / all	1 / 1	0 / 0	
Sepsis			
subjects affected / exposed	0 / 180 (0.00%)	1 / 182 (0.55%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sialoadenitis			
subjects affected / exposed	0 / 180 (0.00%)	1 / 182 (0.55%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			

subjects affected / exposed	0 / 180 (0.00%)	1 / 182 (0.55%)	
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	Anifrolumab 300 mg	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	125 / 180 (69.44%)	99 / 182 (54.40%)	
Injury, poisoning and procedural complications			
Infusion related reaction			
subjects affected / exposed	25 / 180 (13.89%)	14 / 182 (7.69%)	
occurrences (all)	42	27	
Nervous system disorders			
Headache			
subjects affected / exposed	11 / 180 (6.11%)	18 / 182 (9.89%)	
occurrences (all)	13	23	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	7 / 180 (3.89%)	10 / 182 (5.49%)	
occurrences (all)	7	11	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	10 / 180 (5.56%)	7 / 182 (3.85%)	
occurrences (all)	11	7	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	10 / 180 (5.56%)	6 / 182 (3.30%)	
occurrences (all)	11	6	
Back pain			
subjects affected / exposed	11 / 180 (6.11%)	3 / 182 (1.65%)	
occurrences (all)	12	3	
Infections and infestations			
Bronchitis			
subjects affected / exposed	23 / 180 (12.78%)	8 / 182 (4.40%)	
occurrences (all)	31	8	

Herpes zoster			
subjects affected / exposed	12 / 180 (6.67%)	3 / 182 (1.65%)	
occurrences (all)	12	3	
Nasopharyngitis			
subjects affected / exposed	28 / 180 (15.56%)	23 / 182 (12.64%)	
occurrences (all)	42	31	
Sinusitis			
subjects affected / exposed	13 / 180 (7.22%)	9 / 182 (4.95%)	
occurrences (all)	21	10	
Upper respiratory tract infection			
subjects affected / exposed	42 / 180 (23.33%)	19 / 182 (10.44%)	
occurrences (all)	57	24	
Urinary tract infection			
subjects affected / exposed	21 / 180 (11.67%)	26 / 182 (14.29%)	
occurrences (all)	27	40	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
01 February 2016	Added HIV testing at screening.
23 March 2016	Updates were made to the restricted medications regarding B-cell depleter, rituximab, and other biologics.
18 May 2016	Clarified inclusion/exclusion criteria and clarified long term extension design.
06 December 2018	Unable to report dates after End of Trial (EOT). Protocol Amendment dated 23 May 2019: British Isles Lupus Assessment Group-based Composite Lupus Assessment (BICLA) response at Week 52 replaced Systemic Lupus Erythematosus Responder Index ≥4 (SRI[4]) as primary endpoint; rationale for primary endpoint selection updated. Changed 2 key secondary endpoints: 1) SRI(4) response at Week 52 in the interferon (IFN)-high only sub population was replaced with the BICLA response 2) SRI(4) at Week 24 replaced with an organ-specific assessment of joints. Statistical methodology regarding analysis of the primary and key secondary endpoints, the testing strategy, and power estimation updated. Clarified guidance for the use of non-steroidal anti-inflammatory drug (NSAIDs). Added scoring disease activity by modified British Isles Lupus Assessment Group (BILAG) 2004.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported