



Clinical trial results:

A Multicentre, Randomised, Double-blind, Placebo-controlled, Phase 2 Study Evaluating the Efficacy and Safety of Anifrolumab in Adult Subjects with Active Proliferative Lupus Nephritis

Summary

EudraCT number	2015-001442-29
Trial protocol	BE HU DE ES GB FR IT
Global end of trial date	18 January 2021

Results information

Result version number	v1 (current)
This version publication date	24 October 2021
First version publication date	24 October 2021

Trial information

Trial identification

Sponsor protocol code	D3461C00007
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02547922
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	AstraZeneca AB
Sponsor organisation address	Södertälje, Södertälje, Sweden, 151 85
Public contact	Global Clinical Lead, AstraZeneca Clinical study Information Center, 1 8772409479, information.center@astrazeneca.com
Scientific contact	Global Clinical Lead, AstraZeneca Clinical study Information Center, 1 8772409479, information.center@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	24 February 2021
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	18 January 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy of anifrolumab versus placebo by the relative difference in change from baseline to Week 52 in the 24-hour UPCR in patients with active, proliferative LN.

Protection of trial subjects:

This study was performed in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with International Council for Harmonisation/ Good Clinical Practice (GCP), applicable regulatory requirements, and the AstraZeneca policy on Bioethics and Human Biological Samples.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	04 November 2015
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	Korea, Republic of: 9
Country: Number of subjects enrolled	Taiwan: 11
Country: Number of subjects enrolled	Australia: 7
Country: Number of subjects enrolled	Belgium: 2
Country: Number of subjects enrolled	France: 7
Country: Number of subjects enrolled	Germany: 2
Country: Number of subjects enrolled	Hungary: 8
Country: Number of subjects enrolled	Italy: 6
Country: Number of subjects enrolled	Poland: 4
Country: Number of subjects enrolled	Russian Federation: 3
Country: Number of subjects enrolled	Serbia: 6
Country: Number of subjects enrolled	Spain: 3
Country: Number of subjects enrolled	Argentina: 12
Country: Number of subjects enrolled	Mexico: 8
Country: Number of subjects enrolled	Peru: 30
Country: Number of subjects enrolled	United States: 27
Worldwide total number of subjects	145
EEA total number of subjects	32

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)	143
From 65 to 84 years	2
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Subjects who met all the inclusion and none of the exclusion criteria were randomized at 66 sites in 16 countries. The study was conducted from 30 November 2015 to 18 January 2021.

Pre-assignment

Screening details:

The screening period was from Day -30 to Day -1. Informed consent form (ICF) was signed prior to screening procedures. All the study assessments were performed as per the schedule of assessment.

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	Investigator, Subject

Arms

Are arms mutually exclusive?	Yes
Arm title	All Anifrolumab

Arm description:

This arm comprises Anifrolumab - Basic Regimen and Anifrolumab - Intensified Regimen. Anifrolumab - Basic Regimen: Subjects were administered with lower dose of Anifrolumab intravenously (IV) every 4 weeks (Q4W) from Week 0 to Week 100, in addition to pre-specified standard of care (SOC) which continued until Week 112. Anifrolumab - Intensified Regimen: Subjects were administered with higher dose of Anifrolumab IV Q4W for first 3 doses followed by lower dose from Week 12 to Week 100, in addition to pre-specified standard of care (SOC) which continued until Week 112.

Arm type	Experimental
Investigational medicinal product name	Anifrolumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

Subjects were administered with lower dose of Anifrolumab every 4 weeks (Q4W) from Week 0 to Week 100 or higher dose of Anifrolumab Q4W for first 3 doses followed by lower dose from Week 12 to Week 100.

Arm title	Placebo
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Arm description:

Subjects were administered with placebo every 4 week from Week 0 to Week 100 in addition to SOC which continued until Week 112.

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

Dosage and administration details:

Subjects were administered with placebo intravenously every 4 weeks from Week 0 to Week 100.

Number of subjects in period 1	All Anifrolumab	Placebo
Started	96	49
Completed	46	20
Not completed	50	29
Adverse event, serious fatal	1	-
Consent withdrawn by subject	15	10
Physician decision	3	2
PROGRESSIVE DISEASE	1	2
Adverse event, non-fatal	4	2
TECHNICAL PROBLEMS	1	-
Non-responding completer	12	9
Lost to follow-up	1	-
Lack of efficacy	12	4

Baseline characteristics

Reporting groups

Reporting group title	All Anifrolumab
Reporting group description:	
This arm comprises Anifrolumab - Basic Regimen and Anifrolumab - Intensified Regimen. Anifrolumab - Basic Regimen: Subjects were administered with lower dose of Anifrolumab intravenously (IV) every 4 weeks (Q4W) from Week 0 to Week 100, in addition to pre-specified standard of care (SOC) which continued until Week 112. Anifrolumab - Intensified Regimen: Subjects were administered with higher dose of Anifrolumab IV Q4W for first 3 doses followed by lower dose from Week 12 to Week 100, in addition to pre-specified standard of care (SOC) which continued until Week 112.	
Reporting group title	Placebo
Reporting group description:	
Subjects were administered with placebo every 4 week from Week 0 to Week 100 in addition to SOC which continued until Week 112.	

Reporting group values	All Anifrolumab	Placebo	Total
Number of subjects	96	49	145
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)	94	49	143
From 65-84 years	2	0	2
85 years and over	0	0	0
Age Continuous			
Units: years			
arithmetic mean	35.1	34.0	
standard deviation	± 10.96	± 10.18	-
Sex: Female, Male			
Units:			
Female	82	38	120
Male	14	11	25
Ethnicity (NIH/OMB)			
Units: Subjects			
Hispanic or Latino	45	20	65
Not Hispanic or Latino	51	29	80
Unknown or Not Reported	0	0	0
Race/Ethnicity, Customized			
Units: Subjects			
American Indian or Alaska Native	4	0	4
Asian	18	10	28
Native Hawaiian or Other Pacific Islander	1	0	1
Black or African American	6	1	7

White	42	24	66
Other	25	14	39

End points

End points reporting groups

Reporting group title	All Anifrolumab
Reporting group description: This arm comprises Anifrolumab - Basic Regimen and Anifrolumab - Intensified Regimen. Anifrolumab - Basic Regimen: Subjects were administered with lower dose of Anifrolumab intravenously (IV) every 4 weeks (Q4W) from Week 0 to Week 100, in addition to pre-specified standard of care (SOC) which continued until Week 112. Anifrolumab - Intensified Regimen: Subjects were administered with higher dose of Anifrolumab IV Q4W for first 3 doses followed by lower dose from Week 12 to Week 100, in addition to pre-specified standard of care (SOC) which continued until Week 112.	
Reporting group title	Placebo
Reporting group description: Subjects were administered with placebo every 4 week from Week 0 to Week 100 in addition to SOC which continued until Week 112.	

Primary: Relative difference in change from baseline in 24-hour urine protein to creatinine ratio (UPCR)

End point title	Relative difference in change from baseline in 24-hour urine protein to creatinine ratio (UPCR)
End point description: The efficacy of anifrolumab plus SOC (combination of mycophenolate mofetil and corticosteroids) compared with placebo plus SOC in subjects with active proliferative lupus nephritis (LN) was evaluated. Geometric mean ratio of 24-hour UPCR at week 52 over baseline. Values <1 indicate improvement from baseline.	
End point type	Primary
End point timeframe: From Week 1 (Baseline) up to Week 52	

End point values	All Anifrolumab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	91	41		
Units: milligram/milligram (mg/mg)				
geometric mean (confidence interval 95%)	0.305 (0.198 to 0.468)	0.296 (0.175 to 0.499)		

Statistical analyses

Statistical analysis title	All Anifrolumab vs Placebo
Statistical analysis description: The model includes fixed effects for treatment group, visit, stratification factors, log-transformed 24-hour UPCR at baseline, and treatment-by-visit interaction. All data up to and including the date of discontinuation of study treatment were included in the analysis.	
Comparison groups	All Anifrolumab v Placebo

Number of subjects included in analysis	132
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9052 ^[1]
Method	Mixed models analysis
Parameter estimate	Geometric Mean Ratio
Point estimate	1.031
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.621
upper limit	1.713

Notes:

[1] - The p-values presented are unadjusted and was compared with the respective adjusted significance level (α). If α is not displayed, no formal testing can be performed and the corresponding p-value was nominal.

Secondary: Proportion of subjects achieving the composite endpoint Complete Renal Response (CRR)

End point title	Proportion of subjects achieving the composite endpoint Complete Renal Response (CRR)
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End point description:

CRR was defined as meeting all of the following:

-Estimated glomerular filtration rate (eGFR) is ≥ 60 mL/min/1.73 m² or no confirmed decrease of eGFR from baseline of $\geq 20\%$

-24-hour UPCR ≤ 0.7 mg/mg

-No discontinuation of investigational product (IP) or use of restricted medication beyond the protocol allowed threshold before assessment

-eGFR was based on Modification of Diet in Renal Disease (MDRD) formula.

Subjects treated with restricted medication beyond the protocol allowed threshold, or discontinuing study treatment for other reasons, were regarded as non-responders.

End point type	Secondary
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End point timeframe:

Week 52

End point values	All Anifrolumab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	87	45		
Units: Percentage of subjects				
number (not applicable)				
Responder	31.0	31.1		
Non-responder	69.0	68.9		

Statistical analyses

Statistical analysis title	Anifrolumab vs Placebo
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Statistical analysis description:

The responder/non-responder rates (percentages), the difference in estimates and associated 95% CI are weighted and are calculated using a stratified Cochran-Mantel-Haenszel (CMH) approach.

Comparison groups	All Anifrolumab v Placebo
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Number of subjects included in analysis	132
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9929 ^[2]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference in estimates
Point estimate	-0.08
Confidence interval	
level	95 %
sides	2-sided
lower limit	-16.92
upper limit	16.76

Notes:

[2] - At Week 52, the p-values presented are unadjusted and will be compared to the respective adjusted significance level (α). If α is not displayed no formal testing can be performed and the corresponding p-value is nominal.

Other pre-specified: Number of subjects with adverse events

End point title	Number of subjects with adverse events
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End point description:

The AEs (non-serious, serious and adverse event of special interest (AESI)) as variables of safety and tolerability of anifrolumab was assessed.

The AESIs are serious infections, including non-opportunistic serious infections, opportunistic infections, anaphylaxis, malignancy, herpes zoster, TB (including latent TB), influenza, vasculitis (non-SLE), and MACE (including stroke, acute coronary syndrome, myocardial infarction, or cardiovascular death).

Study period: During treatment (DT) and follow-up (FU) data are presented.

IMP refers to investigational medicinal product; EAC refers to Event Adjudication Committee; SLE refers to Systemic lupus erythematosus.

End point type	Other pre-specified
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End point timeframe:

From screening (Day-30 to -1) period until the follow-up period (Week 112)

End point values	All Anifrolumab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	96	49		
Units: Number of subjects				
Subjects with any AE- DT	90	44		
Subjects with any acute AE- DT	26	14		
Any AE with death outcome- DT	0	0		
Any SAE (including events outcome of death)- DT	19	8		
Any AE leading to discontinuation of IMP- DT	11	5		
Any AE related to IMP- DT	37	16		
Any AE of severe intensity- DT	13	8		
Any AESI- DT	24	8		
Non-opportunistic serious infections- DT	1	3		
Opportunistic infections- DT	1	1		
Anaphylaxis- DT	0	0		
Malignancy- DT	1	0		
Herpes zoster- DT	16	4		

Tuberculosis/LTB (latent tuberculosis)- DT	0	0		
Influenza- DT	6	1		
Vasculitis (non-systemic lupus erythematosus)- DT	0	0		
Major adverse CV events (CV-EAC)- DT	0	1		
Any other significant AE- DT	0	0		
Subjects with any AE- FU	20	22		
Any AE death outcome- FU	1	0		
Any SAE (including events with death outcome)- FU	3	3		
Any AE related to IMP- FU	2	1		
Any AE of severe intensity- FU	2	3		
Any AESI- FU	2	2		
Non-opportunistic serious infections- FU	0	1		
Opportunistic infections- FU	0	0		
Anaphylaxis- FU	0	0		
Malignancy- FU	0	0		
Herpes zoster- FU	2	1		
Tuberculosis/LTB- FU	0	0		
Influenza- FU	0	0		
Vasculitis (non-SLE)- FU	0	0		
Major adverse CV events (CV-EAC)- FU	0	0		
Any other significant AE- FU	0	0		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Extra-renal flares using Systemic Lupus Erythematosus (SLE) Disease Activity Index 2000 (SLEDAI 2K) based Flare Assessment Instrument

End point title	Extra-renal flares using Systemic Lupus Erythematosus (SLE) Disease Activity Index 2000 (SLEDAI 2K) based Flare Assessment Instrument
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End point description:

Flare will be defined as any one criterion present in either the Mild/Moderate Flare and/or Severe Flare categories. New or worsened manifestation should only be reported for manifestations of SLE. The SLEDAI-2K score range is 0 to 105 with higher scores representing increased disease activity. Mild/ Moderate flare defined as change in non-renal components of the SLEDAI-2K instrument score of ≥ 3 but < 7 points compared to previous visit. Severe Flare defined as change in non-renal components of the SLEDAI-2K instrument score by ≥ 7 points compared to previous visit. The flare rate per subject year is defined as the number of subjects with a respective flare divided by the sum of exposure time in days for all subjects in the analysis set multiplied by 365.25.

End point type	Other pre-specified
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End point timeframe:

From baseline up to week 112

End point values	All Anifrolumab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	96	49		
Units: Flare rate per subject year				
number (not applicable)				
Mild/moderate: All flares	0.017	0.016		
Mild/moderate: On-treatment	0.014	0.010		
Mild/moderate: Off-treatment	0.003	0.006		
Severe: All flares	0.003	0.006		
Severe: On-treatment	0.002	0.004		
Severe: Off-treatment	0.002	0.002		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From screening (Day-30 to -1) period until follow-up (Week 112).

Assessment type	Non-systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	22.1
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Reporting groups

Reporting group title	All Anifrolumab- Treatment Period
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Reporting group description:

This arm comprises Anifrolumab - Basic Regimen and Anifrolumab - Intensified Regimen. Anifrolumab - Basic Regimen: Subjects were administered with lower dose of Anifrolumab intravenously (IV) every 4 weeks (Q4W) from Week 0 to Week 100, in addition to pre-specified standard of care (SOC) which continued until Week 112. Anifrolumab - Intensified Regimen: Subjects were administered with higher dose of Anifrolumab IV Q4W for first 3 doses followed by lower dose from Week 12 to Week 100, in addition to pre-specified standard of care (SOC) which continued until Week 112.

Reporting group title	All Anifrolumab- Follow up
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Reporting group description:

This arm comprises Anifrolumab - Basic Regimen and Anifrolumab - Intensified Regimen. Anifrolumab - Basic Regimen: Subjects were administered with lower dose of Anifrolumab intravenously (IV) every 4 weeks (Q4W) from Week 0 to Week 100, in addition to pre-specified standard of care (SOC) which continued until Week 112. Anifrolumab - Intensified Regimen: Subjects were administered with higher dose of Anifrolumab IV Q4W for first 3 doses followed by lower dose from Week 12 to Week 100, in addition to pre-specified standard of care (SOC) which continued until Week 112.

Reporting group title	Placebo- Treatment period
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Reporting group description:

Subjects were administered with placebo every 4 week from Week 0 to Week 100 in addition to SOC which continued until Week 112.

Reporting group title	Placebo- Follow up
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Reporting group description:

Subjects were administered with placebo every 4 week from Week 0 to Week 100 in addition to SOC which continued until Week 112.

Serious adverse events	All Anifrolumab- Treatment Period	All Anifrolumab- Follow up	Placebo- Treatment period
Total subjects affected by serious adverse events			
subjects affected / exposed	19 / 96 (19.79%)	3 / 96 (3.13%)	8 / 49 (16.33%)
number of deaths (all causes)	0	1	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Endometrial adenocarcinoma			
subjects affected / exposed	1 / 96 (1.04%)	0 / 96 (0.00%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural			

complications			
Infusion related reaction			
subjects affected / exposed	1 / 96 (1.04%)	0 / 96 (0.00%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tibia fracture			
subjects affected / exposed	0 / 96 (0.00%)	0 / 96 (0.00%)	1 / 49 (2.04%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Lupus endocarditis			
subjects affected / exposed	1 / 96 (1.04%)	0 / 96 (0.00%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute myocardial infarction			
subjects affected / exposed	0 / 96 (0.00%)	0 / 96 (0.00%)	1 / 49 (2.04%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Congestive cardiomyopathy			
subjects affected / exposed	0 / 96 (0.00%)	0 / 96 (0.00%)	0 / 49 (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
Nervous system disorders			
Peripheral sensorimotor neuropathy			
subjects affected / exposed	0 / 96 (0.00%)	0 / 96 (0.00%)	0 / 49 (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
Hypoaesthesia			
subjects affected / exposed	0 / 96 (0.00%)	1 / 96 (1.04%)	0 / 49 (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
Nervous system disorder			

subjects affected / exposed	0 / 96 (0.00%)	1 / 96 (1.04%)	0 / 49 (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
Blood and lymphatic system disorders			
Febrile neutropenia			
subjects affected / exposed	0 / 96 (0.00%)	0 / 96 (0.00%)	1 / 49 (2.04%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	1 / 96 (1.04%)	0 / 96 (0.00%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Malaise			
subjects affected / exposed	1 / 96 (1.04%)	0 / 96 (0.00%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia			
subjects affected / exposed	1 / 96 (1.04%)	0 / 96 (0.00%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Interstitial lung disease			
subjects affected / exposed	1 / 96 (1.04%)	0 / 96 (0.00%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			
subjects affected / exposed	1 / 96 (1.04%)	0 / 96 (0.00%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Lupus nephritis			

subjects affected / exposed	2 / 96 (2.08%)	1 / 96 (1.04%)	1 / 49 (2.04%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Proteinuria			
subjects affected / exposed	1 / 96 (1.04%)	0 / 96 (0.00%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute kidney injury			
subjects affected / exposed	0 / 96 (0.00%)	0 / 96 (0.00%)	1 / 49 (2.04%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nephrotic syndrome			
subjects affected / exposed	0 / 96 (0.00%)	0 / 96 (0.00%)	1 / 49 (2.04%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Systemic lupus erythematosus			
subjects affected / exposed	1 / 96 (1.04%)	0 / 96 (0.00%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Herpes zoster			
subjects affected / exposed	6 / 96 (6.25%)	0 / 96 (0.00%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	4 / 6	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Influenza			
subjects affected / exposed	2 / 96 (2.08%)	0 / 96 (0.00%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abscess bacterial			
subjects affected / exposed	1 / 96 (1.04%)	0 / 96 (0.00%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Pyelonephritis acute			
subjects affected / exposed	1 / 96 (1.04%)	0 / 96 (0.00%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Varicella zoster pneumonia			
subjects affected / exposed	1 / 96 (1.04%)	0 / 96 (0.00%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atypical pneumonia			
subjects affected / exposed	0 / 96 (0.00%)	0 / 96 (0.00%)	1 / 49 (2.04%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Histoplasmosis disseminated			
subjects affected / exposed	0 / 96 (0.00%)	0 / 96 (0.00%)	1 / 49 (2.04%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Meningitis			
subjects affected / exposed	0 / 96 (0.00%)	0 / 96 (0.00%)	1 / 49 (2.04%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Otitis externa bacterial			
subjects affected / exposed	0 / 96 (0.00%)	0 / 96 (0.00%)	1 / 49 (2.04%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	0 / 96 (0.00%)	0 / 96 (0.00%)	1 / 49 (2.04%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Varicella			
subjects affected / exposed	0 / 96 (0.00%)	0 / 96 (0.00%)	0 / 49 (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

Serious adverse events	Placebo- Follow up		
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Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 49 (6.12%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Endometrial adenocarcinoma			
subjects affected / exposed	0 / 49 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Infusion related reaction			
subjects affected / exposed	0 / 49 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Tibia fracture			
subjects affected / exposed	0 / 49 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Lupus endocarditis			
subjects affected / exposed	0 / 49 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Acute myocardial infarction			
subjects affected / exposed	0 / 49 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Congestive cardiomyopathy			
subjects affected / exposed	1 / 49 (2.04%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Peripheral sensorimotor neuropathy			

subjects affected / exposed	1 / 49 (2.04%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hypoaesthesia			
subjects affected / exposed	0 / 49 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Nervous system disorder			
subjects affected / exposed	0 / 49 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Febrile neutropenia			
subjects affected / exposed	0 / 49 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	0 / 49 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Malaise			
subjects affected / exposed	0 / 49 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pyrexia			
subjects affected / exposed	0 / 49 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Interstitial lung disease			

subjects affected / exposed	0 / 49 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pulmonary embolism			
subjects affected / exposed	0 / 49 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Lupus nephritis			
subjects affected / exposed	0 / 49 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Proteinuria			
subjects affected / exposed	0 / 49 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Acute kidney injury			
subjects affected / exposed	0 / 49 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Nephrotic syndrome			
subjects affected / exposed	0 / 49 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Systemic lupus erythematosus			
subjects affected / exposed	0 / 49 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Herpes zoster			
subjects affected / exposed	0 / 49 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Influenza				
subjects affected / exposed	0 / 49 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Abscess bacterial				
subjects affected / exposed	0 / 49 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pyelonephritis acute				
subjects affected / exposed	0 / 49 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Varicella zoster pneumonia				
subjects affected / exposed	0 / 49 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Atypical pneumonia				
subjects affected / exposed	0 / 49 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Histoplasmosis disseminated				
subjects affected / exposed	0 / 49 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Meningitis				
subjects affected / exposed	0 / 49 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Otitis externa bacterial				
subjects affected / exposed	0 / 49 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pneumonia				

subjects affected / exposed	0 / 49 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Varicella			
subjects affected / exposed	1 / 49 (2.04%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	All Anifrolumab-Treatment Period	All Anifrolumab-Follow up	Placebo- Treatment period
Total subjects affected by non-serious adverse events			
subjects affected / exposed	70 / 96 (72.92%)	0 / 96 (0.00%)	33 / 49 (67.35%)
Vascular disorders			
Hypertension			
subjects affected / exposed	2 / 96 (2.08%)	0 / 96 (0.00%)	3 / 49 (6.12%)
occurrences (all)	2	0	4
Nervous system disorders			
Headache			
subjects affected / exposed	5 / 96 (5.21%)	0 / 96 (0.00%)	4 / 49 (8.16%)
occurrences (all)	6	0	4
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	7 / 96 (7.29%)	0 / 96 (0.00%)	10 / 49 (20.41%)
occurrences (all)	8	0	11
Nausea			
subjects affected / exposed	5 / 96 (5.21%)	0 / 96 (0.00%)	2 / 49 (4.08%)
occurrences (all)	5	0	2
Dyspepsia			
subjects affected / exposed	2 / 96 (2.08%)	0 / 96 (0.00%)	4 / 49 (8.16%)
occurrences (all)	2	0	4
Vomiting			
subjects affected / exposed	2 / 96 (2.08%)	0 / 96 (0.00%)	4 / 49 (8.16%)
occurrences (all)	2	0	4
Abdominal pain			

subjects affected / exposed occurrences (all)	0 / 96 (0.00%) 0	0 / 96 (0.00%) 0	4 / 49 (8.16%) 6
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all)	7 / 96 (7.29%) 10	0 / 96 (0.00%) 0	4 / 49 (8.16%) 4
Oropharyngeal pain subjects affected / exposed occurrences (all)	1 / 96 (1.04%) 1	0 / 96 (0.00%) 0	3 / 49 (6.12%) 3
Psychiatric disorders Depression subjects affected / exposed occurrences (all)	1 / 96 (1.04%) 1	0 / 96 (0.00%) 0	3 / 49 (6.12%) 3
Infections and infestations Urinary tract infection subjects affected / exposed occurrences (all)	16 / 96 (16.67%) 19	0 / 96 (0.00%) 0	5 / 49 (10.20%) 7
Nasopharyngitis subjects affected / exposed occurrences (all)	15 / 96 (15.63%) 22	0 / 96 (0.00%) 0	9 / 49 (18.37%) 16
Upper respiratory tract infection subjects affected / exposed occurrences (all)	15 / 96 (15.63%) 26	0 / 96 (0.00%) 0	8 / 49 (16.33%) 10
Bronchitis subjects affected / exposed occurrences (all)	11 / 96 (11.46%) 11	0 / 96 (0.00%) 0	6 / 49 (12.24%) 6
Herpes zoster subjects affected / exposed occurrences (all)	10 / 96 (10.42%) 10	0 / 96 (0.00%) 0	4 / 49 (8.16%) 4
Pharyngitis subjects affected / exposed occurrences (all)	7 / 96 (7.29%) 10	0 / 96 (0.00%) 0	2 / 49 (4.08%) 2
Oral herpes subjects affected / exposed occurrences (all)	6 / 96 (6.25%) 7	0 / 96 (0.00%) 0	2 / 49 (4.08%) 6
Herpes simplex			

subjects affected / exposed	5 / 96 (5.21%)	0 / 96 (0.00%)	2 / 49 (4.08%)
occurrences (all)	5	0	2
Influenza			
subjects affected / exposed	5 / 96 (5.21%)	0 / 96 (0.00%)	1 / 49 (2.04%)
occurrences (all)	5	0	1

Non-serious adverse events	Placebo- Follow up		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 49 (0.00%)		
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 49 (0.00%)		
occurrences (all)	0		
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 49 (0.00%)		
occurrences (all)	0		
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	0 / 49 (0.00%)		
occurrences (all)	0		
Nausea			
subjects affected / exposed	0 / 49 (0.00%)		
occurrences (all)	0		
Dyspepsia			
subjects affected / exposed	0 / 49 (0.00%)		
occurrences (all)	0		
Vomiting			
subjects affected / exposed	0 / 49 (0.00%)		
occurrences (all)	0		
Abdominal pain			
subjects affected / exposed	0 / 49 (0.00%)		
occurrences (all)	0		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	0 / 49 (0.00%)		
occurrences (all)	0		

Oropharyngeal pain subjects affected / exposed occurrences (all)	0 / 49 (0.00%) 0		
Psychiatric disorders Depression subjects affected / exposed occurrences (all)	0 / 49 (0.00%) 0		
Infections and infestations Urinary tract infection subjects affected / exposed occurrences (all)	0 / 49 (0.00%) 0		
Nasopharyngitis subjects affected / exposed occurrences (all)	0 / 49 (0.00%) 0		
Upper respiratory tract infection subjects affected / exposed occurrences (all)	0 / 49 (0.00%) 0		
Bronchitis subjects affected / exposed occurrences (all)	0 / 49 (0.00%) 0		
Herpes zoster subjects affected / exposed occurrences (all)	0 / 49 (0.00%) 0		
Pharyngitis subjects affected / exposed occurrences (all)	0 / 49 (0.00%) 0		
Oral herpes subjects affected / exposed occurrences (all)	0 / 49 (0.00%) 0		
Herpes simplex subjects affected / exposed occurrences (all)	0 / 49 (0.00%) 0		
Influenza subjects affected / exposed occurrences (all)	0 / 49 (0.00%) 0		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
28 April 2016	Minimum dose of MMF updated from ≤ 1.5 g/day to ≤ 1.0 g/day; Inclusion criteria: numbers 4(b), 7, and 9 to 14 were updated; Exclusion criteria: numbers 2, 6, 13(b), 14(g), 15, 17, 19, 26, 27, 32, and 36(b) were updated; Restricted medication list updated: danazol, dapsons, sulfasalazine, and prednisolone removed; cholestyramine added; Clarification that the methylprednisolone pulse can be administered on 2 consecutive days but that the cumulative dose must not exceed 500 mg and that oral corticosteroids (OCS) burst and taper means one burst and taper of corticosteroids between Week 8 and Week 40 for increased extrarenal SLE disease activity or for non-SLE activity is allowed from randomization to Week 40; Section 3.3.3.1 was updated to provide clarity to the Investigators whether reaching the target MMF dose of 2 gm/day was mandatory or just recommended. Texts were added to clarify that the requirements for MMF dose escalation have to be met only once; Text in Section 6.5.1 has been reworded to amend the definition of "serious non-opportunistic" infection; Safety data have been updated in Section 1.3 based on the new Investigator's Brochure (version 9.0, dated 18 November 2015)
03 September 2016	Update of study design with addition of second-year extension period: • Patients who met the renal portion of the PRR definition were eligible to receive blinded IP between Week 52 and Week 100; • Eligible patients continued in the same randomized treatment group from Year 1; • Ineligible patients did not receive IP at Week 52 and completed the follow-up visits; • Clarification of standard of care treatments added.; • Clarification of efficacy and safety assessment time points added; • Clarification of time points for sampling schedule added; • Additional exploratory endpoints and objectives added; • Statistical analyses updated to include second-year extension period. Database was soft-locked and primary analysis performed when all patients completed Week 52 or discontinued the study prior to Week 52. Investigators and patients who continue in the second-year extension will remain blinded; AstraZeneca and AstraZeneca's delegates will be unblinded at primary analysis.
13 December 2017	The renal function and proteinuria components of renal response criteria were modified by changing 24-hour UPCR and eGFR cut-off values; CRR cut-off values for UPCR and eGFR were changed; CRR at Week 52 was made a secondary endpoint; Changes to statistical analysis: • Text added describing strong control of the familywise error rate will be performed for the primary and secondary endpoints for the pooled anifrolumab group compared with placebo as well as the respective tests for the individual anifrolumab regimens; • Considerations described for the testing strategy to account for multiplicity considerations; • The sample size will provide approximately 86% power with a 2-sided alpha of 0.049; • Relevant sections of the CSP were updated to be consistent with the SAP; Possibility of conducting an interim analysis was added; Exclusion criterion no. 14 was modified: changed to $> 2.5 \times \text{ULN}$ for AST and ALT; Clarification on a number of study procedures were added.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported