Clinical trial results:
A Phase 1b/2a Study to Evaluate the Safety and Efficacy of AMG 592 in Subjects With Active Rheumatoid Arthritis With Inadequate Response to Standard of Care Therapy

Summary

EudraCT number	2017-001944-36
Trial protocol	ES PL BG
Global end of trial date	10 December 2019

Results information

Result version number	v1 (current)
This version publication date	27 May 2021
First version publication date	27 May 2021

Trial information

Trial identification

Sponsor protocol code	20170149

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03410056
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Amgen Inc.
Sponsor organisation address	One Amgen Center Drive, Thousand Oaks, CA, United States,
Public contact	IHQ Medical Info-Clinical Trials, Amgen (EUROPE) GmbH, MedInfoInternational@amgen.com
Scientific contact	IHQ Medical Info-Clinical Trials, Amgen (EUROPE) GmbH, MedInfoInternational@amgen.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	10 December 2019
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	10 December 2019
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The main objective of this study was to evaluate the safety and tolerability of subcutaneous (SC) dose administrations of AMG 592 in participants with active rheumatoid arthritis (RA).

Protection of trial subjects:

This study was conducted in accordance with the protocol and with:

• Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines
• Applicable ICH Good Clinical Practice (GCP) Guidelines
• Applicable laws and regulations

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	22 May 2018
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Bulgaria: 3
Country: Number of subjects enrolled	Poland: 18
Country: Number of subjects enrolled	United States: 15
Worldwide total number of subjects	36
EEA total number of subjects	21

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)	31

From 65 to 84 years	5
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants in phase 1b were to be enrolled into 1 of 4 planned dosing cohorts and randomized in a 3:1 ratio to receive AMG 592 or placebo according to 1 of 2 dosing schedules; A (less frequent) and B (more frequent).

Pre-assignment

Screening details:

Enrollment of the phase 1b part of this study was stopped as of 30 September 2019, due to data that suggested that there is not sufficient benefit-risk for the use of AMG 592 plus standard of care therapy in this study population. The study was terminated prior to the enrollment of any participants into phase 1b Cohort 4 and phase 2a cohorts.

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Phase 1b and Phase 2a: Placebo

Arm description:

Phase 1b: Matching placebo administered via subcutaneous injection for a total of up to 12 weeks. Participants received placebo in 1 of 2 dosing schedules (i.e. dosing schedule A [less frequent] or schedule B [more frequent]).

Phase 2a: Matching placebo administered via subcutaneous injection, depending on the recommended phase 2 dose (RP2D) and dosing schedule as determined in phase 1b, for a total of up to 12 weeks.

The study was terminated prior to the start of phase 2a and no participants were enrolled.

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

Dosage and administration details:

Matching placebo administered via subcutaneous injection.

Arm title	Phase 1b and Phase 2a: AMG 592

Arm description:

Phase 1b: AMG 592 at a low, medium, medium/high, or high dose administered via subcutaneous injection for a total of up to 12 weeks. Participants received AMG 592 in 1 of 2 dosing schedules (i.e. dosing schedule A [less frequent] or schedule B [more frequent]).

Phase 2a: AMG 592 administered via subcutaneous injection depending on the RP2D and dosing schedule determined in phase 1b, for up to a total of up to 12 weeks.

The study was terminated prior to the start of phase 2a and no participants were enrolled in phase 2a or into the medium/high dose cohort of phase 1b.

Arm type	Experimental

Investigational medicinal product name	AMG 592
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

AMG 592 at a low, medium, medium/high, or high dose, administered via subcutaneous injection.

Number of subjects in period 1	Phase 1b and Phase 2a: Placebo	Phase 1b and Phase 2a: AMG 592
Started	8	28
Received treatment	8	28
Started Phase 1b	8	28
Started Phase 2a	0 [1]	0 [2]
Completed	8	13
Not completed	0	15
Consent withdrawn by subject	-	12
Decision by Sponsor	-	3

Notes:

[1] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: The study was terminated prior to the start of phase 2a and no participants were enrolled.

[2] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: The study was terminated prior to the start of phase 2a and no participants were enrolled.

Baseline characteristics

Reporting groups

Reporting group title	Overall study

Reporting group description: -

Reporting group values	Overall study	Total	
Number of subjects	36	36	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	31	31	
From 65-84 years	5	5	
85 years and over	0	0	
Age Continuous Units: years			
arithmetic mean	51.9		
standard deviation	± 12.4	-	
Sex: Female, Male Units:			
Female	27	27	
Male	9	9	
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	4	4	
Not Hispanic or Latino	32	32	
Unknown or Not Reported	0	0	
Race/Ethnicity, Customized Units: Subjects			
Black or African American	3	3	
White	33	33	

Subject analysis sets

Subject analysis set title	Phase 1b: Placebo
Subject analysis set type	Full analysis

Subject analysis set description:

Matching placebo administered via subcutaneous injection for a total of up to 12 weeks. Participants received placebo in 1 of 2 dosing schedules (i.e. dosing schedule A [less frequent] or schedule B [more frequent]).

Subject analysis set title	Phase 1b: AMG 592 Cohort 1
Subject analysis set type	Full analysis

Subject analysis set description:

A low dose of AMG 592 administered via subcutaneous injection using dosing schedule A (less frequent than schedule B) for a total of up to 12 weeks.

Subject analysis set title	Phase 1b: AMG 592 Cohort 2
Subject analysis set type	Full analysis

Subject analysis set description:

A high dose of AMG 592 administered via subcutaneous injection using dosing schedule A (less frequent than schedule B) for a total of up to 12 weeks.

Subject analysis set title	Phase 1b: AMG 592 Cohort 3
Subject analysis set type	Full analysis

Subject analysis set description:

A medium dose of AMG 592 administered via subcutaneous injection using dosing schedule B (more frequent than schedule A) for a total of up to 12 weeks.

Reporting group values	Phase 1b: Placebo	Phase 1b: AMG 592 Cohort 1	Phase 1b: AMG 592 Cohort 2
Number of subjects	8	6	11
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)	7	5	10
From 65-84 years	1	1	1
85 years and over	0	0	0
Age Continuous Units: years			
arithmetic mean	46.4	57.8	53.1
standard deviation	± 12.1	± 8.4	± 10.7
Sex: Female, Male Units:			
Female	4	6	9
Male	4	0	2
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	1	0	2
Not Hispanic or Latino	7	6	9
Unknown or Not Reported	0	0	0
Race/Ethnicity, Customized Units: Subjects			
Black or African American	2	1	0
White	6	5	11

Reporting group values	Phase 1b: AMG 592 Cohort 3		
Number of subjects	11		
Age categorical Units: Subjects			
In utero	0		

Preterm newborn infants (gestational age < 37 wks)	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)	9		
From 65-84 years	2		
85 years and over	0		
Age Continuous			
Units: years			
arithmetic mean	51.4		
standard deviation	± 15.3		
Sex: Female, Male			
Units:			
Female	8		
Male	3		
Ethnicity (NIH/OMB)			
Units: Subjects			
Hispanic or Latino	1		
Not Hispanic or Latino	10		
Unknown or Not Reported	0		
Race/Ethnicity, Customized			
Units: Subjects			
Black or African American	0		
White	11		

End points

End points reporting groups

Reporting group title	Phase 1b and Phase 2a: Placebo

Reporting group description:

Phase 1b: Matching placebo administered via subcutaneous injection for a total of up to 12 weeks. Participants received placebo in 1 of 2 dosing schedules (i.e. dosing schedule A [less frequent] or schedule B [more frequent]).

Phase 2a: Matching placebo administered via subcutaneous injection, depending on the recommended phase 2 dose (RP2D) and dosing schedule as determined in phase 1b, for a total of up to 12 weeks.

The study was terminated prior to the start of phase 2a and no participants were enrolled.

Reporting group title	Phase 1b and Phase 2a: AMG 592

Reporting group description:

Phase 1b: AMG 592 at a low, medium, medium/high, or high dose administered via subcutaneous injection for a total of up to 12 weeks. Participants received AMG 592 in 1 of 2 dosing schedules (i.e. dosing schedule A [less frequent] or schedule B [more frequent]).

Phase 2a: AMG 592 administered via subcutaneous injection depending on the RP2D and dosing schedule determined in phase 1b, for up to a total of up to 12 weeks.

The study was terminated prior to the start of phase 2a and no participants were enrolled in phase 2a or into the medium/high dose cohort of phase 1b.

Subject analysis set title	Phase 1b: Placebo
Subject analysis set type	Full analysis

Subject analysis set description:

Matching placebo administered via subcutaneous injection for a total of up to 12 weeks. Participants received placebo in 1 of 2 dosing schedules (i.e. dosing schedule A [less frequent] or schedule B [more frequent]).

Subject analysis set title	Phase 1b: AMG 592 Cohort 1
Subject analysis set type	Full analysis

Subject analysis set description:

A low dose of AMG 592 administered via subcutaneous injection using dosing schedule A (less frequent than schedule B) for a total of up to 12 weeks.

Subject analysis set title	Phase 1b: AMG 592 Cohort 2
Subject analysis set type	Full analysis

Subject analysis set description:

A high dose of AMG 592 administered via subcutaneous injection using dosing schedule A (less frequent than schedule B) for a total of up to 12 weeks.

Subject analysis set title	Phase 1b: AMG 592 Cohort 3
Subject analysis set type	Full analysis

Subject analysis set description:

A medium dose of AMG 592 administered via subcutaneous injection using dosing schedule B (more frequent than schedule A) for a total of up to 12 weeks.

Primary: Phase 1b: Number of Participants who Experienced a Treatment-emergent Adverse Event (TEAE)

End point title	Phase 1b: Number of Participants who Experienced a Treatment-emergent Adverse Event (TEAE)[1]

End point description:

TEAEs were events with an onset after the administration of the first dose of study treatment.

TEAEs were graded using the Common Terminology Criteria for Adverse Events (CTCAE).

Grade 2 Moderate; minimal, local or noninvasive intervention indicated; limited age appropriate instrumental activities of daily life (ADL).

Grade 3 Severe or medically significant but not immediately life-threatening; hospitalization or prolonged hospitalization indicated; disabling; limited self care ADL.

Grade 4 Life-threatening consequences; urgent interventions indicated.

Serious adverse events (SAEs) were defined as meeting at least 1 of the following criteria:
- Results in death (fatal)
- Immediately life-threatening
- Requires in-patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Other medically important serious event

End point type	Primary

End point timeframe:

Day 1 up to end of study, maximum of 18 weeks (12-weeks double-blind treatment, 6-weeks safety follow-up)

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: No formal statistical analyses were planned.

End point values	Phase 1b: Placebo	Phase 1b: AMG 592 Cohort 1	Phase 1b: AMG 592 Cohort 2	Phase 1b: AMG 592 Cohort 3
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	8	6	11	11
Units: Participants				
TEAEs	3	5	11	11
Grade ≥ 2 TEAEs	2	3	8	8
Grade ≥ 3 TEAEs	0	0	1	0
Grade ≥ 4 TEAEs	0	0	0	0
SAEs	0	0	1	0
TEAEs leading to discontinuation of treatment	0	1	7	3
Life-threatening TEAEs	0	0	0	0
Fatal TEAEs	0	0	0	0

Statistical analyses

No statistical analyses for this end point

Primary: Phase 1b: Number of Participants who Experienced a Clinically Significant Change in Vital Signs

End point title	Phase 1b: Number of Participants who Experienced a Clinically Significant Change in Vital Signs[2]

End point description:

Any changes in systolic/diastolic blood pressure, heart rate, respiratory rate, and temperature that were deemed as clinically significant by the Investigator were reported.

End point type	Primary

End point timeframe:

Baseline up to end of study, maximum of 18 weeks (12-weeks double-blind treatment, 6-weeks safety follow-up)

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No formal statistical analyses were planned.

End point values	Phase 1b: Placebo	Phase 1b: AMG 592 Cohort 1	Phase 1b: AMG 592 Cohort 2	Phase 1b: AMG 592 Cohort 3
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	8	6	11	11
Units: Participants	0	0	0	0

Statistical analyses

No statistical analyses for this end point

Primary: Phase 1b: Number of Participants who Experienced a Clinically Significant Change in Laboratory Safety Tests

End point title	Phase 1b: Number of Participants who Experienced a Clinically Significant Change in Laboratory Safety Tests[3]

End point description:

Laboratory safety tests included chemistry and hematology parameters. Clinically significant laboratory safety tests were any events assessed as CTCAE Grade ≥3 at any post-baseline visit.

Grade 3 Severe or medically significant but not immediately life-threatening; hospitalization or prolonged hospitalization indicated; disabling; limited self care ADL.

Grade 4 Life-threatening consequences; urgent interventions indicated.

End point type	Primary

End point timeframe:

Baseline up to end of study, maximum of 18 weeks (12-weeks double-blind treatment, 6-weeks safety follow-up)

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No formal statistical analyses were planned.

End point values	Phase 1b: Placebo	Phase 1b: AMG 592 Cohort 1	Phase 1b: AMG 592 Cohort 2	Phase 1b: AMG 592 Cohort 3
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	8	6	11	11
Units: Participants	0	0	1	0

Statistical analyses

No statistical analyses for this end point

Primary: Phase 1b: Number of Participants who Experienced a Clinically Significant Change in Electrocardiograms (ECGs)

End point title	Phase 1b: Number of Participants who Experienced a Clinically Significant Change in Electrocardiograms (ECGs)[4]

End point description:

Any changes in ECG parameters that were deemed clinically significant by the investigator were reported.

End point type	Primary

End point timeframe:

Baseline up to end of treatment maximum of 12 weeks

Notes:

[4] - 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: No formal statistical analyses were planned.

End point values	Phase 1b: Placebo	Phase 1b: AMG 592 Cohort 1	Phase 1b: AMG 592 Cohort 2	Phase 1b: AMG 592 Cohort 3
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	8	6	11	11
Units: Participants	0	0	0	0

Statistical analyses

No statistical analyses for this end point

Primary: Phase 2a: Number of Participants who Achieved an American College of Rheumatology 20 Percent Improvement Criteria (ACR 20) at Week 12

End point title	Phase 2a: Number of Participants who Achieved an American College of Rheumatology 20 Percent Improvement Criteria (ACR 20) at Week 12[5]

End point description:

ACR 20 response defined as at least 20 percent improvement from baseline in both tender and swollen joint counts, and a 20 percent improvement or more in at least 3 of the following 5 criteria:
- physician global assessment of disease activity (PGA)
- subject global assessment of disease activity (SGA)
- patient global assessment of joint pain
- subject self-assessment of disability (HAQ-DI)
- C-Reactive Protein (CRP)

End point type	Primary

End point timeframe:

Baseline and Week 12

Notes:

[5] - 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: No formal statistical analyses were planned.

End point values	Phase 1b and Phase 2a: Placebo	Phase 1b and Phase 2a: AMG 592		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[6]	0[7]		
Units: Participants				

Notes:

[6] - No participants were enrolled for Phase 2a.

[7] - No participants were enrolled for Phase 2a.

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 1b: AMG 592 Serum Concentrations

End point title	Phase 1b: AMG 592 Serum Concentrations

End point description:

A summary of mean serum concentrations of AMG 592 over time is presented. Any results below the lower limit of quantification were set to 0.00.

99999 = insufficient samples were collected to assess SD.

End point type	Secondary

End point timeframe:

Day 1 (pre-dose), 6 and 12 hours post-dose, and days 2, 3, 4, 8, 11, 15, 22, 29, 36, 43, 50, 57, 64, 71, 78, and Day 85 (pre-dose), 6 and 12 hours post-dose and days 86, 87, 88, 92, 99, 113 and 127

End point values	Phase 1b: AMG 592 Cohort 1	Phase 1b: AMG 592 Cohort 2	Phase 1b: AMG 592 Cohort 3	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	6[8]	11[9]	11[10]	
Units: ng/mL				
arithmetic mean (standard deviation)				
Day 1 (pre-dose)	0.00 (± 0.00)	0.00 (± 0.00)	0.00 (± 0.00)	
Day 1 (6 hours post-dose)	1.35 (± 0.795)	7.67 (± 8.01)	2.13 (± 2.98)	
Day 1 (12 hours post-dose)	2.43 (± 0.867)	14.6 (± 12.1)	4.09 (± 4.70)	
Day 2	2.59 (± 0.875)	22.0 (± 11.5)	5.44 (± 5.09)	
Day 3	1.70 (± 0.850)	18.6 (± 9.16)	3.65 (± 3.13)	
Day 4	0.727 (± 0.277)	7.65 (± 5.85)	2.36 (± 2.84)	
Day 8	0.0555 (± 0.0924)	0.108 (± 0.146)	0.0284 (± 0.0624)	
Day 11	0.0230 (± 0.0514)	0.0115 (± 0.0364)	0.930 (± 0.780)	
Day 15	0.00 (± 0.00)	0.00 (± 0.00)	0.107 (± 0.150)	
Day 22	0.0830 (± 0.144)	0.0703 (± 0.112)	0.235 (± 0.373)	
Day 29	0.00 (± 0.00)	0.00 (± 0.00)	0.217 (± 0.344)	
Day 36	0.0644 (± 0.144)	0.102 (± 0.203)	0.239 (± 0.425)	
Day 43	0.00 (± 0.00)	0.00 (± 0.00)	0.104 (± 0.275)	
Day 50	0.205 (± 0.304)	0.105 (± 0.210)	0.122 (± 0.322)	
Day 57	0.0368 (± 0.0735)	0.00 (± 0.00)	0.0886 (± 0.234)	
Day 64	0.336 (± 99999)	0.212 (± 0.424)	0.0294 (± 0.0657)	
Day 71	0.0635 (± 99999)	0.00 (± 0.00)	0.00 (± 0.00)	
Day 78	0.154 (± 0.267)	0.355 (± 0.614)	0.0508 (± 0.0819)	
Day 85 (pre-dose)	0.00 (± 0.00)	0.00 (± 0.00)	0.0578 (± 0.0958)	
Day 85 (6 hours post-dose)	2.41 (± 1.56)	5.91 (± 99999)	1.92 (± 2.64)	
Day 85 (12 hours post-dose)	4.00 (± 2.05)	12.9 (± 99999)	2.92 (± 4.03)	
Day 86	3.60 (± 2.07)	12.3 (± 99999)	2.97 (± 4.48)	
Day 87	2.10 (± 1.15)	4.39 (± 99999)	1.87 (± 2.43)	
Day 88	1.48 (± 0.623)	1.01 (± 99999)	0.903 (± 1.17)	

Day 92	0.113 (± 99999)	0.00 (± 99999)	0.0953 (± 0.115)	
Day 99	0.00 (± 0.00)	0.00 (± 99999)	0.110 (± 0.268)	
Day 113	0.00 (± 0.00)	0.00 (± 99999)	0.00 (± 0.00)	
Day 127	0.00 (± 0.00)	0.00 (± 99999)	0.00 (± 0.00)	

Notes:

[8] - N values range from 6 to 1 participant(s)

[9] - N values range from 11 to 2 participants.

[10] - N values range from 11 to 5 participants.

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 1b: Maximum Observed Serum Concentration (Cmax) of AMG 592

End point title	Phase 1b: Maximum Observed Serum Concentration (Cmax) of AMG 592

End point description:

99999 = Insufficient samples were collected to assess mean Cmax.

End point type	Secondary

End point timeframe:

Day 1 (pre-dose) and 6 to 48 hours post-dose, and days 4, 8, 11, 15, 22, 29, 36, 43, 50, 57, 64, 71, 78, Day 85 (pre-dose) and 6 to 72 hours post-dose, and days 92, 99, 113 and 127

End point values	Phase 1b: AMG 592 Cohort 1	Phase 1b: AMG 592 Cohort 2	Phase 1b: AMG 592 Cohort 3	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	6[11]	11[12]	11[13]	
Units: ng/mL				
arithmetic mean (standard deviation)				
First dose (Day 1)	2.66 (± 0.852)	23.0 (± 11.2)	5.71 (± 5.10)	
Last dose (Day 85)	4.00 (± 2.05)	99999 (± 99999)	3.22 (± 4.35)	

Notes:

[11] - Day 85 N = 4

[12] - Day 85 N = 2

[13] - Day 85 N = 6

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 1b: Time to Maximum Observed Serum Concentration (Tmax) of AMG 592

End point title	Phase 1b: Time to Maximum Observed Serum Concentration (Tmax) of AMG 592

End point description:

End point type	Secondary

End point timeframe:

Day 1 (pre-dose) and 6 to 48 hours post-dose, and days 4, 8, 11, 15, 22, 29, 36, 43, 50, 57, 64, 71,

End point values	Phase 1b: AMG 592 Cohort 1	Phase 1b: AMG 592 Cohort 2	Phase 1b: AMG 592 Cohort 3	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	6[14]	11[15]	11[16]	
Units: hours				
median (full range (min-max))				
First dose (Day 1)	18 (12 to 24)	24 (24 to 48)	24 (12 to 72)	
Last dose (Day 85)	12 (12 to 12)	30 (12 to 48)	12 (6.0 to 24)	

Notes:

[14] - Day 85 N = 4

[15] - Day 85 N = 2

[16] - Day 85 N = 6

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 1b: Area Under the Concentration-time Curve from Time 0 to 14 Days (AUC0-14) Post Dose

End point title	Phase 1b: Area Under the Concentration-time Curve from Time 0 to 14 Days (AUC0-14) Post Dose

End point description:

AUC0-14 was only assessed for the participants who received AMG 592 using dosing schedule A.

99999 = Insufficient samples were collected to assess AUC0-14.

End point type	Secondary

End point timeframe:

Day 1 (pre-dose) and 6 to 48 hours post-dose, and days 4, 8, 11 and 15, Day 85 (pre-dose) and 6 to 72 hours post-dose, and days 92 and 99

End point values	Phase 1b: AMG 592 Cohort 1	Phase 1b: AMG 592 Cohort 2		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	6[17]	10[18]		
Units: hr*ng/mL				
arithmetic mean (standard deviation)				
First dose (Day 1)	167 (± 60.9)	1570 (± 859)		
Last dose (Day 85)	282 (± 207)	99999 (± 99999)		

Notes:

[17] - Day 85 N = 4

[18] - Day 85 N = 2

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 1b: Area Under the Concentration-time Curve from Time 0 to 7 Days (AUC0-7) Post Dose

End point title	Phase 1b: Area Under the Concentration-time Curve from Time 0 to 7 Days (AUC0-7) Post Dose

End point description:

AUC0-7 was only assessed for the participants who received AMG 592 using dosing schedule B.

End point type	Secondary

End point timeframe:

Day 1 (pre-dose) and 6 to 48 hours post-dose, and days 4 and 8, Day 85 (pre-dose) and 6 to 72 hours post-dose, and Day 92

End point values	Phase 1b: AMG 592 Cohort 3			
Subject group type	Subject analysis set			
Number of subjects analysed	10[19]			
Units: hr*ng/mL				
arithmetic mean (standard deviation)				
First dose (Day 1)	315 (± 239)			
Last dose (Day 85)	195 (± 264)			

Notes:

[19] - Day 85 N = 6

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 1b: Number of Participants with Anti-AMG 592 Binding Antibodies and Anti-Interleukin (IL-2) Binding Antibodies

End point title	Phase 1b: Number of Participants with Anti-AMG 592 Binding Antibodies and Anti-Interleukin (IL-2) Binding Antibodies

End point description:

Number of participants who tested positive for anti-AMG 592 binding antibodies and number of those participants who cross-reacted with native human IL-2 (i.e. with anti-IL-2 binding antibodies) are reported.

Binding anti-AMG 592 antibody positive post-baseline with a negative or no result at baseline.

Binding anti-IL2 antibody positive post-baseline with a negative or no result at baseline.

End point type	Secondary

End point timeframe:

Baseline up to end of study, maximum of 18 weeks (12-weeks double-blind treatment, 6-weeks safety follow-up)

End point values	Phase 1b: Placebo	Phase 1b: AMG 592 Cohort 1	Phase 1b: AMG 592 Cohort 2	Phase 1b: AMG 592 Cohort 3
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	8[20]	6[21]	11[22]	11[23]
Units: Participants				
Binding anti-AMG 592 antibody positive	2	3	6	5
Binding anti-IL2 antibody positive	0	0	1	1

Notes:

[20] - anti-IL2 antibody positive N = 3

[21] - anti-IL2 antibody positive N = 3

[22] - anti-IL2 antibody positive N = 8

[23] - anti-IL2 antibody positive N = 5

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 1b: Number of Participants with Anti-AMG 592 Neutralizing Antibodies and Anti-IL-2 Neutralizing Antibodies

End point title	Phase 1b: Number of Participants with Anti-AMG 592 Neutralizing Antibodies and Anti-IL-2 Neutralizing Antibodies

End point description:

The number of participants who tested positive for anti-AMG 592 neutralizing antibodies and number of participants with anti-IL2 neutralizing antibodies who tested negative or no result at baseline are reported.

Neutralizing anti-AMG592 antibodies positive post-baseline with a negative or no result at baseline.

Neutralizing anti-IL2 antibody positive post-baseline with a negative or no result at baseline.

End point type	Secondary

End point timeframe:

Baseline up to end of study, maximum of 18 weeks (12-weeks double-blind treatment, 6-weeks safety follow-up)

End point values	Phase 1b: Placebo	Phase 1b: AMG 592 Cohort 1	Phase 1b: AMG 592 Cohort 2	Phase 1b: AMG 592 Cohort 3
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	8[24]	5[25]	11[26]	10[27]
Units: Participants				
Neutralizing anti-AMG592 antibodies positive	2	1	7	5
Neutralizing anti-IL2 antibody positive	0	0	1	1

Notes:

[24] - Neutralizing anti-IL2 antibody positive N = 3

[25] - Neutralizing anti-IL2 antibody positive N = 3

[26] - Neutralizing anti-IL2 antibody positive N = 8

[27] - Neutralizing anti-IL2 antibody positive N = 5

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 2a: Number of Participants who Achieved an American College of

Rheumatology 50 Percent Improvement Criteria (ACR 50) or 70 Percent Improvement Criteria (ACR 70) at Week 12

End point title	Phase 2a: Number of Participants who Achieved an American College of Rheumatology 50 Percent Improvement Criteria (ACR 50) or 70 Percent Improvement Criteria (ACR 70) at Week 12

End point description:

ACR 50 and ACR 70 response defined as at least 50 percent or 70 percent improvement from baseline in both tender and swollen joint counts, and a 50 percent or 70 percent improvement or more in at least 3 of the following 5 criteria:
- physician global assessment of disease activity (PGA)
- subject global assessment of disease activity (SGA)
- patient global assessment of joint pain
- subject self-assessment of disability (HAQ-DI)
- C-Reactive Protein (CRP)

End point type	Secondary

End point timeframe:

Baseline and Week 12

End point values	Phase 1b and Phase 2a: Placebo	Phase 1b and Phase 2a: AMG 592		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[28]	0[29]		
Units: Participants				

Notes:

[28] - No participants were enrolled for Phase 2a.

[29] - No participants were enrolled for Phase 2a.

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 2a: Change from Baseline in Disease Activity Score (28 Joint) Calculated Using The Erythrocyte Sedimentation Rate Formula (DAS28-ESR) at Week 12

End point title	Phase 2a: Change from Baseline in Disease Activity Score (28 Joint) Calculated Using The Erythrocyte Sedimentation Rate Formula (DAS28-ESR) at Week 12

End point description:

Change from baseline in DAS28-ER at Week 12. DAS28-ESR was to assess disease activity in patients with rheumatoid arthritis. DAS28-ESR is a composite score that includes 4 variables: tender joint count (TJC) (based on 28 joints); swollen joint count (SJC) (based on 28 joints); participant's global assessment of health activity using 100 mm visual analogue scale (VAS): range 0 (no pain) to 100 (maximum pain imaginable); marker of inflammation assessed by ESR in mm/h. DAS28-ESR total score range from 0-10, higher score indicates more disease activity.

End point type	Secondary

End point timeframe:

Baseline and Week 12

End point values	Phase 1b and Phase 2a: Placebo	Phase 1b and Phase 2a: AMG 592		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[30]	0[31]		
Units: Score on a scale				
arithmetic mean (standard deviation)	()	()		

Notes:

[30] - No participants were enrolled for Phase 2a.

[31] - No participants were enrolled for Phase 2a.

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 2a: Change from Baseline in Disease Activity Score (28 joint) Calculated using the C-reactive Protein Formula (DAS-28-CRP) at Week 12

End point title	Phase 2a: Change from Baseline in Disease Activity Score (28 joint) Calculated using the C-reactive Protein Formula (DAS-28-CRP) at Week 12

End point description:

Change from baseline in DAS28-CRP at Week 12. 2. DAS28-CRP was to assess disease activity in patients with rheumatoid arthritis. DAS28-CRP is a composite score that includes 4 variables: TJC (based on 28 joints); SJC (based on 28 joints); participant's global assessment of health activity using 100 mm VAS: range 0 (no pain) to 100 (maximum pain imaginable); marker of inflammation assessed by CRP in mg/L. DAS28-CRP total score range from 0-10, higher score indicates more disease activity.

End point type	Secondary

End point timeframe:

Baseline and Week 12

End point values	Phase 1b and Phase 2a: Placebo	Phase 1b and Phase 2a: AMG 592		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[32]	0[33]		
Units: Score on a scale				
arithmetic mean (standard deviation)	()	()		

Notes:

[32] - No participants were enrolled for Phase 2a.

[33] - No participants were enrolled for Phase 2a.

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 2a: Number of Participants who Experienced a Treatment-emergent Adverse Event (TEAE)

End point title	Phase 2a: Number of Participants who Experienced a Treatment-emergent Adverse Event (TEAE)

End point description:

TEAEs were events with an onset after the administration of the first dose of study treatment.

TEAEs were graded using the Common Terminology Criteria for Adverse Events (CTCAE).

End point type	Secondary

End point timeframe:

Baseline up to end of study, maximum of 18 weeks (12-weeks double-blind treatment, 6-weeks safety follow-up)

End point values	Phase 1b and Phase 2a: Placebo	Phase 1b and Phase 2a: AMG 592		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[34]	0[35]		
Units: Participants				

Notes:

[34] - No participants were enrolled for Phase 2a.

[35] - No participants were enrolled for Phase 2a.

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 2a: Number of Participants who Experienced a Clinically Significant Change in Vital Signs

End point title	Phase 2a: Number of Participants who Experienced a Clinically Significant Change in Vital Signs

End point description:

Any changes in systolic/diastolic blood pressure, heart rate, respiratory rate, and temperature that were deemed as clinically significant by the Investigator were reported.

End point type	Secondary

End point timeframe:

Baseline up to Week 12

End point values	Phase 1b and Phase 2a: Placebo	Phase 1b and Phase 2a: AMG 592		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[36]	0[37]		
Units: Participants				

Notes:

[36] - No participants were enrolled for Phase 2a.

[37] - No participants were enrolled for Phase 2a.

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 2a: Number of Participants who Experienced a Clinically Significant Change in Laboratory Safety Tests

End point title	Phase 2a: Number of Participants who Experienced a Clinically Significant Change in Laboratory Safety Tests

End point description:

Laboratory safety tests included chemistry and hematology parameters. Clinically significant laboratory safety tests were any events assessed as CTCAE Grade ≥3 at any post-baseline visit.

Grade 3 Severe or medically significant but not immediately life-threatening; hospitalization or prolonged hospitalization indicated; disabling; limited self care ADL.

Grade 4 Life-threatening consequences; urgent interventions indicated.

End point type	Secondary

End point timeframe:

Day 1 up to end of study, maximum of 18 weeks (12-weeks double-blind treatment, 6-weeks safety follow-up)

End point values	Phase 1b and Phase 2a: Placebo	Phase 1b and Phase 2a: AMG 592		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[38]	0[39]		
Units: Participants				

Notes:

[38] - No participants were enrolled for Phase 2a.

[39] - No participants were enrolled for Phase 2a.

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 2a: AMG 592 Serum Concentration

End point title	Phase 2a: AMG 592 Serum Concentration

End point description:

A summary of mean serum concentrations of AMG 592 over time.

End point type	Secondary

End point timeframe:

Day 1 (pre-dose) and weeks 2, 4, 6, 8, 10 and 12

End point values	Phase 1b and Phase 2a: Placebo	Phase 1b and Phase 2a: AMG 592		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[40]	0[41]		
Units: ng/mL				
arithmetic mean (standard deviation)	()	()		

Notes:

[40] - No participants were enrolled for Phase 2a.

[41] - No participants were enrolled for Phase 2a.

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 2a: Maximum Observed Serum Concentration (Cmax) of AMG 592

End point title	Phase 2a: Maximum Observed Serum Concentration (Cmax) of AMG 592

End point description:

End point type	Secondary

End point timeframe:

Day 1 (pre-dose) and weeks 2, 4, 6, 8, 10 and 12

End point values	Phase 1b and Phase 2a: Placebo	Phase 1b and Phase 2a: AMG 592		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[42]	0[43]		
Units: ng/mL				
arithmetic mean (standard deviation)	()	()		

Notes:

[42] - No participants were enrolled for Phase 2a.

[43] - No participants were enrolled for Phase 2a.

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 2a: Time to Maximum Observed Serum Concentration (Tmax) of AMG 592

End point title	Phase 2a: Time to Maximum Observed Serum Concentration (Tmax) of AMG 592

End point description:

End point type	Secondary

End point timeframe:

Day 1 (pre-dose) and weeks 2, 4, 6, 8, 10 and 12

End point values	Phase 1b and Phase 2a: Placebo	Phase 1b and Phase 2a: AMG 592		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[44]	0[45]		
Units: hours				
arithmetic mean (standard deviation)	()	()		

Notes:

[44] - No participants were enrolled for Phase 2a. `

[45] - No participants were enrolled for Phase 2a.

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 2a: Area Under the Concentration-time Curve (AUC) of AMG 592

End point title	Phase 2a: Area Under the Concentration-time Curve (AUC) of AMG 592

End point description:

End point type	Secondary

End point timeframe:

Day 1 (pre-dose) and weeks 2, 4, 6, 8, 10 and 12

End point values	Phase 1b and Phase 2a: Placebo	Phase 1b and Phase 2a: AMG 592		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[46]	0[47]		
Units: hr*ng/mL				
arithmetic mean (standard deviation)	()	()		

Notes:

[46] - No participants were enrolled for Phase 2a.

[47] - No participants were enrolled for Phase 2a.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Day 1 up to end of study, maximum of 18 weeks (12-weeks double-blind treatment, 6-weeks safety follow-up)

Adverse event reporting additional description:

All-cause mortality is reported for all participants enrolled in the study. Treatment emergent SAEs and other AEs, including disease-related AEs are reported for all participants who received at least one dose of study drug.

No data is available for phase 1b medium/high group or phase 2a as the study was terminated prior to participants enrolling.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	22.1

Reporting groups

Reporting group title	Phase 1b: Placebo

Reporting group description:

Matching placebo administered via subcutaneous injection for a total of up to 12 weeks. Participants received placebo in 1 of 2 dosing schedules (i.e. dosing schedule A [less frequent] or schedule [more frequent]).

Reporting group title	Phase 1b: AMG 592 Cohort 1

Reporting group description:

A low dose of AMG 592 administered via subcutaneous injection using dosing schedule A (less frequent than schedule B) for a total of up to 12 weeks.

Reporting group title	Phase 1b: AMG 592 Cohort 2

Reporting group description:

A high dose of AMG 592 administered via subcutaneous injection using dosing schedule A (less frequent than schedule B) for a total of up to 12 weeks.

Reporting group title	Phase 1b: AMG 592 Cohort 3

Reporting group description:

A medium dose of AMG 592 administered via subcutaneous injection using dosing schedule B (more frequent than schedule A) for a total of up to 12 weeks.

Serious adverse events	Phase 1b: Placebo	Phase 1b: AMG 592 Cohort 1	Phase 1b: AMG 592 Cohort 2
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	1 / 11 (9.09%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	1 / 11 (9.09%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Phase 1b: AMG 592 Cohort 3		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 11 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events			
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	0 / 11 (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	Phase 1b: Placebo	Phase 1b: AMG 592 Cohort 1	Phase 1b: AMG 592 Cohort 2
Total subjects affected by non-serious adverse events			
subjects affected / exposed	3 / 8 (37.50%)	5 / 6 (83.33%)	11 / 11 (100.00%)
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 8 (12.50%)	0 / 6 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0
General disorders and administration site conditions			
Administration site reaction			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	2
Asthenia			
subjects affected / exposed	0 / 8 (0.00%)	1 / 6 (16.67%)	1 / 11 (9.09%)
occurrences (all)	0	1	2
Chest pain			
subjects affected / exposed	1 / 8 (12.50%)	0 / 6 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0
Chills			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Influenza like illness			
subjects affected / exposed	0 / 8 (0.00%)	1 / 6 (16.67%)	0 / 11 (0.00%)
occurrences (all)	0	1	0

Injection site erythema			
subjects affected / exposed	0 / 8 (0.00%)	4 / 6 (66.67%)	2 / 11 (18.18%)
occurrences (all)	0	15	4
Injection site hypersensitivity			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Injection site pain			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Injection site pruritus			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Injection site reaction			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	6 / 11 (54.55%)
occurrences (all)	0	0	18
Injection site swelling			
subjects affected / exposed	0 / 8 (0.00%)	1 / 6 (16.67%)	0 / 11 (0.00%)
occurrences (all)	0	2	0
Pain			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Peripheral swelling			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	2 / 11 (18.18%)
occurrences (all)	0	0	3
Pyrexia			
subjects affected / exposed	1 / 8 (12.50%)	0 / 6 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	2
Reproductive system and breast disorders			
Dysmenorrhoea			
subjects affected / exposed	1 / 8 (12.50%)	0 / 6 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0
Respiratory, thoracic and mediastinal disorders			

Asthma			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Cough			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Dyspnoea			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Epistaxis			
subjects affected / exposed	1 / 8 (12.50%)	0 / 6 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0
Oropharyngeal pain			
subjects affected / exposed	0 / 8 (0.00%)	2 / 6 (33.33%)	0 / 11 (0.00%)
occurrences (all)	0	2	0
Psychiatric disorders			
Insomnia			
subjects affected / exposed	1 / 8 (12.50%)	0 / 6 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0
Investigations			
Blood pressure increased			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Body temperature increased			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	3
Eosinophil count increased			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Transaminases increased			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Injury, poisoning and procedural complications			
Administration related reaction			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1

Arthropod bite			
subjects affected / exposed	0 / 8 (0.00%)	1 / 6 (16.67%)	0 / 11 (0.00%)
occurrences (all)	0	1	0
Cardiac disorders			
Tachycardia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Nervous system disorders			
Dizziness			
subjects affected / exposed	1 / 8 (12.50%)	0 / 6 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0
Dizziness postural			
subjects affected / exposed	1 / 8 (12.50%)	0 / 6 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0
Headache			
subjects affected / exposed	1 / 8 (12.50%)	0 / 6 (0.00%)	1 / 11 (9.09%)
occurrences (all)	1	0	1
Blood and lymphatic system disorders			
Eosinophilia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	3 / 11 (27.27%)
occurrences (all)	0	0	3
Eye disorders			
Cataract			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Conjunctival haemorrhage			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	2
Swelling of eyelid			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	2 / 11 (18.18%)
occurrences (all)	0	0	2
Abdominal pain upper			

subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Diarrhoea			
subjects affected / exposed	0 / 8 (0.00%)	1 / 6 (16.67%)	0 / 11 (0.00%)
occurrences (all)	0	1	0
Dyspepsia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Gastritis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Large intestine polyp			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Lower gastrointestinal haemorrhage			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Nausea			
subjects affected / exposed	1 / 8 (12.50%)	0 / 6 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0
Swollen tongue			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Vomiting			
subjects affected / exposed	1 / 8 (12.50%)	0 / 6 (0.00%)	1 / 11 (9.09%)
occurrences (all)	1	0	1
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	1 / 8 (12.50%)	0 / 6 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0
Blister			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	2
Drug eruption			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1

Erythema			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	2 / 11 (18.18%)
occurrences (all)	0	0	9
Pruritus			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	2 / 11 (18.18%)
occurrences (all)	0	0	4
Rash			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	2 / 11 (18.18%)
occurrences (all)	0	0	2
Skin burning sensation			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Skin lesion			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Skin swelling			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	2 / 11 (18.18%)
occurrences (all)	0	0	2
Renal and urinary disorders			
Pollakiuria			
subjects affected / exposed	1 / 8 (12.50%)	0 / 6 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 8 (0.00%)	1 / 6 (16.67%)	3 / 11 (27.27%)
occurrences (all)	0	1	7
Back pain			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Bursitis			
subjects affected / exposed	1 / 8 (12.50%)	0 / 6 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0
Joint stiffness			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	4
Joint swelling			

subjects affected / exposed	0 / 8 (0.00%)	1 / 6 (16.67%)	1 / 11 (9.09%)
occurrences (all)	0	1	1
Musculoskeletal stiffness			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	2
Pain in extremity			
subjects affected / exposed	1 / 8 (12.50%)	0 / 6 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0
Rheumatoid arthritis			
subjects affected / exposed	1 / 8 (12.50%)	0 / 6 (0.00%)	4 / 11 (36.36%)
occurrences (all)	1	0	5
Infections and infestations			
Gingivitis			
subjects affected / exposed	1 / 8 (12.50%)	0 / 6 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0
Influenza			
subjects affected / exposed	0 / 8 (0.00%)	1 / 6 (16.67%)	0 / 11 (0.00%)
occurrences (all)	0	1	0
Nasopharyngitis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Otitis media			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Rhinitis			
subjects affected / exposed	1 / 8 (12.50%)	0 / 6 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0
Sinusitis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Upper respiratory tract infection			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0

Non-serious adverse events	Phase 1b: AMG 592 Cohort 3		
Total subjects affected by non-serious adverse events			

subjects affected / exposed	11 / 11 (100.00%)		
Vascular disorders			
Hypertension			
subjects affected / exposed	2 / 11 (18.18%)		
occurrences (all)	4		
General disorders and administration site conditions			
Administration site reaction			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Asthenia			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Chest pain			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Chills			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Influenza like illness			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Injection site erythema			
subjects affected / exposed	3 / 11 (27.27%)		
occurrences (all)	9		
Injection site hypersensitivity			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Injection site pain			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Injection site pruritus			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	2		
Injection site reaction			
subjects affected / exposed	8 / 11 (72.73%)		
occurrences (all)	38		

Injection site swelling subjects affected / exposed occurrences (all)	1 / 11 (9.09%) 1		
Pain subjects affected / exposed occurrences (all)	0 / 11 (0.00%) 0		
Peripheral swelling subjects affected / exposed occurrences (all)	1 / 11 (9.09%) 1		
Pyrexia subjects affected / exposed occurrences (all)	1 / 11 (9.09%) 3		
Immune system disorders Hypersensitivity subjects affected / exposed occurrences (all)	0 / 11 (0.00%) 0		
Reproductive system and breast disorders Dysmenorrhoea subjects affected / exposed occurrences (all)	0 / 11 (0.00%) 0		
Respiratory, thoracic and mediastinal disorders Asthma subjects affected / exposed occurrences (all)	0 / 11 (0.00%) 0		
Cough subjects affected / exposed occurrences (all)	1 / 11 (9.09%) 1		
Dyspnoea subjects affected / exposed occurrences (all)	1 / 11 (9.09%) 1		
Epistaxis subjects affected / exposed occurrences (all)	0 / 11 (0.00%) 0		
Oropharyngeal pain subjects affected / exposed occurrences (all)	0 / 11 (0.00%) 0		

Psychiatric disorders Insomnia subjects affected / exposed occurrences (all)	 0 / 11 (0.00%) 0		
Investigations Blood pressure increased subjects affected / exposed occurrences (all) Body temperature increased subjects affected / exposed occurrences (all) Eosinophil count increased subjects affected / exposed occurrences (all) Transaminases increased subjects affected / exposed occurrences (all)	 1 / 11 (9.09%) 1 0 / 11 (0.00%) 0 0 / 11 (0.00%) 0 0 / 11 (0.00%) 0		
Injury, poisoning and procedural complications Administration related reaction subjects affected / exposed occurrences (all) Arthropod bite subjects affected / exposed occurrences (all)	 0 / 11 (0.00%) 0 0 / 11 (0.00%) 0		
Cardiac disorders Tachycardia subjects affected / exposed occurrences (all)	 1 / 11 (9.09%) 2		
Nervous system disorders Dizziness subjects affected / exposed occurrences (all) Dizziness postural subjects affected / exposed occurrences (all) Headache	 1 / 11 (9.09%) 1 0 / 11 (0.00%) 0		

subjects affected / exposed	2 / 11 (18.18%)		
occurrences (all)	2		
Blood and lymphatic system disorders			
Eosinophilia			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Eye disorders			
Cataract			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	2		
Conjunctival haemorrhage			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Swelling of eyelid			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Abdominal pain upper			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Diarrhoea			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Dyspepsia			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Gastritis			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Large intestine polyp			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Lower gastrointestinal haemorrhage			

subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Nausea			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Swollen tongue			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Vomiting			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Blister			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Drug eruption			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Erythema			
subjects affected / exposed	2 / 11 (18.18%)		
occurrences (all)	3		
Pruritus			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Rash			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Skin burning sensation			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Skin lesion			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		

Skin swelling			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Renal and urinary disorders			
Pollakiuria			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Back pain			
subjects affected / exposed	2 / 11 (18.18%)		
occurrences (all)	2		
Bursitis			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Joint stiffness			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Joint swelling			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Musculoskeletal stiffness			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Pain in extremity			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Rheumatoid arthritis			
subjects affected / exposed	2 / 11 (18.18%)		
occurrences (all)	3		
Infections and infestations			
Gingivitis			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		

Influenza			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Nasopharyngitis			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Otitis media			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Rhinitis			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Sinusitis			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Upper respiratory tract infection			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	2		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
23 May 2018	* Clarified aspects of Early Termination and Safety Follow-up visits and that PK, PD, and antibody blood samples could not be drawn through a central or peripheral line. * Changed exclusion criteria: - To allow up to 3 prior biologic or oral synthetic DMARD therapies; updated wash out periods for these prior therapies. - To clarify prohibited medications to allow Vitamin D and calcium to be taken. * Replaced sentinel dosing in phase 1b with longer direct observation after the first dose and close telephone follow-up after the second dose of investigational product. * Incorporated a cohort stopping rule of equal to or greater than 2 grade 3 adverse events to replace the existing equal to or greater than 3 grade 3 adverse event stopping rule. * Included PK sampling at day 92, 99, and 113 and clinical laboratory assessments before day 15 for additional safety review.
26 July 2018	* Changed participant urine drug/alcohol testing, during screening, from the local laboratory to the central laboratory.
06 June 2019	* Updated the phase 1b sample size language to allow flexibility for expansion of cohorts, replacement of participants who discontinued product, and over-enrollment of additional eligible participants. * Updated cohort 3 dose to reflect the DLRM recommendation to increase dose. * Reduced the thresholds for white blood cell count and absolute neutrophil count in the exclusion criteria because leukopenia is common in this patient population.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

The study was terminated prior to the enrollment of phase 1b Cohort 4 and phase 2a cohorts due to data that suggested that there is not sufficient benefit-risk for the use of AMG 592 plus standard of care therapy in this study population.

Notes: