Clinical trial results:
A Phase 1b Multicenter, Open-label, Expansion Study to Assess the Safety and Efficacy of AMG 420 in Subjects With Relapsed and/or Refractory Multiple Myeloma

Summary

EudraCT number	2018-002879-17
Trial protocol	BE ES FR
Global end of trial date	21 April 2022

Results information

Result version number	v1
This version publication date	14 April 2023
First version publication date	14 April 2023

Trial information

Trial identification

Sponsor protocol code	20160370

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03836053
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, medinfo@amgen.com
Scientific contact	IHQ Medical Info-Clinical Trials, Amgen (EUROPE) GmbH, medinfo@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	21 April 2022
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	21 April 2022
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The main objective of this trial was to establish the safety and tolerability of AMG 420 at dose levels of 400 mg/day and 600 mg/day in participants with relapsed and/or refractory multiple myeloma (RRMM).

Protection of trial subjects:

This study was conducted in accordance with International Council for Harmonisation (ICH) Good Clinical Practice (GCP) regulations/guidelines.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	04 March 2019
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	5 Years
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United States: 23
Worldwide total number of subjects	23
EEA total number of subjects	0

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)	14
From 65 to 84 years	9
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This study was conducted at 10 centers in Australia, Belgium, Japan, Switzerland, and the United States from 04 March 2019 to 21 April 2022.

Pre-assignment

Screening details:

23 participants were enrolled and all 23 of those participants received study drug.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	AMG 420 200 µg/day

Arm description:

28 day continuous intravenous infusion of AMG 420 200 µg/day followed by a 2 week treatment-free interval, until progressive disease (PD) or relapse as defined by International Myeloma Working Group (IMWG) response criteria, unacceptable safety events, next anti-multiple myeloma treatment, or other reason for permanent treatment discontinuation

Arm type	Experimental
Investigational medicinal product name	AMG 420
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

AMG 420 was given as a 28 day continuous intravenous infusion followed by a 2 week treatment-free interval, until PD or relapse as defined by IMWG response criteria, unacceptable safety events, next anti-multiple myeloma treatment, or other reason for permanent treatment discontinuation

Arm title	AMG 420 400 µg/day

Arm description:

28 day continuous intravenous infusion of AMG 420 400 µg/day followed by a 2 week treatment-free interval, until PD or relapse as defined by IMWG response criteria, unacceptable safety events, next anti-multiple myeloma treatment, or other reason for permanent treatment discontinuation

Arm type	Experimental
Investigational medicinal product name	AMG 420
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

AMG 420 was given as a 28 day continuous intravenous infusion followed by a 2 week treatment-free interval, until PD or relapse as defined by IMWG response criteria, unacceptable safety events, next anti-multiple myeloma treatment, or other reason for permanent treatment discontinuation

Arm title	AMG 420 600 µg/day

Arm description:

28 day continuous intravenous infusion of AMG 420 600 µg/day followed by a 2 week treatment-free interval, until PD or relapse as defined by IMWG response criteria, unacceptable safety events, next

anti-multiple myeloma treatment, or other reason for permanent treatment discontinuation

Arm type	Experimental
Investigational medicinal product name	AMG 420
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

AMG 420 was given as a 28 day continuous intravenous infusion followed by a 2 week treatment-free interval, until PD or relapse as defined by IMWG response criteria, unacceptable safety events, next anti-multiple myeloma treatment, or other reason for permanent treatment discontinuation

Number of subjects in period 1	AMG 420 200 µg/day	AMG 420 400 µg/day	AMG 420 600 µg/day
Started	1	12	10
Completed	0	2	0
Not completed	1	10	10
Adverse event, serious fatal	1	6	4
Withdrawal of consent from study	-	-	1
Protocol-specified criteria	-	2	1
Decision by sponsor	-	2	4

Baseline characteristics

Reporting groups	
Reporting group title	AMG 420 200 µg/day
Reporting group description:	
28 day continuous intravenous infusion of AMG 420 200 µg/day followed by a 2 week treatment-free interval, until progressive disease (PD) or relapse as defined by International Myeloma Working Group (IMWG) response criteria, unacceptable safety events, next anti-multiple myeloma treatment, or other reason for permanent treatment discontinuation	
Reporting group title	AMG 420 400 µg/day
Reporting group description:	
28 day continuous intravenous infusion of AMG 420 400 µg/day followed by a 2 week treatment-free interval, until PD or relapse as defined by IMWG response criteria, unacceptable safety events, next anti-multiple myeloma treatment, or other reason for permanent treatment discontinuation	
Reporting group title	AMG 420 600 µg/day
Reporting group description:	
28 day continuous intravenous infusion of AMG 420 600 µg/day followed by a 2 week treatment-free interval, until PD or relapse as defined by IMWG response criteria, unacceptable safety events, next anti-multiple myeloma treatment, or other reason for permanent treatment discontinuation	

Reporting group values	AMG 420 200 µg/day	AMG 420 400 µg/day	AMG 420 600 µg/day
Number of subjects	1	12	10
Age categorical Units: Subjects			
Adults (18-64 years)	1	6	7
From 65-84 years	0	6	3
85 years and over	0	0	0
Age Continuous			
99999 = No data presented because there was only 1 participant analyzed.			
Units: years			
arithmetic mean	49.0	64.7	60.8
standard deviation	± 99999	± 6.7	± 11.7
Sex: Female, Male Units: participants			
Female	1	3	5
Male	0	9	5
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	0	0	0
Not Hispanic or Latino	1	12	10
Unknown or Not Reported	0	0	0
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	1	0	0
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	0	2	3
White	0	10	7
More than one race	0	0	0
Unknown or Not Reported	0	0	0

Reporting group values	Total		
Number of subjects	23		
Age categorical Units: Subjects			
Adults (18-64 years)	14		
From 65-84 years	9		
85 years and over	0		
Age Continuous			
99999 = No data presented because there was only 1 participant analyzed.			
Units: years arithmetic mean standard deviation	- -		
Sex: Female, Male Units: participants			
Female	9		
Male	14		
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	0		
Not Hispanic or Latino	23		
Unknown or Not Reported	0		
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0		
Asian	1		
Native Hawaiian or Other Pacific Islander	0		
Black or African American	5		
White	17		
More than one race	0		
Unknown or Not Reported	0		

End points

End points reporting groups

Reporting group title	AMG 420 200 µg/day

Reporting group description:

28 day continuous intravenous infusion of AMG 420 200 µg/day followed by a 2 week treatment-free interval, until progressive disease (PD) or relapse as defined by International Myeloma Working Group (IMWG) response criteria, unacceptable safety events, next anti-multiple myeloma treatment, or other reason for permanent treatment discontinuation

Reporting group title	AMG 420 400 µg/day

Reporting group description:

28 day continuous intravenous infusion of AMG 420 400 µg/day followed by a 2 week treatment-free interval, until PD or relapse as defined by IMWG response criteria, unacceptable safety events, next anti-multiple myeloma treatment, or other reason for permanent treatment discontinuation

Reporting group title	AMG 420 600 µg/day

Reporting group description:

28 day continuous intravenous infusion of AMG 420 600 µg/day followed by a 2 week treatment-free interval, until PD or relapse as defined by IMWG response criteria, unacceptable safety events, next anti-multiple myeloma treatment, or other reason for permanent treatment discontinuation

Primary: Number of Participants Who Experienced a Treatment-emergent Adverse Event (TEAE)

End point title	Number of Participants Who Experienced a Treatment-emergent Adverse Event (TEAE)[1]

End point description:

The severity of TEAEs were graded using the CTCAE version 5.0 with the exception of CRS and TLS, which graded using the criteria referenced in the publication by Lee et al, 2014 and the Cairo Bishop criteria referenced in the publication by Coiffier et al, 2008. Any clinically significant changes in vital signs, electrocardiograms (ECGs) and clinical laboratory tests were recorded as TEAEs.

End point type	Primary

End point timeframe:

Up to approximately 3 years

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 statistical analysis was planned for this endpoint.

End point values	AMG 420 200 µg/day	AMG 420 400 µg/day	AMG 420 600 µg/day	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	1	12	10	
Units: Participants	1	12	10	

Statistical analyses

No statistical analyses for this end point

Primary: Number of Participants With Dose-limiting Toxicities (DLTs)

End point title	Number of Participants With Dose-limiting Toxicities (DLTs)[2]

End point description:

DLTs were graded using Common Terminology Criteria for Adverse Events (CTCAE) v5.0, with the exception of cytokine release syndrome (CRS) and tumor lysis syndrome (TLS), which graded using the criteria referenced in the publication by Lee et al, 2014 and the Cairo Bishop criteria referenced in the publication by Coiffier et al, 2008 respectively.

DLT evaluation analysis set includes participants who completed the DLT evaluable period or experienced a DLT any time during the DLT evaluable period.

End point type	Primary

End point timeframe:

Day 1 to Week 4

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 statistical analysis was planned for this endpoint.

End point values	AMG 420 200 µg/day	AMG 420 400 µg/day	AMG 420 600 µg/day	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	1	11	8	
Units: Participants	1	1	0	

Statistical analyses

No statistical analyses for this end point

Primary: Number of Participants Who Experiences a Treatment-related TEAE

End point title	Number of Participants Who Experiences a Treatment-related TEAE[3]

End point description:

The severity of treatment-related TEAEs were graded using the CTCAE version 5.0 with the exception of CRS and TLS, which graded using the criteria referenced in the publication by Lee et al, 2014 and the Cairo Bishop criteria referenced in the publication by Coiffier et al, 2008.

End point type	Primary

End point timeframe:

Up to approximately 3 years

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 statistical analysis was planned for this endpoint.

End point values	AMG 420 200 µg/day	AMG 420 400 µg/day	AMG 420 600 µg/day	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	1	12	10	
Units: Participants	1	12	9	

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Response Rate (ORR)

End point title	Overall Response Rate (ORR)

End point description:

ORR was defined as the percentage of participants for whom the best overall response was a stringent complete response (CR), CR, very good partial response (PR), or partial response as determined by the IMWG Uniform Response Criteria. The ORR along with the associated 95% exact binomial confidence interval (Clopper Pearson Method) was determined.

End point type	Secondary

End point timeframe:

Up to approximately 3 years

End point values	AMG 420 200 µg/day	AMG 420 400 µg/day	AMG 420 600 µg/day	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	1	12	10	
Units: Percentage of Participants				
number (confidence interval 95%)	0 (0.00 to 97.50)	41.7 (15.17 to 72.33)	30.0 (6.67 to 65.25)	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Minimal Residual Disease (MRD) Negativity Response at CR

End point title	Percentage of Participants With Minimal Residual Disease (MRD) Negativity Response at CR

End point description:

MRD negativity at CR or better assessed by using the IMWG criteria.

Percentage of MRD negative responders at CR along with exact 2- sided 95% were provided by using the Clopper Pearson method.

End point type	Secondary

End point timeframe:

Up to approximately 3 years

End point values	AMG 420 200 µg/day	AMG 420 400 µg/day	AMG 420 600 µg/day	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	1	12	10	
Units: Percentage of participants				
number (confidence interval 95%)	0.0 (0.0 to 97.50)	8.3 (0.21 to 38.48)	10.0 (0.25 to 44.50)	

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response (DOR)

End point title	Duration of Response (DOR)

End point description:

DOR was defined as number of months between first objective response to progressive disease or death (due to any cause), whichever occured first. DOR was only calculated for participants who experienced a best overall response of PR or better.

Kaplan-Meier methods were used to estimate the distribution of DOR. The median and corresponding two-sided 95% confidence intervals were calculated.

End point type	Secondary

End point timeframe:

Up to approximately 3 years

End point values	AMG 420 200 µg/day	AMG 420 400 µg/day	AMG 420 600 µg/day	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0[4]	5	3	
Units: Months				
median (confidence interval 95%)	(to)	5.49 (1.41 to 99999)	99999 (1.45 to 99999)	

Notes:

[4] - No participants with a response to measure

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: Up to approximately 3 years	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	25.0

Reporting groups	
Reporting group title	AMG 420 200 µg/day
Reporting group description: -	
Reporting group title	Total
Reporting group description: -	
Reporting group title	AMG 420 600 µg/day
Reporting group description: -	
Reporting group title	AMG 420 400 µg/day
Reporting group description: -	

Serious adverse events	AMG 420 200 µg/day	Total	AMG 420 600 µg/day
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 1 (100.00%)	19 / 23 (82.61%)	8 / 10 (80.00%)
number of deaths (all causes)	1	11	4
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Plasmacytoma			
subjects affected / exposed	0 / 1 (0.00%)	1 / 23 (4.35%)	0 / 10 (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
Plasma cell myeloma			
subjects affected / exposed	1 / 1 (100.00%)	3 / 23 (13.04%)	1 / 10 (10.00%)
occurrences causally related to treatment / all	0 / 1	0 / 3	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 0
Injury, poisoning and procedural complications			
Subdural haematoma			
subjects affected / exposed	0 / 1 (0.00%)	1 / 23 (4.35%)	1 / 10 (10.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1

Vascular disorders			
Hypotension			
subjects affected / exposed	0 / 1 (0.00%)	1 / 23 (4.35%)	1 / 10 (10.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Presyncope			
subjects affected / exposed	0 / 1 (0.00%)	1 / 23 (4.35%)	0 / 10 (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
Headache			
subjects affected / exposed	0 / 1 (0.00%)	1 / 23 (4.35%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	0 / 1 (0.00%)	1 / 23 (4.35%)	0 / 10 (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
Disease progression			
subjects affected / exposed	0 / 1 (0.00%)	2 / 23 (8.70%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 2	0 / 0
Asthenia			
subjects affected / exposed	0 / 1 (0.00%)	1 / 23 (4.35%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia			
subjects affected / exposed	0 / 1 (0.00%)	2 / 23 (8.70%)	2 / 10 (20.00%)
occurrences causally related to treatment / all	0 / 0	1 / 2	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
Cytokine release syndrome			

subjects affected / exposed	0 / 1 (0.00%)	8 / 23 (34.78%)	3 / 10 (30.00%)
occurrences causally related to treatment / all	0 / 0	12 / 14	3 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Myalgia			
subjects affected / exposed	0 / 1 (0.00%)	1 / 23 (4.35%)	0 / 10 (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
Infections and infestations			
Device related infection			
subjects affected / exposed	0 / 1 (0.00%)	1 / 23 (4.35%)	0 / 10 (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
Influenza			
subjects affected / exposed	0 / 1 (0.00%)	1 / 23 (4.35%)	1 / 10 (10.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infusion site infection			
subjects affected / exposed	0 / 1 (0.00%)	1 / 23 (4.35%)	0 / 10 (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
Bacteraemia			
subjects affected / exposed	0 / 1 (0.00%)	2 / 23 (8.70%)	1 / 10 (10.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Staphylococcal sepsis			
subjects affected / exposed	1 / 1 (100.00%)	2 / 23 (8.70%)	1 / 10 (10.00%)
occurrences causally related to treatment / all	1 / 1	1 / 3	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Staphylococcal bacteraemia			
subjects affected / exposed	0 / 1 (0.00%)	1 / 23 (4.35%)	0 / 10 (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

Sepsis			
subjects affected / exposed	0 / 1 (0.00%)	1 / 23 (4.35%)	1 / 10 (10.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 1 (0.00%)	1 / 23 (4.35%)	1 / 10 (10.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	AMG 420 400 µg/day		
Total subjects affected by serious adverse events			
subjects affected / exposed	10 / 12 (83.33%)		
number of deaths (all causes)	6		
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Plasmacytoma			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Plasma cell myeloma			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Subdural haematoma			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Hypotension			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			

Presyncope				
subjects affected / exposed	1 / 12 (8.33%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Headache				
subjects affected / exposed	1 / 12 (8.33%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
General disorders and administration site conditions				
Fatigue				
subjects affected / exposed	1 / 12 (8.33%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Disease progression				
subjects affected / exposed	2 / 12 (16.67%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 2			
Asthenia				
subjects affected / exposed	1 / 12 (8.33%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Pyrexia				
subjects affected / exposed	0 / 12 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Immune system disorders				
Cytokine release syndrome				
subjects affected / exposed	5 / 12 (41.67%)			
occurrences causally related to treatment / all	9 / 11			
deaths causally related to treatment / all	0 / 0			
Musculoskeletal and connective tissue disorders				
Myalgia				

subjects affected / exposed	1 / 12 (8.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Device related infection			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Influenza			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infusion site infection			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Bacteraemia			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Staphylococcal sepsis			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Staphylococcal bacteraemia			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Sepsis			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			

Dehydration			
subjects affected / exposed	0 / 12 (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	AMG 420 200 µg/day	Total	AMG 420 600 µg/day
Total subjects affected by non-serious adverse events			
subjects affected / exposed	1 / 1 (100.00%)	23 / 23 (100.00%)	10 / 10 (100.00%)
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 1 (0.00%)	2 / 23 (8.70%)	1 / 10 (10.00%)
occurrences (all)	0	5	1
Hypotension			
subjects affected / exposed	0 / 1 (0.00%)	3 / 23 (13.04%)	2 / 10 (20.00%)
occurrences (all)	0	6	4
General disorders and administration site conditions			
Chest discomfort			
subjects affected / exposed	0 / 1 (0.00%)	1 / 23 (4.35%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Fatigue			
subjects affected / exposed	0 / 1 (0.00%)	11 / 23 (47.83%)	6 / 10 (60.00%)
occurrences (all)	0	15	8
Chills			
subjects affected / exposed	0 / 1 (0.00%)	1 / 23 (4.35%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Chest pain			
subjects affected / exposed	0 / 1 (0.00%)	1 / 23 (4.35%)	1 / 10 (10.00%)
occurrences (all)	0	1	1
Hypothermia			
subjects affected / exposed	0 / 1 (0.00%)	1 / 23 (4.35%)	1 / 10 (10.00%)
occurrences (all)	0	1	1
Ulcer			

subjects affected / exposed	0 / 1 (0.00%)	1 / 23 (4.35%)	1 / 10 (10.00%)
occurrences (all)	0	1	1
Pyrexia			
subjects affected / exposed	0 / 1 (0.00%)	12 / 23 (52.17%)	6 / 10 (60.00%)
occurrences (all)	0	22	13
Peripheral swelling			
subjects affected / exposed	0 / 1 (0.00%)	1 / 23 (4.35%)	1 / 10 (10.00%)
occurrences (all)	0	1	1
Oedema peripheral			
subjects affected / exposed	0 / 1 (0.00%)	5 / 23 (21.74%)	3 / 10 (30.00%)
occurrences (all)	0	6	3
Oedema			
subjects affected / exposed	0 / 1 (0.00%)	2 / 23 (8.70%)	0 / 10 (0.00%)
occurrences (all)	0	3	0
Malaise			
subjects affected / exposed	0 / 1 (0.00%)	1 / 23 (4.35%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Immune system disorders			
Cytokine release syndrome			
subjects affected / exposed	1 / 1 (100.00%)	17 / 23 (73.91%)	7 / 10 (70.00%)
occurrences (all)	2	50	20
Respiratory, thoracic and mediastinal disorders			
Hypoxia			
subjects affected / exposed	0 / 1 (0.00%)	1 / 23 (4.35%)	0 / 10 (0.00%)
occurrences (all)	0	2	0
Epistaxis			
subjects affected / exposed	0 / 1 (0.00%)	2 / 23 (8.70%)	2 / 10 (20.00%)
occurrences (all)	0	2	2
Dyspnoea			
subjects affected / exposed	0 / 1 (0.00%)	4 / 23 (17.39%)	2 / 10 (20.00%)
occurrences (all)	0	5	2
Cough			
subjects affected / exposed	0 / 1 (0.00%)	4 / 23 (17.39%)	2 / 10 (20.00%)
occurrences (all)	0	8	3
Sinus congestion			

subjects affected / exposed	0 / 1 (0.00%)	3 / 23 (13.04%)	2 / 10 (20.00%)
occurrences (all)	0	3	2
Rhinorrhoea			
subjects affected / exposed	0 / 1 (0.00%)	1 / 23 (4.35%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Respiratory alkalosis			
subjects affected / exposed	0 / 1 (0.00%)	1 / 23 (4.35%)	1 / 10 (10.00%)
occurrences (all)	0	1	1
Oropharyngeal pain			
subjects affected / exposed	0 / 1 (0.00%)	1 / 23 (4.35%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Nasal congestion			
subjects affected / exposed	0 / 1 (0.00%)	2 / 23 (8.70%)	1 / 10 (10.00%)
occurrences (all)	0	2	1
Wheezing			
subjects affected / exposed	0 / 1 (0.00%)	1 / 23 (4.35%)	1 / 10 (10.00%)
occurrences (all)	0	1	1
Psychiatric disorders			
Substance abuse			
subjects affected / exposed	0 / 1 (0.00%)	1 / 23 (4.35%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Nervousness			
subjects affected / exposed	0 / 1 (0.00%)	1 / 23 (4.35%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Insomnia			
subjects affected / exposed	0 / 1 (0.00%)	1 / 23 (4.35%)	1 / 10 (10.00%)
occurrences (all)	0	1	1
Disorientation			
subjects affected / exposed	0 / 1 (0.00%)	1 / 23 (4.35%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Confusional state			
subjects affected / exposed	0 / 1 (0.00%)	1 / 23 (4.35%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Investigations			
Electrocardiogram T wave abnormal			

subjects affected / exposed	0 / 1 (0.00%)	2 / 23 (8.70%)	1 / 10 (10.00%)
occurrences (all)	0	2	1
Carbon dioxide decreased			
subjects affected / exposed	0 / 1 (0.00%)	1 / 23 (4.35%)	1 / 10 (10.00%)
occurrences (all)	0	1	1
C-reactive protein increased			
subjects affected / exposed	0 / 1 (0.00%)	2 / 23 (8.70%)	1 / 10 (10.00%)
occurrences (all)	0	4	1
Blood fibrinogen increased			
subjects affected / exposed	0 / 1 (0.00%)	1 / 23 (4.35%)	1 / 10 (10.00%)
occurrences (all)	0	1	1
Blood creatinine increased			
subjects affected / exposed	0 / 1 (0.00%)	1 / 23 (4.35%)	0 / 10 (0.00%)
occurrences (all)	0	2	0
Blood creatine increased			
subjects affected / exposed	0 / 1 (0.00%)	1 / 23 (4.35%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Activated partial thromboplastin time prolonged			
subjects affected / exposed	0 / 1 (0.00%)	1 / 23 (4.35%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Fibrin D dimer increased			
subjects affected / exposed	0 / 1 (0.00%)	2 / 23 (8.70%)	2 / 10 (20.00%)
occurrences (all)	0	5	5
Immature granulocyte count increased			
subjects affected / exposed	0 / 1 (0.00%)	1 / 23 (4.35%)	1 / 10 (10.00%)
occurrences (all)	0	1	1
Lipase increased			
subjects affected / exposed	0 / 1 (0.00%)	1 / 23 (4.35%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Lymphocyte count decreased			
subjects affected / exposed	0 / 1 (0.00%)	2 / 23 (8.70%)	1 / 10 (10.00%)
occurrences (all)	0	3	1
Neutrophil count decreased			

subjects affected / exposed	0 / 1 (0.00%)	1 / 23 (4.35%)	0 / 10 (0.00%)
occurrences (all)	0	8	0
Nitrite urine present			
subjects affected / exposed	0 / 1 (0.00%)	1 / 23 (4.35%)	1 / 10 (10.00%)
occurrences (all)	0	1	1
Platelet count decreased			
subjects affected / exposed	0 / 1 (0.00%)	3 / 23 (13.04%)	1 / 10 (10.00%)
occurrences (all)	0	10	5
Protein total increased			
subjects affected / exposed	0 / 1 (0.00%)	1 / 23 (4.35%)	1 / 10 (10.00%)
occurrences (all)	0	2	2
Weight decreased			
subjects affected / exposed	0 / 1 (0.00%)	4 / 23 (17.39%)	2 / 10 (20.00%)
occurrences (all)	0	4	2
Weight increased			
subjects affected / exposed	0 / 1 (0.00%)	1 / 23 (4.35%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
White blood cell count decreased			
subjects affected / exposed	0 / 1 (0.00%)	2 / 23 (8.70%)	1 / 10 (10.00%)
occurrences (all)	0	3	2
Injury, poisoning and procedural complications			
Sternal fracture			
subjects affected / exposed	0 / 1 (0.00%)	1 / 23 (4.35%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Skin laceration			
subjects affected / exposed	0 / 1 (0.00%)	1 / 23 (4.35%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Fibula fracture			
subjects affected / exposed	1 / 1 (100.00%)	1 / 23 (4.35%)	0 / 10 (0.00%)
occurrences (all)	1	1	0
Fall			
subjects affected / exposed	0 / 1 (0.00%)	1 / 23 (4.35%)	1 / 10 (10.00%)
occurrences (all)	0	3	3
Cardiac disorders			

Atrial fibrillation			
subjects affected / exposed	0 / 1 (0.00%)	1 / 23 (4.35%)	1 / 10 (10.00%)
occurrences (all)	0	1	1
Tachycardia			
subjects affected / exposed	0 / 1 (0.00%)	1 / 23 (4.35%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Sinus tachycardia			
subjects affected / exposed	0 / 1 (0.00%)	2 / 23 (8.70%)	1 / 10 (10.00%)
occurrences (all)	0	2	1
Nervous system disorders			
Carpal tunnel syndrome			
subjects affected / exposed	0 / 1 (0.00%)	1 / 23 (4.35%)	1 / 10 (10.00%)
occurrences (all)	0	1	1
Aphasia			
subjects affected / exposed	0 / 1 (0.00%)	1 / 23 (4.35%)	1 / 10 (10.00%)
occurrences (all)	0	3	3
Presyncope			
subjects affected / exposed	0 / 1 (0.00%)	1 / 23 (4.35%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Peripheral sensory neuropathy			
subjects affected / exposed	0 / 1 (0.00%)	1 / 23 (4.35%)	1 / 10 (10.00%)
occurrences (all)	0	6	6
Neuralgia			
subjects affected / exposed	0 / 1 (0.00%)	1 / 23 (4.35%)	1 / 10 (10.00%)
occurrences (all)	0	1	1
Headache			
subjects affected / exposed	0 / 1 (0.00%)	12 / 23 (52.17%)	4 / 10 (40.00%)
occurrences (all)	0	25	9
Dysgeusia			
subjects affected / exposed	0 / 1 (0.00%)	1 / 23 (4.35%)	1 / 10 (10.00%)
occurrences (all)	0	2	2
Dizziness			
subjects affected / exposed	0 / 1 (0.00%)	5 / 23 (21.74%)	3 / 10 (30.00%)
occurrences (all)	0	5	3
Seizure			

subjects affected / exposed	0 / 1 (0.00%)	1 / 23 (4.35%)	1 / 10 (10.00%)
occurrences (all)	0	1	1
Tremor			
subjects affected / exposed	0 / 1 (0.00%)	2 / 23 (8.70%)	1 / 10 (10.00%)
occurrences (all)	0	2	1
Sinus headache			
subjects affected / exposed	0 / 1 (0.00%)	1 / 23 (4.35%)	1 / 10 (10.00%)
occurrences (all)	0	1	1
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 1 (0.00%)	8 / 23 (34.78%)	4 / 10 (40.00%)
occurrences (all)	0	15	7
Lymphopenia			
subjects affected / exposed	0 / 1 (0.00%)	1 / 23 (4.35%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Leukopenia			
subjects affected / exposed	0 / 1 (0.00%)	2 / 23 (8.70%)	2 / 10 (20.00%)
occurrences (all)	0	4	4
Leukocytosis			
subjects affected / exposed	0 / 1 (0.00%)	1 / 23 (4.35%)	1 / 10 (10.00%)
occurrences (all)	0	1	1
Neutrophilia			
subjects affected / exposed	0 / 1 (0.00%)	2 / 23 (8.70%)	2 / 10 (20.00%)
occurrences (all)	0	2	2
Neutropenia			
subjects affected / exposed	0 / 1 (0.00%)	5 / 23 (21.74%)	3 / 10 (30.00%)
occurrences (all)	0	12	10
Leukocyte vacuolisation			
subjects affected / exposed	0 / 1 (0.00%)	2 / 23 (8.70%)	2 / 10 (20.00%)
occurrences (all)	0	3	3
Thrombocytopenia			
subjects affected / exposed	0 / 1 (0.00%)	3 / 23 (13.04%)	3 / 10 (30.00%)
occurrences (all)	0	3	3
Hyperfibrinogenaemia			
subjects affected / exposed	0 / 1 (0.00%)	1 / 23 (4.35%)	0 / 10 (0.00%)
occurrences (all)	0	2	0

Eye disorders			
Vision blurred			
subjects affected / exposed	0 / 1 (0.00%)	2 / 23 (8.70%)	1 / 10 (10.00%)
occurrences (all)	0	2	1
Diplopia			
subjects affected / exposed	0 / 1 (0.00%)	1 / 23 (4.35%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Cataract			
subjects affected / exposed	0 / 1 (0.00%)	1 / 23 (4.35%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Conjunctival haemorrhage			
subjects affected / exposed	0 / 1 (0.00%)	1 / 23 (4.35%)	1 / 10 (10.00%)
occurrences (all)	0	1	1
Gastrointestinal disorders			
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 1 (0.00%)	1 / 23 (4.35%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Lip dry			
subjects affected / exposed	0 / 1 (0.00%)	1 / 23 (4.35%)	1 / 10 (10.00%)
occurrences (all)	0	1	1
Mouth haemorrhage			
subjects affected / exposed	0 / 1 (0.00%)	1 / 23 (4.35%)	1 / 10 (10.00%)
occurrences (all)	0	1	1
Nausea			
subjects affected / exposed	0 / 1 (0.00%)	8 / 23 (34.78%)	3 / 10 (30.00%)
occurrences (all)	0	12	6
Oral pain			
subjects affected / exposed	0 / 1 (0.00%)	1 / 23 (4.35%)	1 / 10 (10.00%)
occurrences (all)	0	1	1
Stomatitis			
subjects affected / exposed	0 / 1 (0.00%)	1 / 23 (4.35%)	0 / 10 (0.00%)
occurrences (all)	0	2	0
Vomiting			
subjects affected / exposed	0 / 1 (0.00%)	2 / 23 (8.70%)	2 / 10 (20.00%)
occurrences (all)	0	2	2
Dyspepsia			

subjects affected / exposed	0 / 1 (0.00%)	2 / 23 (8.70%)	2 / 10 (20.00%)
occurrences (all)	0	2	2
Diarrhoea			
subjects affected / exposed	0 / 1 (0.00%)	4 / 23 (17.39%)	2 / 10 (20.00%)
occurrences (all)	0	7	4
Constipation			
subjects affected / exposed	0 / 1 (0.00%)	8 / 23 (34.78%)	5 / 10 (50.00%)
occurrences (all)	0	9	6
Abdominal pain			
subjects affected / exposed	0 / 1 (0.00%)	2 / 23 (8.70%)	2 / 10 (20.00%)
occurrences (all)	0	2	2
Hepatobiliary disorders			
Hypertransaminasaemia			
subjects affected / exposed	0 / 1 (0.00%)	1 / 23 (4.35%)	0 / 10 (0.00%)
occurrences (all)	0	2	0
Skin and subcutaneous tissue disorders			
Skin exfoliation			
subjects affected / exposed	0 / 1 (0.00%)	3 / 23 (13.04%)	2 / 10 (20.00%)
occurrences (all)	0	4	3
Rash maculo-papular			
subjects affected / exposed	0 / 1 (0.00%)	1 / 23 (4.35%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Rash			
subjects affected / exposed	0 / 1 (0.00%)	1 / 23 (4.35%)	1 / 10 (10.00%)
occurrences (all)	0	2	2
Pruritus			
subjects affected / exposed	0 / 1 (0.00%)	3 / 23 (13.04%)	2 / 10 (20.00%)
occurrences (all)	0	4	3
Dry skin			
subjects affected / exposed	0 / 1 (0.00%)	1 / 23 (4.35%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Renal and urinary disorders			
Pollakiuria			
subjects affected / exposed	0 / 1 (0.00%)	1 / 23 (4.35%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Musculoskeletal and connective tissue disorders			

Arthritis			
subjects affected / exposed	0 / 1 (0.00%)	1 / 23 (4.35%)	1 / 10 (10.00%)
occurrences (all)	0	1	1
Back pain			
subjects affected / exposed	0 / 1 (0.00%)	5 / 23 (21.74%)	2 / 10 (20.00%)
occurrences (all)	0	6	3
Bone pain			
subjects affected / exposed	0 / 1 (0.00%)	1 / 23 (4.35%)	1 / 10 (10.00%)
occurrences (all)	0	1	1
Muscle spasms			
subjects affected / exposed	0 / 1 (0.00%)	4 / 23 (17.39%)	2 / 10 (20.00%)
occurrences (all)	0	4	2
Muscular weakness			
subjects affected / exposed	0 / 1 (0.00%)	1 / 23 (4.35%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Musculoskeletal chest pain			
subjects affected / exposed	0 / 1 (0.00%)	1 / 23 (4.35%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Myalgia			
subjects affected / exposed	0 / 1 (0.00%)	1 / 23 (4.35%)	1 / 10 (10.00%)
occurrences (all)	0	1	1
Neck pain			
subjects affected / exposed	0 / 1 (0.00%)	2 / 23 (8.70%)	1 / 10 (10.00%)
occurrences (all)	0	3	1
Pain in extremity			
subjects affected / exposed	0 / 1 (0.00%)	4 / 23 (17.39%)	2 / 10 (20.00%)
occurrences (all)	0	4	2
Rheumatoid arthritis			
subjects affected / exposed	0 / 1 (0.00%)	1 / 23 (4.35%)	1 / 10 (10.00%)
occurrences (all)	0	1	1
Synovial cyst			
subjects affected / exposed	0 / 1 (0.00%)	1 / 23 (4.35%)	1 / 10 (10.00%)
occurrences (all)	0	1	1
Arthralgia			
subjects affected / exposed	0 / 1 (0.00%)	5 / 23 (21.74%)	3 / 10 (30.00%)
occurrences (all)	0	8	4

Infections and infestations			
Rhinitis			
subjects affected / exposed	0 / 1 (0.00%)	1 / 23 (4.35%)	1 / 10 (10.00%)
occurrences (all)	0	1	1
Oral candidiasis			
subjects affected / exposed	0 / 1 (0.00%)	2 / 23 (8.70%)	2 / 10 (20.00%)
occurrences (all)	0	2	2
Nasopharyngitis			
subjects affected / exposed	0 / 1 (0.00%)	1 / 23 (4.35%)	1 / 10 (10.00%)
occurrences (all)	0	1	1
Metapneumovirus infection			
subjects affected / exposed	0 / 1 (0.00%)	1 / 23 (4.35%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Clostridium difficile colitis			
subjects affected / exposed	0 / 1 (0.00%)	1 / 23 (4.35%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Bronchitis			
subjects affected / exposed	0 / 1 (0.00%)	1 / 23 (4.35%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Rhinovirus infection			
subjects affected / exposed	0 / 1 (0.00%)	3 / 23 (13.04%)	2 / 10 (20.00%)
occurrences (all)	0	4	2
Staphylococcal sepsis			
subjects affected / exposed	1 / 1 (100.00%)	1 / 23 (4.35%)	0 / 10 (0.00%)
occurrences (all)	1	1	0
Viral upper respiratory tract infection			
subjects affected / exposed	0 / 1 (0.00%)	1 / 23 (4.35%)	1 / 10 (10.00%)
occurrences (all)	0	1	1
Urinary tract infection bacterial			
subjects affected / exposed	0 / 1 (0.00%)	1 / 23 (4.35%)	1 / 10 (10.00%)
occurrences (all)	0	2	2
Urinary tract infection			
subjects affected / exposed	0 / 1 (0.00%)	1 / 23 (4.35%)	1 / 10 (10.00%)
occurrences (all)	0	1	1
Upper respiratory tract infection			

subjects affected / exposed	0 / 1 (0.00%)	5 / 23 (21.74%)	1 / 10 (10.00%)
occurrences (all)	0	5	1
Sinusitis			
subjects affected / exposed	0 / 1 (0.00%)	1 / 23 (4.35%)	1 / 10 (10.00%)
occurrences (all)	0	1	1
Metabolism and nutrition disorders			
Alkalosis			
subjects affected / exposed	0 / 1 (0.00%)	1 / 23 (4.35%)	1 / 10 (10.00%)
occurrences (all)	0	1	1
Decreased appetite			
subjects affected / exposed	0 / 1 (0.00%)	5 / 23 (21.74%)	3 / 10 (30.00%)
occurrences (all)	0	5	3
Dehydration			
subjects affected / exposed	0 / 1 (0.00%)	2 / 23 (8.70%)	1 / 10 (10.00%)
occurrences (all)	0	2	1
Gout			
subjects affected / exposed	0 / 1 (0.00%)	1 / 23 (4.35%)	1 / 10 (10.00%)
occurrences (all)	0	1	1
Hypercalcaemia			
subjects affected / exposed	0 / 1 (0.00%)	1 / 23 (4.35%)	1 / 10 (10.00%)
occurrences (all)	0	1	1
Hypoalbuminaemia			
subjects affected / exposed	0 / 1 (0.00%)	1 / 23 (4.35%)	1 / 10 (10.00%)
occurrences (all)	0	1	1
Hypocalcaemia			
subjects affected / exposed	0 / 1 (0.00%)	1 / 23 (4.35%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Hypoglycaemia			
subjects affected / exposed	0 / 1 (0.00%)	1 / 23 (4.35%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Iron deficiency			
subjects affected / exposed	0 / 1 (0.00%)	1 / 23 (4.35%)	1 / 10 (10.00%)
occurrences (all)	0	2	2
Hypophosphataemia			
subjects affected / exposed	0 / 1 (0.00%)	6 / 23 (26.09%)	4 / 10 (40.00%)
occurrences (all)	0	9	7

Hypomagnesaemia			
subjects affected / exposed	0 / 1 (0.00%)	1 / 23 (4.35%)	1 / 10 (10.00%)
occurrences (all)	0	1	1
Hypokalaemia			
subjects affected / exposed	0 / 1 (0.00%)	5 / 23 (21.74%)	4 / 10 (40.00%)
occurrences (all)	0	10	9

Non-serious adverse events	AMG 420 400 µg/day		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	12 / 12 (100.00%)		
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	4		
Hypotension			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	2		
General disorders and administration site conditions			
Chest discomfort			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Fatigue			
subjects affected / exposed	5 / 12 (41.67%)		
occurrences (all)	7		
Chills			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Chest pain			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Hypothermia			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Ulcer			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		

Pyrexia			
subjects affected / exposed	6 / 12 (50.00%)		
occurrences (all)	9		
Peripheral swelling			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Oedema peripheral			
subjects affected / exposed	2 / 12 (16.67%)		
occurrences (all)	3		
Oedema			
subjects affected / exposed	2 / 12 (16.67%)		
occurrences (all)	3		
Malaise			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Immune system disorders			
Cytokine release syndrome			
subjects affected / exposed	9 / 12 (75.00%)		
occurrences (all)	28		
Respiratory, thoracic and mediastinal disorders			
Hypoxia			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	2		
Epistaxis			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Dyspnoea			
subjects affected / exposed	2 / 12 (16.67%)		
occurrences (all)	3		
Cough			
subjects affected / exposed	2 / 12 (16.67%)		
occurrences (all)	5		
Sinus congestion			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Rhinorrhoea			

subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Respiratory alkalosis			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Oropharyngeal pain			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Nasal congestion			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Wheezing			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Psychiatric disorders			
Substance abuse			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Nervousness			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Insomnia			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Disorientation			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Confusional state			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Investigations			
Electrocardiogram T wave abnormal			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Carbon dioxide decreased			

subjects affected / exposed	0 / 12 (0.00%)			
occurrences (all)	0			
C-reactive protein increased				
subjects affected / exposed	1 / 12 (8.33%)			
occurrences (all)	3			
Blood fibrinogen increased				
subjects affected / exposed	0 / 12 (0.00%)			
occurrences (all)	0			
Blood creatinine increased				
subjects affected / exposed	1 / 12 (8.33%)			
occurrences (all)	2			
Blood creatine increased				
subjects affected / exposed	1 / 12 (8.33%)			
occurrences (all)	1			
Activated partial thromboplastin time prolonged				
subjects affected / exposed	1 / 12 (8.33%)			
occurrences (all)	1			
Fibrin D dimer increased				
subjects affected / exposed	0 / 12 (0.00%)			
occurrences (all)	0			
Immature granulocyte count increased				
subjects affected / exposed	0 / 12 (0.00%)			
occurrences (all)	0			
Lipase increased				
subjects affected / exposed	1 / 12 (8.33%)			
occurrences (all)	1			
Lymphocyte count decreased				
subjects affected / exposed	1 / 12 (8.33%)			
occurrences (all)	2			
Neutrophil count decreased				
subjects affected / exposed	1 / 12 (8.33%)			
occurrences (all)	8			
Nitrite urine present				

subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Platelet count decreased			
subjects affected / exposed	2 / 12 (16.67%)		
occurrences (all)	5		
Protein total increased			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Weight decreased			
subjects affected / exposed	2 / 12 (16.67%)		
occurrences (all)	2		
Weight increased			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
White blood cell count decreased			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Injury, poisoning and procedural complications			
Sternal fracture			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Skin laceration			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Fibula fracture			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Fall			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Tachycardia			

subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Sinus tachycardia			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Nervous system disorders			
Carpal tunnel syndrome			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Aphasia			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Presyncope			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Peripheral sensory neuropathy			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Neuralgia			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Headache			
subjects affected / exposed	8 / 12 (66.67%)		
occurrences (all)	16		
Dysgeusia			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Dizziness			
subjects affected / exposed	2 / 12 (16.67%)		
occurrences (all)	2		
Seizure			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Tremor			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		

Sinus headache subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0		
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all)	4 / 12 (33.33%) 8		
Lymphopenia subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1		
Leukopenia subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0		
Leukocytosis subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0		
Neutrophilia subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0		
Neutropenia subjects affected / exposed occurrences (all)	2 / 12 (16.67%) 2		
Leukocyte vacuolisation subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0		
Thrombocytopenia subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0		
Hyperfibrinogenaemia subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 2		
Eye disorders Vision blurred subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1		
Diplopia			

subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Cataract			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Conjunctival haemorrhage			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Gastrointestinal disorders			
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Lip dry			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Mouth haemorrhage			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Nausea			
subjects affected / exposed	5 / 12 (41.67%)		
occurrences (all)	6		
Oral pain			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Stomatitis			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	2		
Vomiting			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Dyspepsia			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Diarrhoea			
subjects affected / exposed	2 / 12 (16.67%)		
occurrences (all)	3		

Constipation subjects affected / exposed occurrences (all) Abdominal pain subjects affected / exposed occurrences (all)	3 / 12 (25.00%) 3 0 / 12 (0.00%) 0		
Hepatobiliary disorders Hypertransaminasaemia subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 2		
Skin and subcutaneous tissue disorders Skin exfoliation subjects affected / exposed occurrences (all) Rash maculo-papular subjects affected / exposed occurrences (all) Rash subjects affected / exposed occurrences (all) Pruritus subjects affected / exposed occurrences (all) Dry skin subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1 1 / 12 (8.33%) 1 0 / 12 (0.00%) 0 1 / 12 (8.33%) 1 1 / 12 (8.33%) 1		
Renal and urinary disorders Pollakiuria subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1		
Musculoskeletal and connective tissue disorders Arthritis subjects affected / exposed occurrences (all) Back pain	0 / 12 (0.00%) 0		

subjects affected / exposed	3 / 12 (25.00%)		
occurrences (all)	3		
Bone pain			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Muscle spasms			
subjects affected / exposed	2 / 12 (16.67%)		
occurrences (all)	2		
Muscular weakness			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Musculoskeletal chest pain			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Myalgia			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Neck pain			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	2		
Pain in extremity			
subjects affected / exposed	2 / 12 (16.67%)		
occurrences (all)	2		
Rheumatoid arthritis			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Synovial cyst			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Arthralgia			
subjects affected / exposed	2 / 12 (16.67%)		
occurrences (all)	4		
Infections and infestations			
Rhinitis			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		

Oral candidiasis				
subjects affected / exposed	0 / 12 (0.00%)			
occurrences (all)	0			
Nasopharyngitis				
subjects affected / exposed	0 / 12 (0.00%)			
occurrences (all)	0			
Metapneumovirus infection				
subjects affected / exposed	1 / 12 (8.33%)			
occurrences (all)	1			
Clostridium difficile colitis				
subjects affected / exposed	1 / 12 (8.33%)			
occurrences (all)	1			
Bronchitis				
subjects affected / exposed	1 / 12 (8.33%)			
occurrences (all)	1			
Rhinovirus infection				
subjects affected / exposed	1 / 12 (8.33%)			
occurrences (all)	2			
Staphylococcal sepsis				
subjects affected / exposed	0 / 12 (0.00%)			
occurrences (all)	0			
Viral upper respiratory tract infection				
subjects affected / exposed	0 / 12 (0.00%)			
occurrences (all)	0			
Urinary tract infection bacterial				
subjects affected / exposed	0 / 12 (0.00%)			
occurrences (all)	0			
Urinary tract infection				
subjects affected / exposed	0 / 12 (0.00%)			
occurrences (all)	0			
Upper respiratory tract infection				
subjects affected / exposed	4 / 12 (33.33%)			
occurrences (all)	4			
Sinusitis				
subjects affected / exposed	0 / 12 (0.00%)			
occurrences (all)	0			

Metabolism and nutrition disorders			
Alkalosis			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Decreased appetite			
subjects affected / exposed	2 / 12 (16.67%)		
occurrences (all)	2		
Dehydration			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Gout			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Hypercalcaemia			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Hypoalbuminaemia			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Hypocalcaemia			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Hypoglycaemia			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Iron deficiency			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Hypophosphataemia			
subjects affected / exposed	2 / 12 (16.67%)		
occurrences (all)	2		
Hypomagnesaemia			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Hypokalaemia			

subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
11 October 2018	The protocol was amended for the following reasons: • DLT criteria was revised to specify the grade and time to resolution for the DLT exceptions of headache, insomnia, and fever. • Removed exclusion for Grade 3 neurological events that improve to Grade 0 or Grade 1 within 14 days from DLT evaluation • Clarification added to indicate mandatory dose interruption for Grade 4 adverse events (AMG 420 related or non-related) and restart after improvement of the toxicity to a specified lower grade. • Incorporated Phase 2 stopping rules that apply to Grade 4 or higher drug-related adverse events, excluding lymphopenia (or reduced lymphocyte counts). • Stopping rules for Phase 2 adjusted to be applied by the DRT after every 20 subjects have had the chance to receive at least 1 cycle of treatment at the determined dose level. • Clarifications/minor corrections for consistency throughout protocol • Clarifications/minor corrections to Schedule of Assessments. • The table of contents and all references are updated accordingly.
12 December 2018	The protocol was amended for the following reasons: • Language added regarding management of patients who develop fevers during treatment with AMG 420.
22 May 2019	The protocol was amended for the following reasons: • Include new phase 1b part 2 combination cohort (AMG 420 + pomalidomide/dexamethasone, maximum 20 additional subjects to be enrolled in this cohort). • Addition of adverse event management guidance for phase 2 study, including dose reduction and discontinuation parameters for discrete event occurring on treatment. • Changes made to clarify guidance on infusion reactions and tumor lysis syndrome. • Adjustment made to platelet count eligibility criteria. • Addition of patient interviews for phase 1b study and patient reported outcome measurement tools to phase 2 study. • Updated timing of imaging assessments for extramedullary disease, providing option for multiple assessments while responders remain on treatment. • Change primary analysis time point.
20 May 2020	The protocol was amended for the following reasons: • Removal of Phase 1b Part 2 (combination cohort) and Phase 2 text globally.
17 September 2021	The protocol was amended for the following reasons: • To put clarifications around delays of treatment cycles in place. To add clarity around treatment free intervals. • To add table for management of COVID infection.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported