Clinical trial results:
A Multicenter, Phase 2, Single Arm, Two Cohort Study Evaluating the Efficacy, Safety, and Pharmacokinetics of AMG 337 in Subjects with MET Amplified Gastric/Gastroesophageal Junction/Esophageal Adenocarcinoma or Other MET Amplified Solid Tumors

Summary

EudraCT number	2013-001277-24
Trial protocol	CZ GR DE BE GB IT AT HU PL ES
Global end of trial date	10 October 2016

Results information

Result version number	v1 (current)
This version publication date	22 October 2017
First version publication date	22 October 2017

Trial information

Trial identification

Sponsor protocol code	20130111

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02016534
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Amgen Inc.
Sponsor organisation address	One Amgen Center Drive, Thousand Oaks, CA, United States, 91320
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	16 May 2016
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	10 October 2016
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The primary objective was to determine antitumor activity of AMG 337 in subjects with mesenchymal epithelial transition factor (MET)-amplified gastric (G), gastroesophageal junction (GEJ), or esophageal (E) adenocarcinoma.

Protection of trial subjects:

This study was conducted in accordance with the principles of the applicable country, Food and Drug Administration and International Conference on Harmonization (ICH) Good Clinical Practice (GCP) regulations/guidelines.
All subjects provided written informed consent before undergoing any study-related procedures, including screening procedures.
The study protocol, amendments, and the informed consent form (ICF) were reviewed by the Institutional Review Boards (IRBs) and Independent Ethics Committees (IECs). No subjects were recruited into the study and no investigational product (IP) was shipped until the IRB/IEC gave written approval of the protocol and ICF and Amgen received copies of these approvals.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	14 February 2014
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	Australia: 6
Country: Number of subjects enrolled	Belgium: 3
Country: Number of subjects enrolled	France: 4
Country: Number of subjects enrolled	Germany: 2
Country: Number of subjects enrolled	Greece: 1
Country: Number of subjects enrolled	Hungary: 1
Country: Number of subjects enrolled	Italy: 5
Country: Number of subjects enrolled	Korea, Republic of: 20
Country: Number of subjects enrolled	Poland: 7
Country: Number of subjects enrolled	Spain: 5
Country: Number of subjects enrolled	United Kingdom: 1
Country: Number of subjects enrolled	United States: 5
Worldwide total number of subjects	60
EEA total number of subjects	29

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)	38
From 65 to 84 years	21
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

This study was conducted at 34 centers across 12 countries in Asia, Australia, Europe, and North America. Adults with mesenchymal epithelial transition factor (MET)-amplified gastric (G), gastroesophageal junction (GEJ), or esophageal (E) adenocarcinoma or other MET-amplified solid tumors were enrolled.

Pre-assignment

Screening details:

Participants were enrolled in the following 2 cohorts:
- Cohort 1: MET-amplified G/GEJ/E adenocarcinoma with measurable tumor per RECIST version 1.1
- Cohort 2: Non-measurable G/GEJ/E adenocarcinoma (2A), measurable G/GEJ/E adenocarcinoma with prior MET antibody therapy (2B), or MET-amplified mixed solid tumors with measurable tumor (2C).

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	Measurable G/GEJ/E

Arm description:

Participants with measurable G/GEJ/E adenocarcinoma were assigned to receive 300 mg AMG 337 orally once a day for up to 12 months.

Arm type	Experimental
Investigational medicinal product name	AMG 337
Investigational medicinal product code	AMG 337
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Subjects self-administered AMG 337 300 mg orally daily on an empty stomach.

Arm title	Non-measurable G/GEJ/E

Arm description:

Participants with non-measurable G/GEJ/E adenocarcinoma were assigned to receive 300 mg AMG 337 orally once a day for up to 12 months.

Arm type	Experimental
Investigational medicinal product name	AMG 337
Investigational medicinal product code	AMG 337
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Subjects self-administered AMG 337 300 mg orally daily on an empty stomach.

Arm title	Measurable G/GEJ/E + Prior MET Antibody Therapy

Arm description:

Participants with measurable G/GEJ/E adenocarcinoma who received prior MET antibody therapy were assigned to receive 300 mg AMG 337 orally once a day for up to 12 months.

Arm type	Experimental

Investigational medicinal product name	AMG 337
Investigational medicinal product code	AMG 337
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Subjects self-administered AMG 337 300 mg orally daily on an empty stomach.

Arm title	NSCLC

Arm description:

Participants with non-small cell lung cancer (NSCLC) were assigned to receive 300 mg AMG 337 orally once a day for up to 12 months.

Arm type	Experimental
Investigational medicinal product name	AMG 337
Investigational medicinal product code	AMG 337
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Subjects self-administered AMG 337 300 mg orally daily on an empty stomach.

Number of subjects in period 1	Measurable G/GEJ/E	Non-measurable G/GEJ/E	Measurable G/GEJ/E + Prior MET Antibody Therapy
Started	45	10	1
Received AMG 337	45	9	1
Completed	1	0	0
Not completed	44	10	1
Consent withdrawn by subject	4	2	-
Death	29	7	1
Lost to follow-up	2	-	-
Decision by sponsor	9	1	-

Number of subjects in period 1	NSCLC
Started	4
Received AMG 337	3
Completed	0
Not completed	4
Consent withdrawn by subject	-
Death	4
Lost to follow-up	-
Decision by sponsor	-

Baseline characteristics

Reporting groups	
Reporting group title	Measurable G/GEJ/E
Reporting group description:	
Participants with measurable G/GEJ/E adenocarcinoma were assigned to receive 300 mg AMG 337 orally once a day for up to 12 months.	
Reporting group title	Non-measurable G/GEJ/E
Reporting group description:	
Participants with non-measurable G/GEJ/E adenocarcinoma were assigned to receive 300 mg AMG 337 orally once a day for up to 12 months.	
Reporting group title	Measurable G/GEJ/E + Prior MET Antibody Therapy
Reporting group description:	
Participants with measurable G/GEJ/E adenocarcinoma who received prior MET antibody therapy were assigned to receive 300 mg AMG 337 orally once a day for up to 12 months.	
Reporting group title	NSCLC
Reporting group description:	
Participants with non-small cell lung cancer (NSCLC) were assigned to receive 300 mg AMG 337 orally once a day for up to 12 months.	

Reporting group values	Measurable G/GEJ/E	Non-measurable G/GEJ/E	Measurable G/GEJ/E + Prior MET Antibody Therapy
Number of subjects	45	10	1
Age Categorical Units: Subjects			
18 - 64 years	28	6	1
65 - 84 years	16	4	0
85 years and over	1	0	0
Age Continuous Units: years			
arithmetic mean	60	59.6	59
standard deviation	± 13.4	± 17.3	± 99999
Gender, Male/Female Units: Subjects			
Female	11	4	1
Male	34	6	0
Race/Ethnicity, Customized Units: Subjects			
Asian	17	4	0
Other	1	0	0
White	27	6	1
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	0	1	0
Not Hispanic or Latino	45	9	1
Unknown or Not Reported	0	0	0
Region Units: Subjects			
Asia	17	3	0
Australia	3	0	1

Europe	23	4	0
North America	2	3	0
Eastern Cooperative Oncology Group (ECOG) Performance Status			
Eastern Cooperative Oncology Group (ECOG) Performance Status is used by doctors and researchers to assess how a participants disease is progressing, assess how the disease affects the daily living activities of the participant and determine appropriate treatment and prognosis. 0 = Fully Active; 1 = Restricted activity but ambulatory; 2 = Ambulatory but unable to carry out work activities; 3 = Limited Self- Care; 4 = Completely Disabled, no self-care, confined to bed or chair; 5 = Dead.			
Units: Subjects			
0 (Fully active)	15	3	1
1 (Restrictive but ambulatory)	30	7	0
Disease Stage at Screening Units: Subjects			
Locally advanced	2	0	0
Metastatic	43	10	1

Reporting group values	NSCLC	Total	
Number of subjects	4	60	
Age Categorical Units: Subjects			
18 - 64 years	3	38	
65 - 84 years	1	21	
85 years and over	0	1	
Age Continuous Units: years			
arithmetic mean	62.5		
standard deviation	± 3.87	-	
Gender, Male/Female Units: Subjects			
Female	2	18	
Male	2	42	
Race/Ethnicity, Customized Units: Subjects			
Asian	1	22	
Other	0	1	
White	3	37	
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	0	1	
Not Hispanic or Latino	4	59	
Unknown or Not Reported	0	0	
Region Units: Subjects			
Asia	0	20	
Australia	2	6	
Europe	2	29	
North America	0	5	
Eastern Cooperative Oncology Group (ECOG) Performance Status			
Eastern Cooperative Oncology Group (ECOG) Performance Status is used by doctors and researchers to assess how a participants disease is progressing, assess how the disease affects the daily living activities of the participant and determine appropriate treatment and prognosis. 0 = Fully Active; 1 = Restricted activity but ambulatory; 2 = Ambulatory but unable to carry out work activities; 3 = Limited Self- Care;			

4 = Completely Disabled, no self-care, confined to bed or chair; 5 = Dead.			
Units: Subjects			
0 (Fully active)	0	19	
1 (Restrictive but ambulatory)	4	41	
Disease Stage at Screening Units: Subjects			
Locally advanced	0	2	
Metastatic	4	58	

End points

End points reporting groups

Reporting group title	Measurable G/GEJ/E
Reporting group description:	
Participants with measurable G/GEJ/E adenocarcinoma were assigned to receive 300 mg AMG 337 orally once a day for up to 12 months.	
Reporting group title	Non-measurable G/GEJ/E
Reporting group description:	
Participants with non-measurable G/GEJ/E adenocarcinoma were assigned to receive 300 mg AMG 337 orally once a day for up to 12 months.	
Reporting group title	Measurable G/GEJ/E + Prior MET Antibody Therapy
Reporting group description:	
Participants with measurable G/GEJ/E adenocarcinoma who received prior MET antibody therapy were assigned to receive 300 mg AMG 337 orally once a day for up to 12 months.	
Reporting group title	NSCLC
Reporting group description:	
Participants with non-small cell lung cancer (NSCLC) were assigned to receive 300 mg AMG 337 orally once a day for up to 12 months.	
Subject analysis set title	Cohort 1
Subject analysis set type	Full analysis
Subject analysis set description:	
Subjects with MET-amplified gastric/gastroesophageal junction/esophageal adenocarcinoma	
Subject analysis set title	Cohort 2A, 2B and 2C
Subject analysis set type	Full analysis
Subject analysis set description:	
Subjects with non-measurable G/GEJ/E, measurable G/GEJ/E with prior MET antibody therapy.	

Primary: Objective Response Rate in Participants with MET-amplified Measurable G/GEJ/E Adenocarcinoma (Cohort 1)

End point title	Objective Response Rate in Participants with MET-amplified Measurable G/GEJ/E Adenocarcinoma (Cohort 1)[1][2]
End point description:	
Tumor assessments were based on Investigator assessment of disease progression as per Response Evaluation Criteria In Solid Tumors (RECIST) 1.1. Objective response rate was defined as the percentage of subjects who achieved either a complete response (CR) or a partial response (PR) per RECIST v1.1. Subjects who did not meet the criteria for response by the data cutoff date were considered non-responders. The Response Analysis Set was defined as all enrolled subjects with measurable tumor per RECIST v1.1 at baseline who received at least one dose of AMG 337.	
End point type	Primary
End point timeframe:	
Tumor assessment scans were performed every 8 weeks during study treatment until week 32, thereafter tumor assessment scans were taken every 12 weeks during study treatment. Median follow-up time was 5.5 months.	

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: A formal hypothesis was not tested in this study.

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The primary endpoint was analyzed in cohort 1 subjects only

End point values	Measurable G/GEJ/E			
Subject group type	Reporting group			
Number of subjects analysed	45			
Units: percentage of participants				
number (confidence interval 95%)	17.8 (8 to 32.1)			

Statistical analyses

No statistical analyses for this end point

Secondary: Objective Response Rate in Participants in Cohort 2

End point title	Objective Response Rate in Participants in Cohort 2[3]

End point description:

Tumor assessments were based on Investigator assessment of disease progression as per Response Evaluation Criteria In Solid Tumors (RECIST) 1.1. Objective response rate was defined as the percentage of subjects who achieved either a complete response (CR) or a partial response (PR) per RECIST v1.1. Subjects who did not meet the criteria for response by the data cutoff date were considered non-responders.
The Response Analysis Set was defined as all enrolled subjects with measurable tumor per RECIST v1.1 at baseline who received at least one dose of AMG 337.

End point type	Secondary

End point timeframe:

Tumor assessment scans were performed every 8 weeks during study treatment until week 32, and thereafter every 12 weeks during study treatment. Median follow-up time was 11.4, 20.3, and 2.2 months in each group respectively.

Notes:

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was analyzed in cohort 2 subjects only

End point values	Non-measurable G/GEJ/E	Measurable G/GEJ/E + Prior MET Antibody Therapy	NSCLC	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0[4]	0[5]	0[6]	
Units: percentage of participants				
number (not applicable)				

Notes:

[4] - Response analysis set (only includes subjects with measurable tumor at baseline)

[5] - Not analyzed due to small number of subjects

[6] - Not analyzed due to small number of subjects

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response

End point title	Duration of Response

End point description:

Duration of response was calculated for responders only and defined as the time from the first

observation of a response to the first observation of a disease progression per RECIST v1.1 or death due to any cause. If a responding subject had not progressed or died by the data cutoff date, duration of response was censored at the time of the last evaluable tumor assessment.

End point type	Secondary

End point timeframe:

Tumor assessment scans were performed every 8 weeks during study treatment until week 32, and thereafter every 12 weeks during study treatment. Median follow-up time was 5.5, 11.4, 20.3, and 2.2 months in each group respectively.

End point values	Measurable G/GEJ/E	Non-measurable G/GEJ/E	Measurable G/GEJ/E + Prior MET Antibody Therapy	NSCLC
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	8[7]	0[8]	0[9]	0[10]
Units: months				
median (confidence interval 95%)	6 (3.7 to 16.7)	(to)	(to)	(to)

Notes:

[7] - Response analysis set with an objective response

[8] - Not analyzed due to small number of subjects

[9] - Not analyzed due to small number of subjects

[10] - Not analyzed due to small number of subjects

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Response

End point title	Time to Response

End point description:

Time to response was calculated for those subjects with an objective response and defined as the time from the first dose date to the first observation of a response (CR or PR) per RECIST v1.1.

End point type	Secondary

End point timeframe:

Tumor assessment scans were performed every 8 weeks during study treatment until week 32, and thereafter every 12 weeks during study treatment. Median follow-up time was 5.5, 11.4, 20.3, and 2.2 months in each group respectively.

End point values	Measurable G/GEJ/E	Non-measurable G/GEJ/E	Measurable G/GEJ/E + Prior MET Antibody Therapy	NSCLC
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	8[11]	0[12]	0[13]	0[14]
Units: weeks				
median (inter-quartile range (Q1-Q3))	7.64 (7.14 to 11.86)	(to)	(to)	(to)

Notes:

[11] - Response analysis set with an objective response

[12] - Not analyzed due to small number of subjects

[13] - Not analyzed due to small number of subjects

[14] - Not analyzed due to small number of subjects

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-free Survival

End point title	Progression-free Survival

End point description:

Progression-free survival (PFS) was defined as the time from the first dose date to the first observation of a disease progression per RECIST v1.1 or death due to any cause. If a subject had not progressed or died by the data cutoff date, progression-free survival was censored at the time of the last evaluable tumor assessment.
The analysis of PFS was conducted on the Full Analysis Set.

End point type	Secondary

End point timeframe:

Tumor assessment scans were performed every 8 weeks during study treatment until week 32, and thereafter every 12 weeks during study treatment. Median follow-up time was 5.5, 11.4, 20.3, and 2.2 months in each group respectively.

End point values	Measurable G/GEJ/E	Non-measurable G/GEJ/E	Measurable G/GEJ/E + Prior MET Antibody Therapy	NSCLC
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	45	9	0[15]	0[16]
Units: months				
median (confidence interval 95%)	3.4 (2.1 to 5)	3.6 (2.2 to 10.3)	(to)	(to)

Notes:

[15] - Measurable G/GEJ/E subjects with prior MET therapy were excluded

[16] - NSCLC subjects were excluded

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival

End point title	Overall Survival

End point description:

Overall survival was defined as the time from the first dose date to the date of death due to any cause. If a subject was lost to follow-up before the data cutoff date or still alive at the data cutoff date, overall survival was censored at the last contact date.
This analysis was conducted in the full analysis set.

End point type	Secondary

End point timeframe:

Median follow-up time was 5.5, 11.4, 20.3, and 2.2 months in each group respectively.

End point values	Measurable G/GEJ/E	Non-measurable G/GEJ/E	Measurable G/GEJ/E + Prior MET Antibody Therapy	NSCLC
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	45	9	0[17]	0[18]
Units: months				
median (confidence interval 95%)	7 (4.4 to 10.9)	11.4 (4.9 to 18.5)	(to)	(to)

Notes:

[17] - Measurable G/GEJ/E subjects with prior MET therapy were excluded

[18] - NSCLC subjects were excluded

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with Adverse Events

End point title	Number of Participants with Adverse Events

End point description:

The adverse event grading scale used was the Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0.
A serious adverse event was defined as an adverse event that meets at least 1 of the following serious criteria:
• fatal
• life threatening (places the subject at immediate risk of death)
• requires in-patient hospitalization or prolongation of existing hospitalization
• results in persistent or significant disability/incapacity
• congenital anomaly/birth defect
• other medically important serious event

The Safety Analysis Set included all enrolled subjects who received at least one dose of AMG 337.

End point type	Secondary

End point timeframe:

From the first dose of study drug up to 30 days after the last dose; median duration of treatment was 2.3, 2.4, 2.1, and 1.6 months in each group respectively.

End point values	Measurable G/GEJ/E	Non-measurable G/GEJ/E	Measurable G/GEJ/E + Prior MET Antibody Therapy	NSCLC
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	45[19]	9[20]	1[21]	3[22]
Units: participants				
All adverse events	44	9	1	3
Adverse events ≥ grade 2	41	9	1	2
Adverse events ≥ grade 3	34	4	1	2
Adverse events ≥ grade 4	9	1	0	2
Serious adverse events	26	5	1	2

Leading to discontinuation of study drug	7	1	1	1
Fatal adverse events	7	0	0	2

Notes:

[19] - Safety analysis set

[20] - Safety analysis set

[21] - Safety analysis set

[22] - Safety analysis set

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Treatment

End point title	Duration of Treatment

End point description:

End point type	Secondary

End point timeframe:

From first dose until last dose

End point values	Measurable G/GEJ/E	Non-measurable G/GEJ/E	Measurable G/GEJ/E + Prior MET Antibody Therapy	NSCLC
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	45[23]	9[24]	1[25]	3[26]
Units: months				
median (inter-quartile range (Q1-Q3))	2.3 (0.9 to 5.4)	2.4 (1.2 to 5.7)	2.1 (2.1 to 2.1)	1.6 (1 to 3.9)

Notes:

[23] - Safety analysis set

[24] - Safety analysis set

[25] - Safety analysis set

[26] - Safety analysis set

Statistical analyses

No statistical analyses for this end point

Secondary: Actual Dose Intensity

End point title	Actual Dose Intensity

End point description:

Actual dose intensity is defined as the average amount of drug delivered per day.

End point type	Secondary

End point timeframe:

From first dose to last dose of study drug

End point values	Measurable G/GEJ/E	Non-measurable G/GEJ/E	Measurable G/GEJ/E + Prior MET Antibody Therapy	NSCLC
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	45	9	1	3
Units: mg/day				
median (inter-quartile range (Q1-Q3))	288.5 (208.2 to 300)	300 (300 to 301.9)	300 (300 to 300)	265 (104.1 to 300)

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum Observed Drug Concentration of AMG 337

End point title	Maximum Observed Drug Concentration of AMG 337

End point description:

Intensive pharmacokinetic sampling was conducted at selected sites. Plasma concentrations below the lower limit of quantification (5.0 ng/mL) were set to 0 before the analysis.
The PK Analysis Set includes all subjects in the Safety Analysis Set who underwent blood sampling during the study and had measurable concentrations above the assay's limit of quantification. In addition, the non-compartmental analyses excluded subjects for whom non-compartmental parameters could not be derived.

End point type	Secondary

End point timeframe:

Day 1 and day 28, predose up to 24 hours post-dose

End point values	Cohort 1	Cohort 2A, 2B and 2C		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	12[27]	4[28]		
Units: ng/mL				
arithmetic mean (standard deviation)				
Day 1 (N = 12, 4)	4110 (± 1850)	3080 (± 535)		
Day 28 (N = 8, 3)	3260 (± 832)	3100 (± 448)		

Notes:

[27] - PK analysis set exclude subjects for whom non-compartmental parameters could be derived

[28] - PK analysis set exclude subjects for whom non-compartmental parameters could be derived

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Maximum Observed Concentration of AMG 337

End point title	Time to Maximum Observed Concentration of AMG 337

End point description:

Intensive pharmacokinetic sampling was conducted at selected sites. Plasma concentrations below the lower limit of quantification (5.0 ng/mL) were set to 0 before the analysis.
The PK Analysis Set includes all subjects in the Safety Analysis Set who underwent blood sampling

during the study and had measurable concentrations above the assay's limit of quantification. In addition, the non-compartmental analyses excluded subjects for whom non-compartmental parameters could not be derived.

End point type	Secondary

End point timeframe:

Day 1 and day 28, predose up to 24 hours post-dose

End point values	Cohort 1	Cohort 2A, 2B and 2C		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	12[29]	4[30]		
Units: hours				
median (full range (min-max))				
Day 1 (N = 12, 4)	3 (1.5 to 6.1)	2.3 (1.5 to 6)		
Day 28 (N = 8, 3)	3 (1.5 to 6)	1.9 (0.48 to 3)		

Notes:

[29] - PK analysis set exclude subjects for whom non-compartmental parameters could be derived

[30] - PK analysis set exclude subjects for whom non-compartmental parameters could be derived

Statistical analyses

No statistical analyses for this end point

Secondary: Area Under the Plasma Concentration-time Curve From time 0 to 24 hours

End point title	Area Under the Plasma Concentration-time Curve From time 0 to 24 hours

End point description:

Intensive pharmacokinetic sampling was conducted at selected sites. Plasma concentrations below the lower limit of quantification (5.0 ng/mL) were set to 0 before the analysis.
The PK Analysis Set includes all subjects in the Safety Analysis Set who underwent blood sampling during the study and had measurable concentrations above the assay's limit of quantification. In addition, the non-compartmental analyses excluded subjects for whom non-compartmental parameters could not be derived.

End point type	Secondary

End point timeframe:

Day 1 and day 28, predose up to 24 hours post-dose

End point values	Cohort 1	Cohort 2A, 2B and 2C		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	12[31]	3[32]		
Units: hr*ng/mL				
arithmetic mean (standard deviation)				
Day 1 (N = 12, 3)	48200 (± 22900)	36000 (± 7530)		
Day 28 (N = 7, 3)	36800 (± 11800)	32800 (± 9020)		

Notes:
[31] - PK analysis set exclude subjects for whom non-compartmental parameters could be derived
[32] - PK analysis set exclude subjects for whom non-compartmental parameters could be derived

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
From the first dose of study drug up to 30 days after the last dose; median duration of treatment was 2.3, 2.4, 2.1, and 1.6 months in each group respectively.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	19.0

Reporting groups	
Reporting group title	Measurable G/GEJ/E
Reporting group description:	
Participants with measurable G/GEJ/E adenocarcinoma received 300 mg AMG 337 orally once a day for up to 12 months.	
Reporting group title	Measurable G/GEJ/E + Prior MET Antibody Therapy
Reporting group description:	
Participants with measurable G/GEJ/E adenocarcinoma who received prior MET antibody therapy received 300 mg AMG 337 orally once a day for up to 12 months.	
Reporting group title	NSCLC
Reporting group description:	
Participants with NSCLC received 300 mg AMG 337 orally once a day for up to 12 months.	
Reporting group title	Non-measurable G/GEJ/E
Reporting group description:	
Participants with non-measurable G/GEJ/E adenocarcinoma received 300 mg AMG 337 orally once a day for up to 12 months.	

Serious adverse events	Measurable G/GEJ/E	Measurable G/GEJ/E + Prior MET Antibody Therapy	NSCLC
Total subjects affected by serious adverse events			
subjects affected / exposed	26 / 45 (57.78%)	1 / 1 (100.00%)	2 / 3 (66.67%)
number of deaths (all causes)	7	0	2
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Gastric cancer			
subjects affected / exposed	2 / 45 (4.44%)	0 / 1 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Lung neoplasm malignant			
subjects affected / exposed	0 / 45 (0.00%)	0 / 1 (0.00%)	1 / 3 (33.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1

Non-small cell lung cancer			
subjects affected / exposed	0 / 45 (0.00%)	0 / 1 (0.00%)	1 / 3 (33.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Tumour pain			
subjects affected / exposed	1 / 45 (2.22%)	0 / 1 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	1 / 45 (2.22%)	0 / 1 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypotension			
subjects affected / exposed	1 / 45 (2.22%)	0 / 1 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 45 (0.00%)	0 / 1 (0.00%)	1 / 3 (33.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fatigue			
subjects affected / exposed	1 / 45 (2.22%)	0 / 1 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Multiple organ dysfunction syndrome			
subjects affected / exposed	1 / 45 (2.22%)	0 / 1 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Non-cardiac chest pain			
subjects affected / exposed	1 / 45 (2.22%)	0 / 1 (0.00%)	1 / 3 (33.33%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Pyrexia			
subjects affected / exposed	1 / 45 (2.22%)	0 / 1 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	3 / 45 (6.67%)	0 / 1 (0.00%)	1 / 3 (33.33%)
occurrences causally related to treatment / all	0 / 4	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Pulmonary embolism			
subjects affected / exposed	1 / 45 (2.22%)	0 / 1 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Psychiatric disorders			
Anxiety			
subjects affected / exposed	1 / 45 (2.22%)	0 / 1 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 45 (2.22%)	0 / 1 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 45 (2.22%)	0 / 1 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood bilirubin increased			
subjects affected / exposed	1 / 45 (2.22%)	0 / 1 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Blood creatinine increased			

subjects affected / exposed	1 / 45 (2.22%)	0 / 1 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic enzyme increased			
subjects affected / exposed	0 / 45 (0.00%)	1 / 1 (100.00%)	0 / 3 (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
Congenital, familial and genetic disorders			
Pyloric stenosis			
subjects affected / exposed	1 / 45 (2.22%)	0 / 1 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Aphasia			
subjects affected / exposed	1 / 45 (2.22%)	0 / 1 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Headache			
subjects affected / exposed	3 / 45 (6.67%)	0 / 1 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	3 / 4	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hemiparesis			
subjects affected / exposed	1 / 45 (2.22%)	0 / 1 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			
subjects affected / exposed	0 / 45 (0.00%)	0 / 1 (0.00%)	1 / 3 (33.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 45 (2.22%)	0 / 1 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Abdominal pain upper			
subjects affected / exposed	0 / 45 (0.00%)	0 / 1 (0.00%)	1 / 3 (33.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ascites			
subjects affected / exposed	0 / 45 (0.00%)	0 / 1 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	1 / 45 (2.22%)	0 / 1 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspepsia			
subjects affected / exposed	1 / 45 (2.22%)	0 / 1 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dysphagia			
subjects affected / exposed	1 / 45 (2.22%)	0 / 1 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastric haemorrhage			
subjects affected / exposed	1 / 45 (2.22%)	0 / 1 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ileus			
subjects affected / exposed	2 / 45 (4.44%)	0 / 1 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Inguinal hernia			
subjects affected / exposed	1 / 45 (2.22%)	0 / 1 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal obstruction			

subjects affected / exposed	1 / 45 (2.22%)	0 / 1 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Large intestinal obstruction			
subjects affected / exposed	1 / 45 (2.22%)	0 / 1 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			
subjects affected / exposed	1 / 45 (2.22%)	0 / 1 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Obstruction gastric			
subjects affected / exposed	1 / 45 (2.22%)	0 / 1 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Small intestinal obstruction			
subjects affected / exposed	2 / 45 (4.44%)	0 / 1 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	1 / 45 (2.22%)	0 / 1 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholangitis			
subjects affected / exposed	1 / 45 (2.22%)	0 / 1 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Drug-induced liver injury			
subjects affected / exposed	0 / 45 (0.00%)	0 / 1 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			

Nephrolithiasis			
subjects affected / exposed	0 / 45 (0.00%)	0 / 1 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 45 (2.22%)	0 / 1 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Flank pain			
subjects affected / exposed	1 / 45 (2.22%)	0 / 1 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Clostridium difficile colitis			
subjects affected / exposed	1 / 45 (2.22%)	0 / 1 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peritonitis			
subjects affected / exposed	1 / 45 (2.22%)	0 / 1 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	2 / 45 (4.44%)	0 / 1 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	0 / 45 (0.00%)	0 / 1 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Soft tissue infection			
subjects affected / exposed	1 / 45 (2.22%)	0 / 1 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Non-measurable G/GEJ/E		
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 9 (55.56%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Gastric cancer			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Lung neoplasm malignant			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Non-small cell lung cancer			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Tumour pain			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hypotension			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Asthenia			

subjects affected / exposed	0 / 9 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Fatigue				
subjects affected / exposed	0 / 9 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Multiple organ dysfunction syndrome				
subjects affected / exposed	0 / 9 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Non-cardiac chest pain				
subjects affected / exposed	0 / 9 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pyrexia				
subjects affected / exposed	0 / 9 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Respiratory, thoracic and mediastinal disorders				
Dyspnoea				
subjects affected / exposed	0 / 9 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pulmonary embolism				
subjects affected / exposed	2 / 9 (22.22%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Psychiatric disorders				
Anxiety				
subjects affected / exposed	0 / 9 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			

Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Blood bilirubin increased			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Blood creatinine increased			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hepatic enzyme increased			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Congenital, familial and genetic disorders			
Pyloric stenosis			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Aphasia			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Headache			

subjects affected / exposed	1 / 9 (11.11%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Hemiparesis				
subjects affected / exposed	0 / 9 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Syncope				
subjects affected / exposed	0 / 9 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal disorders				
Abdominal pain				
subjects affected / exposed	0 / 9 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Abdominal pain upper				
subjects affected / exposed	0 / 9 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Ascites				
subjects affected / exposed	1 / 9 (11.11%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Diarrhoea				
subjects affected / exposed	0 / 9 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Dyspepsia				
subjects affected / exposed	1 / 9 (11.11%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Dysphagia				

subjects affected / exposed	0 / 9 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastric haemorrhage				
subjects affected / exposed	0 / 9 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Ileus				
subjects affected / exposed	0 / 9 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Inguinal hernia				
subjects affected / exposed	0 / 9 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Intestinal obstruction				
subjects affected / exposed	0 / 9 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Large intestinal obstruction				
subjects affected / exposed	0 / 9 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Nausea				
subjects affected / exposed	0 / 9 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Obstruction gastric				
subjects affected / exposed	0 / 9 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Small intestinal obstruction				

subjects affected / exposed	0 / 9 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Vomiting				
subjects affected / exposed	0 / 9 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hepatobiliary disorders				
Cholangitis				
subjects affected / exposed	0 / 9 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Drug-induced liver injury				
subjects affected / exposed	1 / 9 (11.11%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Renal and urinary disorders				
Nephrolithiasis				
subjects affected / exposed	1 / 9 (11.11%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Musculoskeletal and connective tissue disorders				
Back pain				
subjects affected / exposed	0 / 9 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Flank pain				
subjects affected / exposed	0 / 9 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Infections and infestations				
Clostridium difficile colitis				

subjects affected / exposed	0 / 9 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Peritonitis				
subjects affected / exposed	0 / 9 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pneumonia				
subjects affected / exposed	0 / 9 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Sepsis				
subjects affected / exposed	1 / 9 (11.11%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Soft tissue infection				
subjects affected / exposed	0 / 9 (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	Measurable G/GEJ/E	Measurable G/GEJ/E + Prior MET Antibody Therapy	NSCLC
Total subjects affected by non-serious adverse events			
subjects affected / exposed	44 / 45 (97.78%)	1 / 1 (100.00%)	3 / 3 (100.00%)
Vascular disorders			
Hypotension			
subjects affected / exposed	1 / 45 (2.22%)	0 / 1 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Lymphoedema			
subjects affected / exposed	3 / 45 (6.67%)	0 / 1 (0.00%)	1 / 3 (33.33%)
occurrences (all)	6	0	2
Orthostatic hypotension			

subjects affected / exposed	0 / 45 (0.00%)	0 / 1 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Thrombosis			
subjects affected / exposed	1 / 45 (2.22%)	0 / 1 (0.00%)	1 / 3 (33.33%)
occurrences (all)	1	0	1
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	10 / 45 (22.22%)	0 / 1 (0.00%)	0 / 3 (0.00%)
occurrences (all)	18	0	0
Chills			
subjects affected / exposed	2 / 45 (4.44%)	0 / 1 (0.00%)	0 / 3 (0.00%)
occurrences (all)	2	0	0
Face oedema			
subjects affected / exposed	2 / 45 (4.44%)	0 / 1 (0.00%)	0 / 3 (0.00%)
occurrences (all)	2	0	0
Fatigue			
subjects affected / exposed	8 / 45 (17.78%)	1 / 1 (100.00%)	2 / 3 (66.67%)
occurrences (all)	10	2	2
General physical health deterioration			
subjects affected / exposed	0 / 45 (0.00%)	0 / 1 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Localised oedema			
subjects affected / exposed	3 / 45 (6.67%)	0 / 1 (0.00%)	0 / 3 (0.00%)
occurrences (all)	3	0	0
Non-cardiac chest pain			
subjects affected / exposed	0 / 45 (0.00%)	0 / 1 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Oedema			
subjects affected / exposed	24 / 45 (53.33%)	0 / 1 (0.00%)	2 / 3 (66.67%)
occurrences (all)	81	0	6
Oedema peripheral			
subjects affected / exposed	14 / 45 (31.11%)	0 / 1 (0.00%)	3 / 3 (100.00%)
occurrences (all)	22	0	3
Pain			

subjects affected / exposed	3 / 45 (6.67%)	0 / 1 (0.00%)	0 / 3 (0.00%)
occurrences (all)	3	0	0
Pyrexia			
subjects affected / exposed	5 / 45 (11.11%)	0 / 1 (0.00%)	0 / 3 (0.00%)
occurrences (all)	7	0	0
Reproductive system and breast disorders			
Testicular pain			
subjects affected / exposed	0 / 45 (0.00%)	0 / 1 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	3 / 45 (6.67%)	0 / 1 (0.00%)	1 / 3 (33.33%)
occurrences (all)	4	0	1
Dyspnoea			
subjects affected / exposed	2 / 45 (4.44%)	0 / 1 (0.00%)	1 / 3 (33.33%)
occurrences (all)	3	0	1
Psychiatric disorders			
Anxiety			
subjects affected / exposed	2 / 45 (4.44%)	0 / 1 (0.00%)	0 / 3 (0.00%)
occurrences (all)	2	0	0
Insomnia			
subjects affected / exposed	4 / 45 (8.89%)	0 / 1 (0.00%)	0 / 3 (0.00%)
occurrences (all)	4	0	0
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	4 / 45 (8.89%)	0 / 1 (0.00%)	1 / 3 (33.33%)
occurrences (all)	7	0	1
Aspartate aminotransferase increased			
subjects affected / exposed	3 / 45 (6.67%)	0 / 1 (0.00%)	1 / 3 (33.33%)
occurrences (all)	6	0	1
Blood alkaline phosphatase increased			
subjects affected / exposed	2 / 45 (4.44%)	0 / 1 (0.00%)	1 / 3 (33.33%)
occurrences (all)	2	0	1
Neutrophil count decreased			

subjects affected / exposed	3 / 45 (6.67%)	0 / 1 (0.00%)	0 / 3 (0.00%)
occurrences (all)	6	0	0
Transaminases increased			
subjects affected / exposed	0 / 45 (0.00%)	0 / 1 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	0 / 45 (0.00%)	0 / 1 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Cardiac disorders			
Sinus tachycardia			
subjects affected / exposed	0 / 45 (0.00%)	0 / 1 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Tachycardia			
subjects affected / exposed	2 / 45 (4.44%)	0 / 1 (0.00%)	0 / 3 (0.00%)
occurrences (all)	2	0	0
Nervous system disorders			
Dizziness			
subjects affected / exposed	5 / 45 (11.11%)	0 / 1 (0.00%)	0 / 3 (0.00%)
occurrences (all)	6	0	0
Headache			
subjects affected / exposed	24 / 45 (53.33%)	1 / 1 (100.00%)	2 / 3 (66.67%)
occurrences (all)	41	1	3
Peripheral sensory neuropathy			
subjects affected / exposed	0 / 45 (0.00%)	0 / 1 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Presyncope			
subjects affected / exposed	0 / 45 (0.00%)	0 / 1 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Syncope			
subjects affected / exposed	0 / 45 (0.00%)	0 / 1 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Tremor			
subjects affected / exposed	0 / 45 (0.00%)	0 / 1 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Blood and lymphatic system disorders			

Anaemia			
subjects affected / exposed	2 / 45 (4.44%)	0 / 1 (0.00%)	0 / 3 (0.00%)
occurrences (all)	3	0	0
Neutropenia			
subjects affected / exposed	0 / 45 (0.00%)	0 / 1 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	15 / 45 (33.33%)	0 / 1 (0.00%)	0 / 3 (0.00%)
occurrences (all)	18	0	0
Abdominal pain upper			
subjects affected / exposed	5 / 45 (11.11%)	0 / 1 (0.00%)	1 / 3 (33.33%)
occurrences (all)	5	0	1
Ascites			
subjects affected / exposed	3 / 45 (6.67%)	0 / 1 (0.00%)	0 / 3 (0.00%)
occurrences (all)	3	0	0
Constipation			
subjects affected / exposed	8 / 45 (17.78%)	0 / 1 (0.00%)	1 / 3 (33.33%)
occurrences (all)	8	0	1
Diarrhoea			
subjects affected / exposed	8 / 45 (17.78%)	0 / 1 (0.00%)	0 / 3 (0.00%)
occurrences (all)	8	0	0
Dry mouth			
subjects affected / exposed	1 / 45 (2.22%)	0 / 1 (0.00%)	1 / 3 (33.33%)
occurrences (all)	1	0	1
Dyspepsia			
subjects affected / exposed	7 / 45 (15.56%)	0 / 1 (0.00%)	0 / 3 (0.00%)
occurrences (all)	9	0	0
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 45 (2.22%)	0 / 1 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Melaena			
subjects affected / exposed	0 / 45 (0.00%)	0 / 1 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Nausea			

subjects affected / exposed	15 / 45 (33.33%)	1 / 1 (100.00%)	1 / 3 (33.33%)
occurrences (all)	17	1	1
Oesophagitis			
subjects affected / exposed	0 / 45 (0.00%)	0 / 1 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Proctalgia			
subjects affected / exposed	1 / 45 (2.22%)	0 / 1 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Vomiting			
subjects affected / exposed	16 / 45 (35.56%)	0 / 1 (0.00%)	1 / 3 (33.33%)
occurrences (all)	21	0	1
Hepatobiliary disorders			
Hepatotoxicity			
subjects affected / exposed	0 / 45 (0.00%)	0 / 1 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Skin and subcutaneous tissue disorders			
Dry skin			
subjects affected / exposed	5 / 45 (11.11%)	1 / 1 (100.00%)	0 / 3 (0.00%)
occurrences (all)	6	1	0
Pruritus			
subjects affected / exposed	6 / 45 (13.33%)	0 / 1 (0.00%)	0 / 3 (0.00%)
occurrences (all)	6	0	0
Rash			
subjects affected / exposed	5 / 45 (11.11%)	0 / 1 (0.00%)	0 / 3 (0.00%)
occurrences (all)	7	0	0
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	0 / 45 (0.00%)	0 / 1 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	7 / 45 (15.56%)	0 / 1 (0.00%)	0 / 3 (0.00%)
occurrences (all)	8	0	0
Flank pain			
subjects affected / exposed	4 / 45 (8.89%)	0 / 1 (0.00%)	0 / 3 (0.00%)
occurrences (all)	6	0	0

Muscle spasms			
subjects affected / exposed	0 / 45 (0.00%)	0 / 1 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal pain			
subjects affected / exposed	2 / 45 (4.44%)	0 / 1 (0.00%)	0 / 3 (0.00%)
occurrences (all)	2	0	0
Myalgia			
subjects affected / exposed	4 / 45 (8.89%)	0 / 1 (0.00%)	0 / 3 (0.00%)
occurrences (all)	6	0	0
Pain in extremity			
subjects affected / exposed	2 / 45 (4.44%)	0 / 1 (0.00%)	1 / 3 (33.33%)
occurrences (all)	2	0	1
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	16 / 45 (35.56%)	0 / 1 (0.00%)	1 / 3 (33.33%)
occurrences (all)	21	0	1
Dehydration			
subjects affected / exposed	1 / 45 (2.22%)	0 / 1 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Hyperglycaemia			
subjects affected / exposed	0 / 45 (0.00%)	0 / 1 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Hyperkalaemia			
subjects affected / exposed	3 / 45 (6.67%)	0 / 1 (0.00%)	0 / 3 (0.00%)
occurrences (all)	4	0	0
Hypoalbuminaemia			
subjects affected / exposed	9 / 45 (20.00%)	0 / 1 (0.00%)	0 / 3 (0.00%)
occurrences (all)	10	0	0
Hypokalaemia			
subjects affected / exposed	3 / 45 (6.67%)	0 / 1 (0.00%)	0 / 3 (0.00%)
occurrences (all)	4	0	0
Hyponatraemia			
subjects affected / exposed	0 / 45 (0.00%)	0 / 1 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1

Non-serious adverse events	Non-measurable G/GEJ/E		

Total subjects affected by non-serious adverse events subjects affected / exposed	9 / 9 (100.00%)		
Vascular disorders			
Hypotension			
subjects affected / exposed	5 / 9 (55.56%)		
occurrences (all)	5		
Lymphoedema			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Orthostatic hypotension			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	2		
Thrombosis			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Chills			
subjects affected / exposed	2 / 9 (22.22%)		
occurrences (all)	2		
Face oedema			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Fatigue			
subjects affected / exposed	2 / 9 (22.22%)		
occurrences (all)	2		
General physical health deterioration			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Localised oedema			
subjects affected / exposed	2 / 9 (22.22%)		
occurrences (all)	2		
Non-cardiac chest pain			

subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Oedema			
subjects affected / exposed	4 / 9 (44.44%)		
occurrences (all)	31		
Oedema peripheral			
subjects affected / exposed	2 / 9 (22.22%)		
occurrences (all)	5		
Pain			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Pyrexia			
subjects affected / exposed	2 / 9 (22.22%)		
occurrences (all)	2		
Reproductive system and breast disorders			
Testicular pain			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Dyspnoea			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Psychiatric disorders			
Anxiety			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Insomnia			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	2 / 9 (22.22%)		
occurrences (all)	2		

Aspartate aminotransferase increased			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	2		
Blood alkaline phosphatase increased			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Neutrophil count decreased			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Transaminases increased			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Cardiac disorders			
Sinus tachycardia			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Tachycardia			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Nervous system disorders			
Dizziness			
subjects affected / exposed	2 / 9 (22.22%)		
occurrences (all)	2		
Headache			
subjects affected / exposed	7 / 9 (77.78%)		
occurrences (all)	10		
Peripheral sensory neuropathy			
subjects affected / exposed	2 / 9 (22.22%)		
occurrences (all)	2		
Presyncope			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		

Syncope			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Tremor			
subjects affected / exposed	2 / 9 (22.22%)		
occurrences (all)	3		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Neutropenia			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	3 / 9 (33.33%)		
occurrences (all)	4		
Abdominal pain upper			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Ascites			
subjects affected / exposed	2 / 9 (22.22%)		
occurrences (all)	2		
Constipation			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Diarrhoea			
subjects affected / exposed	3 / 9 (33.33%)		
occurrences (all)	3		
Dry mouth			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Dyspepsia			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Gastrooesophageal reflux disease			

subjects affected / exposed occurrences (all)	1 / 9 (11.11%) 1		
Melaena subjects affected / exposed occurrences (all)	1 / 9 (11.11%) 1		
Nausea subjects affected / exposed occurrences (all)	4 / 9 (44.44%) 5		
Oesophagitis subjects affected / exposed occurrences (all)	1 / 9 (11.11%) 1		
Proctalgia subjects affected / exposed occurrences (all)	1 / 9 (11.11%) 1		
Vomiting subjects affected / exposed occurrences (all)	4 / 9 (44.44%) 6		
Hepatobiliary disorders Hepatotoxicity subjects affected / exposed occurrences (all)	1 / 9 (11.11%) 1		
Skin and subcutaneous tissue disorders Dry skin subjects affected / exposed occurrences (all)	3 / 9 (33.33%) 5		
Pruritus subjects affected / exposed occurrences (all)	2 / 9 (22.22%) 2		
Rash subjects affected / exposed occurrences (all)	2 / 9 (22.22%) 4		
Endocrine disorders Hypothyroidism subjects affected / exposed occurrences (all)	1 / 9 (11.11%) 1		
Musculoskeletal and connective tissue disorders			

Back pain			
subjects affected / exposed	2 / 9 (22.22%)		
occurrences (all)	2		
Flank pain			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Muscle spasms			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Musculoskeletal pain			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Myalgia			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Pain in extremity			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	2 / 9 (22.22%)		
occurrences (all)	2		
Dehydration			
subjects affected / exposed	2 / 9 (22.22%)		
occurrences (all)	2		
Hyperglycaemia			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Hyperkalaemia			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Hypoalbuminaemia			
subjects affected / exposed	2 / 9 (22.22%)		
occurrences (all)	3		
Hypokalaemia			

subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Hyponatraemia			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
30 May 2014	The protocol was amended for the following reasons: 1. Allow ECOG Performance Status 2 subjects to participate in the study 2. Reduce the time interval when no food or liquids can be consumed relative to administration of AMG 337 3. Add dose modifications for when subjects experience ≥ grade 3 headache for which AMG 337 is considered as a cause 4. Add information about management of headaches 5. Add collection of lymphocyte results 6. Add an collection of cell pellet, circulating tumor cells, and optional tumor biopsy at the time of disease progression 7. Include details and clarification of planned efficacy and safety reviews 8. Clarification of minor inconsistencies and correction of minor errors

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported