Clinical trial results:
A Cancer Research UK randomised, double-blind, placebo-controlled Phase IIa trial of AMG 319 given orally as a neoadjuvant therapy in patients with human papillomavirus (HPV) positive and negative head and neck squamous cell carcinoma (HNSCC)

Summary

EudraCT number	2014-004388-20
Trial protocol	GB
Global end of trial date	03 May 2018

Results information

Result version number	v1 (current)
This version publication date	16 May 2019
First version publication date	16 May 2019

Trial information

Trial identification

Sponsor protocol code	CRUKD/15/004

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02540928
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Cancer Research UK
Sponsor organisation address	407 St John Street, London, United Kingdom, EC1V 4AD
Public contact	Centre for Drug Development, Cancer Research UK, +44 02072420200, regulatory@cancer.org.uk
Scientific contact	Centre for Drug Development, Cancer Research UK, +44 02072420200, regulatory@cancer.org.uk

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	09 April 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	03 May 2018
Global end of trial reached?	Yes
Global end of trial date	03 May 2018
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The primary objectives of the trial were:
a) To assess changes in immune infiltration in tumour before and after treatment with AMG 319.
b) To assess the safety and toxicity profile of AMG 319 in patients with HNSCC.

The secondary objectives of the trial were:
a) To investigate the steady state pharmacokinetic behaviour of AMG 319.
b) To document possible tumour response to neoadjuvant AMG 319.

Protection of trial subjects:

None.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	20 October 2015
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	United Kingdom: 32
Worldwide total number of subjects	32
EEA total number of subjects	32

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	14
From 65 to 84 years	18

85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Trial patients were enrolled from 20 October 2015 to 03 May 2018 in six clinical trial centres in the UK.

Pre-assignment

Screening details:

Male or female patients aged ≥18 years, with histologically proven HNSCC for whom surgery was the primary treatment option, with laboratory results within specified ranges. Patients had to be fit to have resection surgery and those who had undergone prior radio/immuno/chemotherapy or other anti-cancer therapy for their current HNSCC, were excluded.

Period 1

Period 1 title	Overall Trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Investigator, Monitor, Subject, Data analyst

Blinding implementation details:

Eligible patients were randomised to either the AMG 319 or placebo treatment group using an interactive web response system (IWRS). Patients, investigators, site staff and clinical study team members were not aware of the treatment allocation to individual patients. AMG 319 capsules and placebo capsules were identical in appearance, packaging and labelling. During the trial, patients were only to be unblinded for valid medical or safety reasons. Unblinding information was held within the IWRS.

Arms

Are arms mutually exclusive?	Yes
Arm title	AMG 319 400 mg

Arm description:

AMG 319 at 400 mg once daily

Arm type	Experimental
Investigational medicinal product name	AMG 319
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Patients in the AMG 319 400 mg group received AMG 319 as an oral capsule once daily for a minimum of 20 days and a maximum of 29 days prior to resection surgery.

Arm title	AMG 319 300 mg

Arm description:

AMG 319 at 300 mg once daily

Arm type	Experimental
Investigational medicinal product name	AMG 319
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Patients in the AMG 319 300 mg group received AMG 319 as an oral capsule once daily for a minimum of 20 days and a maximum of 29 days prior to resection surgery.

Arm title	Placebo

Arm description:

Placebo once daily

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

Dosage and administration details:

Patients in the placebo group received placebo as an oral capsule once daily for a minimum of 20 days and a maximum of 29 days prior to resection surgery.

Number of subjects in period 1[1]	AMG 319 400 mg	AMG 319 300 mg	Placebo
Started	15	6	9
Completed	15	6	9

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: Only the safety population (i.e. enrolled patients who received AMG 319 or placebo) have been included (n=30). Two enrolled patients were withdrawn prior to the start of administration of IMP (one patient because they were unable to swallow the trial medication and one patient due to a delay to their planned Cycle 1 Day 1 dose due to an AE of rash which resulted in an insufficient number of possible dosing days before their planned surgery).

Baseline characteristics

Reporting groups	
Reporting group title	AMG 319 400 mg
Reporting group description: AMG 319 at 400 mg once daily	
Reporting group title	AMG 319 300 mg
Reporting group description: AMG 319 at 300 mg once daily	
Reporting group title	Placebo
Reporting group description: Placebo once daily	

Reporting group values	AMG 319 400 mg	AMG 319 300 mg	Placebo
Number of subjects	15	6	9
Age categorical Units: Subjects			
Adults (18-64 years)	7	3	3
From 65-84 years	8	3	6
Gender categorical Units: Subjects			
Female	7	3	1
Male	8	3	8
Human Papillomavirus (HPV) Status Units: Subjects			
HPV Positive	1	1	1
HPV Negative	13	5	8
HPV Status Not Recorded	1	0	0

Reporting group values	Total		
Number of subjects	30		
Age categorical Units: Subjects			
Adults (18-64 years)	13		
From 65-84 years	17		
Gender categorical Units: Subjects			
Female	11		
Male	19		
Human Papillomavirus (HPV) Status Units: Subjects			
HPV Positive	3		
HPV Negative	26		
HPV Status Not Recorded	1		

Subject analysis sets

Subject analysis set title	Intention to Treat Population
Subject analysis set type	Intention-to-treat

Subject analysis set description:

All randomised patients. Patients who were randomised in error (due to ineligibility or administrative error), and who did not receive any trial medication (AMG 319 or placebo) were excluded from the intention to treat (ITT) population.

Subject analysis set title	Safety Population
Subject analysis set type	Safety analysis

Subject analysis set description:

All patients who were randomised and received at least one administration of AMG 319 or placebo.

Subject analysis set title	Per Protocol Population
Subject analysis set type	Per protocol

Subject analysis set description:

All patients who were randomised, met eligibility criteria, received at least 80% of trial medication (AMG 319 or placebo) and had pre and post treatment tumour tissue available for assessment of immune infiltration by immunohistochemistry.

Reporting group values	Intention to Treat Population	Safety Population	Per Protocol Population
Number of subjects	32	30	19
Age categorical Units: Subjects			
Adults (18-64 years)	14	13	8
From 65-84 years	18	17	11
Gender categorical Units: Subjects			
Female	11	11	4
Male	21	19	15
Human Papillomavirus (HPV) Status Units: Subjects			
HPV Positive	3	3	1
HPV Negative	27	26	18
HPV Status Not Recorded	2	1	0

End points

End points reporting groups

Reporting group title	AMG 319 400 mg
Reporting group description: AMG 319 at 400 mg once daily	
Reporting group title	AMG 319 300 mg
Reporting group description: AMG 319 at 300 mg once daily	
Reporting group title	Placebo
Reporting group description: Placebo once daily	
Subject analysis set title	Intention to Treat Population
Subject analysis set type	Intention-to-treat
Subject analysis set description: All randomised patients. Patients who were randomised in error (due to ineligibility or administrative error), and who did not receive any trial medication (AMG 319 or placebo) were excluded from the intention to treat (ITT) population.	
Subject analysis set title	Safety Population
Subject analysis set type	Safety analysis
Subject analysis set description: All patients who were randomised and received at least one administration of AMG 319 or placebo.	
Subject analysis set title	Per Protocol Population
Subject analysis set type	Per protocol
Subject analysis set description: All patients who were randomised, met eligibility criteria, received at least 80% of trial medication (AMG 319 or placebo) and had pre and post treatment tumour tissue available for assessment of immune infiltration by immunohistochemistry.	

Primary: Safety

End point title	Safety[1]
End point description: AEs were recorded according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version 4.02 and coded according to the Medical Dictionary for Regulatory Activities (MedDRA) Version 21.0. Safety was evaluated from reported AEs, physical/vital signs, laboratory toxicities and ECG assessments.	
End point type	Primary
End point timeframe: Safety data was collected for randomised patients from date of written informed consent and continued until the off-study visit or start of chemo-radiotherapy. Post surgery, only drug-related AEs and SAEs were collected until events resolved or stabilised	

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: Safety variables were summarised predominantly by descriptive statistics. Adverse events and laboratory values were collected and graded according to NCI CTCAE Version 4.02 and coded according to MedDRA Version 21.0.
Statistical analyses were performed of the treatment related AEs experienced between treatment arms and of the AEs experienced between treatment arms. These analyses are summarised in the associated attachment.

End point values	AMG 319 400 mg	AMG 319 300 mg	Placebo	Safety Population
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	15	6	9	30
Units: Number of Adverse Events				
All AEs	176	58	27	261
Treatment Emergent AEs	167	58	24	249
Related AEs	136	36	17	189

Attachments (see zip file)	AMG 319_Safety and Toxicity Extract_Final V1.0_prepared

Statistical analyses

No statistical analyses for this end point

Primary: Assessment of Immune Infiltration (CD8+ Effector T Cells)

End point title	Assessment of Immune Infiltration (CD8+ Effector T Cells)[2]

End point description:

All patients who were randomised, met eligibility criteria, received at least 80% of trial medication (AMG 319 or placebo) and had pre and post treatment tumour tissue available for assessment of immune infiltration by immunohistochemistry (IHC), were included in the per protocol population analysis. Detection of a greater than two-fold increase in CD8+ effector T cell numbers in tumour tissue after treatment with AMG 319 was assessed by IHC.

End point type	Primary

End point timeframe:

Formalin-fixed paraffin embedded tumour tissue sections from a pre treatment biopsy and from resected tumour tissue (sample taken post treatment on Day 21 - 29). All tumour tissue samples were analysed and reported after the last patients off study visit.

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: A number of statistical analyses were performed and are summarised in the associated attachment.

End point values	AMG 319 400 mg	AMG 319 300 mg	Placebo	Per Protocol Population
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	15	6	9	19
Units: Number of Patients				
Doubling of CD8+	5	1	5	8

Attachments (see zip file)	AMG 319_Immune Infiltration Extract_Final V1.0_prepared

Statistical analyses

No statistical analyses for this end point

Secondary: Analysis of Tumour Response

End point title	Analysis of Tumour Response

End point description:

All patients who were randomised, met the eligibility criteria, received at least 80% of trial medication and had a pre and post treatment head and neck magnetic resonance imaging (MRI) or computerised tomography (CT) scan were evaluable for response. Tumour response was determined according to the according to the modified Immune Related Response Criteria (irRC). The overall tumour response was categorised as complete response (irCR), partial response (irPR), stable disease (irSD), progressive disease (irPD) or not evaluable (NE). A patients' best overall response was defined as the best response across all timepoints measured.

End point type	Secondary

End point timeframe:

Estimate of tumour burden made at baseline (within six weeks prior to the patient's first dose) and used as a comparator for a subsequent measurement performed following the last dose of AMG 319 or placebo (within three days prior to resection surgery).

End point values	Intention to Treat Population	Per Protocol Population		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	32	19		
Units: Number of Patients				
irCR	0	0		
irPR	2	1		
irSD	16	14		
irPD	5	2		
NE	4	2		
Not done	5	0		

Attachments (see zip file)	AMG 319_Tumour Response Extract_Final V1.0_prepared

Statistical analyses

No statistical analyses for this end point

Secondary: AMG 319 Pharmacokinetic Analysis

End point title	AMG 319 Pharmacokinetic Analysis

End point description:

AMG 319 was measured in plasma using ultra performance liquid chromatography tandem mass spectrometry (UPLC/MS/MS). The purpose of collecting blood samples in the trial was to confirm the plasma AMG 319 concentration at steady state dosing and that the concentrations were zero in placebo patients.

End point type	Secondary

End point timeframe:

AMG 319 levels were measured in plasma in all patients who received AMG 319 or placebo. A 4 mL sample of blood was collected from all patients pre dose on Day 8, pre dose on Day 15 and again on Day 22.

End point values	AMG 319 400 mg	AMG 319 300 mg	Placebo	Per Protocol Population
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	15	6	9	19
Units: Number of Patients	14	6	9	18

Attachments (see zip file)	AMG 319_PK Extract_Final V1.0_prepared 30Apr19.pdf

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From the date of written informed consent and continued for all serious adverse events (SAEs) and adverse events (AEs) until surgical resection. After surgical resection, only drug-related AEs and SAEs were collected.

Adverse event reporting additional description:

All patients who were randomised and received at least one dose of AMG 319 or placebo were included in the safety analysis. National Cancer Institute CTCAE Version 4.02 was used to grade the severity of AEs, which were coded according to MedDRA Version 21.0.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	21.0

Reporting groups

Reporting group title	AMG 319 400 mg

Reporting group description:

AMG 319 at 400 mg once daily

Reporting group title	AMG 319 300 mg

Reporting group description:

AMG 319 at 300 mg once daily

Reporting group title	Placebo

Reporting group description:

Placebo once daily

Reporting group title	Overall Safety Population

Reporting group description:

All randomised patients who received at least one administration of AMG 319 or placebo.

Serious adverse events	AMG 319 400 mg	AMG 319 300 mg	Placebo
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 15 (40.00%)	3 / 6 (50.00%)	1 / 9 (11.11%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 15 (0.00%)	1 / 6 (16.67%)	0 / 9 (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			
Pyrexia			

subjects affected / exposed	4 / 15 (26.67%)	1 / 6 (16.67%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	4 / 4	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
Immune-mediated adverse reaction			
subjects affected / exposed	1 / 15 (6.67%)	0 / 6 (0.00%)	0 / 9 (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
Gastrointestinal disorders			
Colitis			
subjects affected / exposed	1 / 15 (6.67%)	1 / 6 (16.67%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	3 / 15 (20.00%)	1 / 6 (16.67%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	3 / 3	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	1 / 15 (6.67%)	1 / 6 (16.67%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Vaginal haemorrhage			
subjects affected / exposed	0 / 15 (0.00%)	1 / 6 (16.67%)	0 / 9 (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
Skin and subcutaneous tissue disorders			
Erythema			
subjects affected / exposed	1 / 15 (6.67%)	0 / 6 (0.00%)	0 / 9 (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
Rash maculo-papular			

subjects affected / exposed	3 / 15 (20.00%)	0 / 6 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	3 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Post procedural infection			
subjects affected / exposed	0 / 15 (0.00%)	0 / 6 (0.00%)	1 / 9 (11.11%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Overall Safety Population		
Total subjects affected by serious adverse events			
subjects affected / exposed	10 / 30 (33.33%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	5 / 30 (16.67%)		
occurrences causally related to treatment / all	5 / 5		
deaths causally related to treatment / all	0 / 0		
Immune system disorders			
Immune-mediated adverse reaction			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Colitis			
subjects affected / exposed	2 / 30 (6.67%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Diarrhoea			

subjects affected / exposed	4 / 30 (13.33%)		
occurrences causally related to treatment / all	4 / 4		
deaths causally related to treatment / all	0 / 0		
Vomiting			
subjects affected / exposed	2 / 30 (6.67%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Reproductive system and breast disorders			
Vaginal haemorrhage			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Erythema			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Rash maculo-papular			
subjects affected / exposed	3 / 30 (10.00%)		
occurrences causally related to treatment / all	3 / 3		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Post procedural infection			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	AMG 319 400 mg	AMG 319 300 mg	Placebo
Total subjects affected by non-serious adverse events			
subjects affected / exposed	14 / 15 (93.33%)	5 / 6 (83.33%)	7 / 9 (77.78%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			

Tumour pain			
subjects affected / exposed	0 / 15 (0.00%)	0 / 6 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	0	1
Vascular disorders			
Hot flush			
subjects affected / exposed	0 / 15 (0.00%)	1 / 6 (16.67%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Hypertension			
subjects affected / exposed	1 / 15 (6.67%)	1 / 6 (16.67%)	1 / 9 (11.11%)
occurrences (all)	2	1	2
Hypotension			
subjects affected / exposed	0 / 15 (0.00%)	1 / 6 (16.67%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Pelvic venous thrombosis			
subjects affected / exposed	0 / 15 (0.00%)	1 / 6 (16.67%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
General disorders and administration site conditions			
Facial pain			
subjects affected / exposed	1 / 15 (6.67%)	0 / 6 (0.00%)	0 / 9 (0.00%)
occurrences (all)	1	0	0
Fatigue			
subjects affected / exposed	4 / 15 (26.67%)	1 / 6 (16.67%)	1 / 9 (11.11%)
occurrences (all)	4	1	1
Feeling hot			
subjects affected / exposed	0 / 15 (0.00%)	0 / 6 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	0	1
Influenza like illness			
subjects affected / exposed	7 / 15 (46.67%)	3 / 6 (50.00%)	0 / 9 (0.00%)
occurrences (all)	8	3	0
Mucosal inflammation			
subjects affected / exposed	1 / 15 (6.67%)	0 / 6 (0.00%)	0 / 9 (0.00%)
occurrences (all)	1	0	0
Oedema peripheral			
subjects affected / exposed	1 / 15 (6.67%)	0 / 6 (0.00%)	0 / 9 (0.00%)
occurrences (all)	1	0	0
Pyrexia			

subjects affected / exposed	2 / 15 (13.33%)	1 / 6 (16.67%)	1 / 9 (11.11%)
occurrences (all)	3	1	1
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	0 / 15 (0.00%)	1 / 6 (16.67%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Cough			
subjects affected / exposed	1 / 15 (6.67%)	0 / 6 (0.00%)	0 / 9 (0.00%)
occurrences (all)	1	0	0
Dyspnoea			
subjects affected / exposed	1 / 15 (6.67%)	0 / 6 (0.00%)	0 / 9 (0.00%)
occurrences (all)	1	0	0
Oropharyngeal pain			
subjects affected / exposed	2 / 15 (13.33%)	0 / 6 (0.00%)	0 / 9 (0.00%)
occurrences (all)	2	0	0
Rhinorrhoea			
subjects affected / exposed	0 / 15 (0.00%)	1 / 6 (16.67%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Psychiatric disorders			
Hallucination, visual			
subjects affected / exposed	1 / 15 (6.67%)	0 / 6 (0.00%)	0 / 9 (0.00%)
occurrences (all)	1	0	0
Insomnia			
subjects affected / exposed	1 / 15 (6.67%)	0 / 6 (0.00%)	2 / 9 (22.22%)
occurrences (all)	1	0	2
Investigations			
Adjusted calcium decreased			
subjects affected / exposed	3 / 15 (20.00%)	0 / 6 (0.00%)	0 / 9 (0.00%)
occurrences (all)	3	0	0
Alanine aminotransferase increased			
subjects affected / exposed	6 / 15 (40.00%)	1 / 6 (16.67%)	0 / 9 (0.00%)
occurrences (all)	6	1	0
Aspartate aminotransferase increased			
subjects affected / exposed	3 / 15 (20.00%)	0 / 6 (0.00%)	0 / 9 (0.00%)
occurrences (all)	3	0	0
Blood alkaline phosphatase increased			

subjects affected / exposed	1 / 15 (6.67%)	1 / 6 (16.67%)	0 / 9 (0.00%)
occurrences (all)	1	1	0
Blood creatinine increased			
subjects affected / exposed	2 / 15 (13.33%)	0 / 6 (0.00%)	0 / 9 (0.00%)
occurrences (all)	2	0	0
Blood phosphorus decreased			
subjects affected / exposed	1 / 15 (6.67%)	0 / 6 (0.00%)	0 / 9 (0.00%)
occurrences (all)	1	0	0
Blood potassium decreased			
subjects affected / exposed	1 / 15 (6.67%)	0 / 6 (0.00%)	0 / 9 (0.00%)
occurrences (all)	3	0	0
Blood urine present			
subjects affected / exposed	0 / 15 (0.00%)	2 / 6 (33.33%)	0 / 9 (0.00%)
occurrences (all)	0	2	0
Electrocardiogram QT prolonged			
subjects affected / exposed	1 / 15 (6.67%)	0 / 6 (0.00%)	1 / 9 (11.11%)
occurrences (all)	2	0	1
Lymphocyte count decreased			
subjects affected / exposed	4 / 15 (26.67%)	2 / 6 (33.33%)	0 / 9 (0.00%)
occurrences (all)	5	2	0
Neutrophil count increased			
subjects affected / exposed	1 / 15 (6.67%)	0 / 6 (0.00%)	0 / 9 (0.00%)
occurrences (all)	1	0	0
Platelet count decreased			
subjects affected / exposed	3 / 15 (20.00%)	0 / 6 (0.00%)	0 / 9 (0.00%)
occurrences (all)	3	0	0
White blood cell count decreased			
subjects affected / exposed	1 / 15 (6.67%)	0 / 6 (0.00%)	0 / 9 (0.00%)
occurrences (all)	1	0	0
White blood cell count increased			
subjects affected / exposed	1 / 15 (6.67%)	0 / 6 (0.00%)	0 / 9 (0.00%)
occurrences (all)	1	0	0
Cardiac disorders			
Palpitations			
subjects affected / exposed	1 / 15 (6.67%)	0 / 6 (0.00%)	0 / 9 (0.00%)
occurrences (all)	1	0	0

Tachycardia			
subjects affected / exposed	1 / 15 (6.67%)	0 / 6 (0.00%)	0 / 9 (0.00%)
occurrences (all)	1	0	0
Nervous system disorders			
Dizziness			
subjects affected / exposed	3 / 15 (20.00%)	1 / 6 (16.67%)	0 / 9 (0.00%)
occurrences (all)	3	1	0
Dysgeusia			
subjects affected / exposed	4 / 15 (26.67%)	1 / 6 (16.67%)	0 / 9 (0.00%)
occurrences (all)	5	1	0
Headache			
subjects affected / exposed	3 / 15 (20.00%)	1 / 6 (16.67%)	2 / 9 (22.22%)
occurrences (all)	3	1	2
Lethargy			
subjects affected / exposed	1 / 15 (6.67%)	0 / 6 (0.00%)	0 / 9 (0.00%)
occurrences (all)	1	0	0
Paraesthesia			
subjects affected / exposed	1 / 15 (6.67%)	0 / 6 (0.00%)	0 / 9 (0.00%)
occurrences (all)	1	0	0
Syncope			
subjects affected / exposed	1 / 15 (6.67%)	0 / 6 (0.00%)	0 / 9 (0.00%)
occurrences (all)	1	0	0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 15 (13.33%)	1 / 6 (16.67%)	0 / 9 (0.00%)
occurrences (all)	2	1	0
Neutropenia			
subjects affected / exposed	1 / 15 (6.67%)	0 / 6 (0.00%)	0 / 9 (0.00%)
occurrences (all)	1	0	0
Thrombocytosis			
subjects affected / exposed	1 / 15 (6.67%)	0 / 6 (0.00%)	0 / 9 (0.00%)
occurrences (all)	1	0	0
Ear and labyrinth disorders			
Ear pain			
subjects affected / exposed	0 / 15 (0.00%)	0 / 6 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	0	1
Eye disorders			

Conjunctival haemorrhage			
subjects affected / exposed	1 / 15 (6.67%)	0 / 6 (0.00%)	0 / 9 (0.00%)
occurrences (all)	1	0	0
Dry eye			
subjects affected / exposed	1 / 15 (6.67%)	0 / 6 (0.00%)	0 / 9 (0.00%)
occurrences (all)	1	0	0
Periorbital oedema			
subjects affected / exposed	1 / 15 (6.67%)	0 / 6 (0.00%)	0 / 9 (0.00%)
occurrences (all)	1	0	0
Presbyopia			
subjects affected / exposed	0 / 15 (0.00%)	1 / 6 (16.67%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Visual impairment			
subjects affected / exposed	1 / 15 (6.67%)	0 / 6 (0.00%)	0 / 9 (0.00%)
occurrences (all)	1	0	0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 15 (6.67%)	1 / 6 (16.67%)	1 / 9 (11.11%)
occurrences (all)	1	1	1
Constipation			
subjects affected / exposed	1 / 15 (6.67%)	1 / 6 (16.67%)	2 / 9 (22.22%)
occurrences (all)	1	2	2
Diarrhoea			
subjects affected / exposed	9 / 15 (60.00%)	3 / 6 (50.00%)	1 / 9 (11.11%)
occurrences (all)	11	4	1
Dry mouth			
subjects affected / exposed	0 / 15 (0.00%)	1 / 6 (16.67%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Dyspepsia			
subjects affected / exposed	2 / 15 (13.33%)	1 / 6 (16.67%)	0 / 9 (0.00%)
occurrences (all)	2	1	0
Flatulence			
subjects affected / exposed	1 / 15 (6.67%)	0 / 6 (0.00%)	0 / 9 (0.00%)
occurrences (all)	1	0	0
Gastrointestinal hypermotility			

subjects affected / exposed	1 / 15 (6.67%)	0 / 6 (0.00%)	0 / 9 (0.00%)
occurrences (all)	1	0	0
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 15 (6.67%)	1 / 6 (16.67%)	0 / 9 (0.00%)
occurrences (all)	1	1	0
Glossodynia			
subjects affected / exposed	1 / 15 (6.67%)	0 / 6 (0.00%)	0 / 9 (0.00%)
occurrences (all)	1	0	0
Haemorrhoids			
subjects affected / exposed	0 / 15 (0.00%)	1 / 6 (16.67%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Lip swelling			
subjects affected / exposed	0 / 15 (0.00%)	1 / 6 (16.67%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Nausea			
subjects affected / exposed	4 / 15 (26.67%)	3 / 6 (50.00%)	2 / 9 (22.22%)
occurrences (all)	4	4	2
Oral dysaesthesia			
subjects affected / exposed	0 / 15 (0.00%)	1 / 6 (16.67%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Oral pain			
subjects affected / exposed	1 / 15 (6.67%)	1 / 6 (16.67%)	0 / 9 (0.00%)
occurrences (all)	1	1	0
Paraesthesia oral			
subjects affected / exposed	0 / 15 (0.00%)	0 / 6 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	0	1
Swollen tongue			
subjects affected / exposed	0 / 15 (0.00%)	1 / 6 (16.67%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Tongue blistering			
subjects affected / exposed	1 / 15 (6.67%)	0 / 6 (0.00%)	0 / 9 (0.00%)
occurrences (all)	1	0	0
Vomiting			
subjects affected / exposed	2 / 15 (13.33%)	2 / 6 (33.33%)	0 / 9 (0.00%)
occurrences (all)	3	2	0
Skin and subcutaneous tissue disorders			

Dry skin			
subjects affected / exposed	1 / 15 (6.67%)	0 / 6 (0.00%)	0 / 9 (0.00%)
occurrences (all)	1	0	0
Hyperhidrosis			
subjects affected / exposed	1 / 15 (6.67%)	0 / 6 (0.00%)	0 / 9 (0.00%)
occurrences (all)	1	0	0
Night sweats			
subjects affected / exposed	1 / 15 (6.67%)	0 / 6 (0.00%)	0 / 9 (0.00%)
occurrences (all)	1	0	0
Pruritus			
subjects affected / exposed	1 / 15 (6.67%)	0 / 6 (0.00%)	2 / 9 (22.22%)
occurrences (all)	1	0	2
Rash			
subjects affected / exposed	2 / 15 (13.33%)	0 / 6 (0.00%)	0 / 9 (0.00%)
occurrences (all)	2	0	0
Rash macular			
subjects affected / exposed	1 / 15 (6.67%)	0 / 6 (0.00%)	0 / 9 (0.00%)
occurrences (all)	1	0	0
Rash maculo-papular			
subjects affected / exposed	6 / 15 (40.00%)	4 / 6 (66.67%)	1 / 9 (11.11%)
occurrences (all)	7	4	1
Skin exfoliation			
subjects affected / exposed	1 / 15 (6.67%)	0 / 6 (0.00%)	0 / 9 (0.00%)
occurrences (all)	1	0	0
Urticaria			
subjects affected / exposed	1 / 15 (6.67%)	0 / 6 (0.00%)	1 / 9 (11.11%)
occurrences (all)	1	0	1
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 15 (6.67%)	0 / 6 (0.00%)	0 / 9 (0.00%)
occurrences (all)	1	0	0
Glycosuria			
subjects affected / exposed	1 / 15 (6.67%)	0 / 6 (0.00%)	0 / 9 (0.00%)
occurrences (all)	1	0	0
Haematuria			

subjects affected / exposed	3 / 15 (20.00%)	0 / 6 (0.00%)	0 / 9 (0.00%)
occurrences (all)	3	0	0
Proteinuria			
subjects affected / exposed	1 / 15 (6.67%)	1 / 6 (16.67%)	0 / 9 (0.00%)
occurrences (all)	1	1	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 15 (6.67%)	0 / 6 (0.00%)	0 / 9 (0.00%)
occurrences (all)	1	0	0
Back pain			
subjects affected / exposed	1 / 15 (6.67%)	0 / 6 (0.00%)	0 / 9 (0.00%)
occurrences (all)	1	0	0
Muscular weakness			
subjects affected / exposed	1 / 15 (6.67%)	0 / 6 (0.00%)	0 / 9 (0.00%)
occurrences (all)	1	0	0
Infections and infestations			
Bronchitis			
subjects affected / exposed	1 / 15 (6.67%)	0 / 6 (0.00%)	0 / 9 (0.00%)
occurrences (all)	1	0	0
Nasopharyngitis			
subjects affected / exposed	0 / 15 (0.00%)	0 / 6 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	0	1
Oral candidiasis			
subjects affected / exposed	3 / 15 (20.00%)	1 / 6 (16.67%)	0 / 9 (0.00%)
occurrences (all)	3	1	0
Staphylococcal infection			
subjects affected / exposed	0 / 15 (0.00%)	1 / 6 (16.67%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Upper respiratory tract infection			
subjects affected / exposed	1 / 15 (6.67%)	0 / 6 (0.00%)	0 / 9 (0.00%)
occurrences (all)	1	0	0
Urinary tract infection			
subjects affected / exposed	2 / 15 (13.33%)	1 / 6 (16.67%)	0 / 9 (0.00%)
occurrences (all)	2	1	0
Vulvovaginal candidiasis			

subjects affected / exposed	1 / 15 (6.67%)	0 / 6 (0.00%)	0 / 9 (0.00%)
occurrences (all)	1	0	0
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	1 / 15 (6.67%)	0 / 6 (0.00%)	0 / 9 (0.00%)
occurrences (all)	1	0	0
Hyperamylasaemia			
subjects affected / exposed	0 / 15 (0.00%)	0 / 6 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	0	1
Hypermagnesaemia			
subjects affected / exposed	0 / 15 (0.00%)	1 / 6 (16.67%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Hypoalbuminaemia			
subjects affected / exposed	3 / 15 (20.00%)	0 / 6 (0.00%)	0 / 9 (0.00%)
occurrences (all)	3	0	0
Hypokalaemia			
subjects affected / exposed	3 / 15 (20.00%)	0 / 6 (0.00%)	0 / 9 (0.00%)
occurrences (all)	4	0	0
Hypomagnesaemia			
subjects affected / exposed	1 / 15 (6.67%)	0 / 6 (0.00%)	1 / 9 (11.11%)
occurrences (all)	2	0	1
Hyponatraemia			
subjects affected / exposed	4 / 15 (26.67%)	0 / 6 (0.00%)	0 / 9 (0.00%)
occurrences (all)	4	0	0
Hypophosphataemia			
subjects affected / exposed	4 / 15 (26.67%)	0 / 6 (0.00%)	0 / 9 (0.00%)
occurrences (all)	5	0	0

Non-serious adverse events	Overall Safety Population		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	26 / 30 (86.67%)		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Tumour pain			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		
Vascular disorders			

Hot flush subjects affected / exposed occurrences (all)	1 / 30 (3.33%) 1		
Hypertension subjects affected / exposed occurrences (all)	3 / 30 (10.00%) 5		
Hypotension subjects affected / exposed occurrences (all)	1 / 30 (3.33%) 1		
Pelvic venous thrombosis subjects affected / exposed occurrences (all)	1 / 30 (3.33%) 1		
General disorders and administration site conditions Facial pain subjects affected / exposed occurrences (all)	1 / 30 (3.33%) 1		
Fatigue subjects affected / exposed occurrences (all)	6 / 30 (20.00%) 6		
Feeling hot subjects affected / exposed occurrences (all)	1 / 30 (3.33%) 1		
Influenza like illness subjects affected / exposed occurrences (all)	10 / 30 (33.33%) 11		
Mucosal inflammation subjects affected / exposed occurrences (all)	1 / 30 (3.33%) 1		
Oedema peripheral subjects affected / exposed occurrences (all)	1 / 30 (3.33%) 1		
Pyrexia subjects affected / exposed occurrences (all)	4 / 30 (13.33%) 5		
Respiratory, thoracic and mediastinal disorders			

Asthma			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		
Cough			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		
Dyspnoea			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		
Oropharyngeal pain			
subjects affected / exposed	2 / 30 (6.67%)		
occurrences (all)	2		
Rhinorrhoea			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		
Psychiatric disorders			
Hallucination, visual			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		
Insomnia			
subjects affected / exposed	3 / 30 (10.00%)		
occurrences (all)	3		
Investigations			
Adjusted calcium decreased			
subjects affected / exposed	3 / 30 (10.00%)		
occurrences (all)	3		
Alanine aminotransferase increased			
subjects affected / exposed	7 / 30 (23.33%)		
occurrences (all)	7		
Aspartate aminotransferase increased			
subjects affected / exposed	3 / 30 (10.00%)		
occurrences (all)	3		
Blood alkaline phosphatase increased			
subjects affected / exposed	2 / 30 (6.67%)		
occurrences (all)	2		
Blood creatinine increased			

subjects affected / exposed	2 / 30 (6.67%)		
occurrences (all)	2		
Blood phosphorus decreased			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		
Blood potassium decreased			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	3		
Blood urine present			
subjects affected / exposed	2 / 30 (6.67%)		
occurrences (all)	2		
Electrocardiogram QT prolonged			
subjects affected / exposed	2 / 30 (6.67%)		
occurrences (all)	3		
Lymphocyte count decreased			
subjects affected / exposed	6 / 30 (20.00%)		
occurrences (all)	7		
Neutrophil count increased			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		
Platelet count decreased			
subjects affected / exposed	3 / 30 (10.00%)		
occurrences (all)	3		
White blood cell count decreased			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		
White blood cell count increased			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		
Cardiac disorders			
Palpitations			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		
Tachycardia			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		

Nervous system disorders			
Dizziness			
subjects affected / exposed	4 / 30 (13.33%)		
occurrences (all)	4		
Dysgeusia			
subjects affected / exposed	5 / 30 (16.67%)		
occurrences (all)	6		
Headache			
subjects affected / exposed	6 / 30 (20.00%)		
occurrences (all)	6		
Lethargy			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		
Paraesthesia			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		
Syncope			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	3 / 30 (10.00%)		
occurrences (all)	3		
Neutropenia			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		
Thrombocytosis			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		
Ear and labyrinth disorders			
Ear pain			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		
Eye disorders			
Conjunctival haemorrhage			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		

Dry eye subjects affected / exposed occurrences (all)	1 / 30 (3.33%) 1		
Periorbital oedema subjects affected / exposed occurrences (all)	1 / 30 (3.33%) 1		
Presbyopia subjects affected / exposed occurrences (all)	1 / 30 (3.33%) 1		
Visual impairment subjects affected / exposed occurrences (all)	1 / 30 (3.33%) 1		
Gastrointestinal disorders Abdominal pain subjects affected / exposed occurrences (all)	3 / 30 (10.00%) 3		
Constipation subjects affected / exposed occurrences (all)	4 / 30 (13.33%) 5		
Diarrhoea subjects affected / exposed occurrences (all)	13 / 30 (43.33%) 16		
Dry mouth subjects affected / exposed occurrences (all)	1 / 30 (3.33%) 1		
Dyspepsia subjects affected / exposed occurrences (all)	3 / 30 (10.00%) 3		
Flatulence subjects affected / exposed occurrences (all)	1 / 30 (3.33%) 1		
Gastrointestinal hypermotility subjects affected / exposed occurrences (all)	1 / 30 (3.33%) 1		
Gastrooesophageal reflux disease			

subjects affected / exposed	2 / 30 (6.67%)		
occurrences (all)	2		
Glossodynia			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		
Haemorrhoids			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		
Lip swelling			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		
Nausea			
subjects affected / exposed	9 / 30 (30.00%)		
occurrences (all)	10		
Oral dysaesthesia			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		
Oral pain			
subjects affected / exposed	2 / 30 (6.67%)		
occurrences (all)	2		
Paraesthesia oral			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		
Swollen tongue			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		
Tongue blistering			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		
Vomiting			
subjects affected / exposed	4 / 30 (13.33%)		
occurrences (all)	5		
Skin and subcutaneous tissue disorders			
Dry skin			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		

Hyperhidrosis			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		
Night sweats			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		
Pruritus			
subjects affected / exposed	3 / 30 (10.00%)		
occurrences (all)	3		
Rash			
subjects affected / exposed	2 / 30 (6.67%)		
occurrences (all)	2		
Rash macular			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		
Rash maculo-papular			
subjects affected / exposed	11 / 30 (36.67%)		
occurrences (all)	12		
Skin exfoliation			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		
Urticaria			
subjects affected / exposed	2 / 30 (6.67%)		
occurrences (all)	2		
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		
Glycosuria			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		
Haematuria			
subjects affected / exposed	3 / 30 (10.00%)		
occurrences (all)	3		
Proteinuria			

subjects affected / exposed	2 / 30 (6.67%)		
occurrences (all)	2		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		
Back pain			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		
Muscular weakness			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		
Infections and infestations			
Bronchitis			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		
Nasopharyngitis			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		
Oral candidiasis			
subjects affected / exposed	4 / 30 (13.33%)		
occurrences (all)	4		
Staphylococcal infection			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		
Upper respiratory tract infection			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		
Urinary tract infection			
subjects affected / exposed	3 / 30 (10.00%)		
occurrences (all)	3		
Vulvovaginal candidiasis			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		
Metabolism and nutrition disorders			

Decreased appetite			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		
Hyperamylasaemia			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		
Hypermagnesaemia			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		
Hypoalbuminaemia			
subjects affected / exposed	3 / 30 (10.00%)		
occurrences (all)	3		
Hypokalaemia			
subjects affected / exposed	3 / 30 (10.00%)		
occurrences (all)	4		
Hypomagnesaemia			
subjects affected / exposed	2 / 30 (6.67%)		
occurrences (all)	3		
Hyponatraemia			
subjects affected / exposed	4 / 30 (13.33%)		
occurrences (all)	4		
Hypophosphataemia			
subjects affected / exposed	4 / 30 (13.33%)		
occurrences (all)	5		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
11 March 2016	Changes to adverse event collection requirements post resection surgery. Changes to eligibility criteria relating to patients with a previous primary HNSCC, inclusion of supraglottis and T4 larynx tumours. Changes to treatment with medications known to cause QTc prolongation.
23 June 2016	Changes to the eligibility criteria relating to HPV status. Update to disease assessment criteria and timing of informed consent.
28 September 2016	Revision to the eligibility criteria to include HPV positive patients and patients who had current or previous malignancies of other types. Changes to the HIV exclusion criteria and testing requirements. Changes to timings of the pAKT sampling and tumour processing for RNA sequencing. Minimum number of days dosing reduced to 20 days and maximum reduced to 29 days. This amendment was approved by the Medicines and Healthcare products Regulatory Agency (MHRA) on 28 September 2016 but was not approved by the Research Ethics Committee (REC). The REC provided Grounds for Non Acceptance and requested an explanation as to why the serology PCR sequencing had been removed from the protocol and what the new testing would be.
06 October 2017	Following the temporary halt of the trial on 26 May 2017 and review of the safety data, an amendment was submitted to reopen the trial and update the protocol as follows: An update to clarify which staff members were blinded to the treatment assigned to patients as documented in the AMG 319 blinding manual. Blinded data was reviewed by the Sponsor’s independent Protocol Safety Review Board (PSRB). Following this review, the PSRB recommended that a small number of the Sponsor's team were unblinded in order to confirm that those patients who had been treated on the trial and who had experienced the more severe adverse events while on treatment had received AMG 319 rather than placebo. A specific procedure for unblinding trial data in this instance was established. Reduction of the AMG 319/placebo dose level from 400 mg once daily to 300 mg once daily. Further dose reductions of the fixed dose were permitted if one or more patients experienced either a clinically significant ≥Grade 3 toxicity considered to be immunologically mediated or a drug related toxicity which caused the patient to receive less than 80% of their planned doses. The potential dose de-escalation options were 200 mg once daily, followed by 100 mg once daily, after which point no further dose reductions would be allowed and the trial could be terminated.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date

26 May 2017	The trial was temporarily halted (on hold) as a precautionary measure based on the review of emerging clinical safety data for the first 27 patients enrolled on the trial by the Safety Review Committee. It was noted that there was a higher than expected incidence of early onset adverse events leading to premature discontinuation of treatment and adverse events resulting in either delayed or problematic surgery. Following the temporary halt and review of the safety data, a CSP amendment (06 October 2017) was made.	06 October 2017
09 March 2018	Following a safety review of the blinded data from the eight patients who had been recruited to receive AMG 319 300 mg or placebo, the decision was taken to reduce the AMG 319 dose further to 200 mg once daily. However, based on additional emerging clinical safety data, the trial was placed on temporary halt on 09 March 2018 so that a further review of the available clinical safety data could be performed before further patients were recruited to the trial. Following the review, the risk benefit profile of AMG 319 in the trial population using the dose levels and schedule of administration within the CSP was no longer considered favourable and the trial was terminated early (completion date 03 May 2018). Survival information was therefore only collected up to the point of trial closure and the AMG 319 200 mg dose level was not explored in this trial. At the time of this temporary halt and subsequent early termination, 32 patients had been recruited to the trial.	-

Notes:

Limitations and caveats

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

Due to early termination, there were insufficient patients to meet the planned statistical sample size for the primary endpoint of immune infiltration. Also, the protocol specified survival follow-up data was collected only until termination.

Notes: