Clinical trial results:
Safety and pharmacokinetics of ODM-207 in patients with selected advanced solid tumours: an open-label, non-randomised, uncontrolled, multicentre, first-in-human study with cohort expansion

Summary

EudraCT number	2015-004826-32
Trial protocol	GB FI ES FR
Global end of trial date	10 May 2019

Results information

Result version number	v1 (current)
This version publication date	27 November 2019
First version publication date	27 November 2019

Trial information

Trial identification

Sponsor protocol code	3121001

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03035591
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Orion Corporation, Orion Pharma
Sponsor organisation address	Orionintie 1, Espoo, Finland, 02200
Public contact	Clinical Trial Information desk, Orion Corporation, Orion Pharma, +358 104261, clinicaltrials@orionpharma.com
Scientific contact	Clinical Trial Information desk, Orion Corporation, Orion Pharma, +358 104261, clinicaltrials@orionpharma.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	10 May 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	10 May 2019
Global end of trial reached?	Yes
Global end of trial date	10 May 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Part 1:
To evaluate the safety and tolerability, define the maximum tolerated dose (MTD) and dose limiting toxicities (DLTs) if possible, and define the recommended doses and dosing schedules of ODM-207 for Part 2 of the study.

Part 2:
To further evaluate the safety and tolerability, and preliminary antitumour activity of ODM-207 at the dose levels recommended for further clinical studies in patient populations with selected tumour types.

Protection of trial subjects:

Adequate medical expertise and facilities to handle possible emergency situations were available throughout the study. Study subjects were carefully monitored during the study. The dose escalation for following cohort were decided with a support of the SMB after a minimum of 3 patients had provided evaluable dose limiting toxicity -data.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	22 December 2016
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Spain: 9
Country: Number of subjects enrolled	United Kingdom: 14
Country: Number of subjects enrolled	Finland: 6
Country: Number of subjects enrolled	France: 7
Worldwide total number of subjects	36
EEA total number of subjects	36

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)	1
Adults (18-64 years)	23
From 65 to 84 years	12
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Male and female patients with confirmed advanced solid tumors which were refractory or resistant to therapy or for which no effective standard therapy exists were enrolled into this study.

Pre-assignment

Screening details:

Male/female subjects with selected locally advanced/metastatic solid tumours refractory or resistant to therapy or with no effective standard therapy and life expectancy >12 weeks at baseline. Subjects >15 years with written informed consent. Adequate haemopoietic, hepatic and renal function. Eastern Cooperative Oncology Group status of 0 or 1.

Period 1

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

Blinding implementation details:

NA

Arms

Are arms mutually exclusive?	Yes
Arm title	Cohort 1

Arm description:

A dose of 50 mg of ODM-207 once daily

Arm type	Experimental
Investigational medicinal product name	ODM-207
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Once daily as defined by the cohort using 50 mg tablets

Arm title	Cohort 2

Arm description:

A dose of 100 mg of ODM-207 once daily

Arm type	Experimental
Investigational medicinal product name	ODM-207
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Once daily as defined by the cohort using 50 mg tablets

Arm title	Cohort 3

Arm description:

A dose of 1.5 mg/kg of ODM-207 once daily

Arm type	Experimental

Investigational medicinal product name	ODM-207
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Once daily as defined by the cohort using tablets of the following strength: 15, 25 and 50 mg

Arm title	Cohort 4

Arm description:

A dose of 2.0 mg/kg of ODM-207 once daily

Arm type	Experimental
Investigational medicinal product name	ODM-207
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Once daily as defined by the cohort using tablets of the following strength: 15, 25 and 50 mg

Arm title	Cohort 5

Arm description:

A dose of 1.1 mg/kg of ODM-207 once daily for to study food effect

Arm type	Experimental
Investigational medicinal product name	ODM-207
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Once daily as defined by the cohort using tablets of the following strength: 25 and 50 mg

Arm title	Cohort 6

Arm description:

A dose of 1.4 mg/kg of ODM-207 once daily to study 72 h elimination

Arm type	Experimental
Investigational medicinal product name	ODM-207
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Once daily as defined by the cohort using tablets of the following strength: 15, 25 and 50 mg

Number of subjects in period 1	Cohort 1	Cohort 2	Cohort 3
Started	3	7	6
Completed	3	7	5
Not completed	0	0	1
Did not start study treatment	-	-	1

Number of subjects in period 1	Cohort 4	Cohort 5	Cohort 6
Started	6	10	4
Completed	6	10	4
Not completed	0	0	0
Did not start study treatment	-	-	-

Baseline characteristics

Reporting groups	
Reporting group title	Part I

Reporting group description: -

Reporting group values	Part I	Total	
Number of subjects	36	36	
Age categorical Units: Subjects			
Adolescents (12-17 years)	1	1	
Adults (18-64 years)	23	23	
From 65-84 years	12	12	
Gender categorical Units: Subjects			
Female	14	14	
Male	22	22	

End points

End points reporting groups

Reporting group title	Cohort 1
Reporting group description: A dose of 50 mg of ODM-207 once daily	
Reporting group title	Cohort 2
Reporting group description: A dose of 100 mg of ODM-207 once daily	
Reporting group title	Cohort 3
Reporting group description: A dose of 1.5 mg/kg of ODM-207 once daily	
Reporting group title	Cohort 4
Reporting group description: A dose of 2.0 mg/kg of ODM-207 once daily	
Reporting group title	Cohort 5
Reporting group description: A dose of 1.1 mg/kg of ODM-207 once daily for to study food effect	
Reporting group title	Cohort 6
Reporting group description: A dose of 1.4 mg/kg of ODM-207 once daily to study 72 h elimination	

Primary: Frequency of Adverse Events

End point title	Frequency of Adverse Events[1]
End point description:	
End point type	Primary
End point timeframe: Treatment emergent adverse events	

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: Descriptive statistics because only part 1 was conducted.

End point values	Cohort 1	Cohort 2	Cohort 3	Cohort 4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3	7	5	6
Units: Subjects	3	7	5	6

End point values	Cohort 5	Cohort 6		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	4		
Units: Subjects	10	4		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Treatment emergent adverse events	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	21.0

Reporting groups	
Reporting group title	Cohort 1
Reporting group description:	
A dose of 50 mg of ODM-207 once daily	
Reporting group title	Cohort 2
Reporting group description:	
A dose of 100 mg of ODM-207 once daily	
Reporting group title	Cohort 3
Reporting group description:	
A dose of 1.5 mg/kg of ODM-207 once daily	
Reporting group title	Cohort 5
Reporting group description:	
A dose of 1.1 mg/kg of ODM-207 once daily for to study food effect	
Reporting group title	Cohort 6
Reporting group description:	
A dose of 1.4 mg/kg of ODM-207 once daily to study 72 h elimination	
Reporting group title	Cohort 4
Reporting group description:	
A dose of 2.0 mg/kg of ODM-207 once daily	

Serious adverse events	Cohort 1	Cohort 2	Cohort 3
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 3 (0.00%)	2 / 7 (28.57%)	2 / 5 (40.00%)
number of deaths (all causes)	0	0	1
number of deaths resulting from adverse events	0	0	1
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	0 / 3 (0.00%)	0 / 7 (0.00%)	0 / 5 (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
Fall			

subjects affected / exposed	0 / 3 (0.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Spinal cord compression			
subjects affected / exposed	0 / 3 (0.00%)	0 / 7 (0.00%)	0 / 5 (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
Blood and lymphatic system disorders			
B-cell lymphoma			
subjects affected / exposed	0 / 3 (0.00%)	0 / 7 (0.00%)	1 / 5 (20.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Metastases to spine			
subjects affected / exposed	0 / 3 (0.00%)	0 / 7 (0.00%)	1 / 5 (20.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
NUT midline carcinoma			
subjects affected / exposed	0 / 3 (0.00%)	0 / 7 (0.00%)	0 / 5 (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
Thrombocytopenia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 7 (0.00%)	0 / 5 (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
Tumour pain			
subjects affected / exposed	0 / 3 (0.00%)	0 / 7 (0.00%)	0 / 5 (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
Anaemia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 7 (0.00%)	0 / 5 (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
General disorders and administration			

site conditions			
Fatigue			
subjects affected / exposed	0 / 3 (0.00%)	0 / 7 (0.00%)	0 / 5 (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
Pyrexia			
subjects affected / exposed	0 / 3 (0.00%)	1 / 7 (14.29%)	0 / 5 (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
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	0 / 3 (0.00%)	0 / 7 (0.00%)	0 / 5 (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
Intestinal obstruction			
subjects affected / exposed	0 / 3 (0.00%)	0 / 7 (0.00%)	0 / 5 (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
Large intestine perforation			
subjects affected / exposed	0 / 3 (0.00%)	0 / 7 (0.00%)	1 / 5 (20.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower gastrointestinal haemorrhage			
subjects affected / exposed	0 / 3 (0.00%)	0 / 7 (0.00%)	0 / 5 (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
Nausea			
subjects affected / exposed	0 / 3 (0.00%)	0 / 7 (0.00%)	0 / 5 (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
Pancreatitis necrotising			
subjects affected / exposed	0 / 3 (0.00%)	0 / 7 (0.00%)	1 / 5 (20.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Vomiting			
subjects affected / exposed	0 / 3 (0.00%)	1 / 7 (14.29%)	0 / 5 (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
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	0 / 3 (0.00%)	0 / 7 (0.00%)	0 / 5 (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
Respiratory distress			
subjects affected / exposed	0 / 3 (0.00%)	0 / 7 (0.00%)	0 / 5 (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
Metabolism and nutrition disorders			
Hypokalaemia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Cohort 5	Cohort 6	Cohort 4
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 10 (30.00%)	4 / 4 (100.00%)	3 / 6 (50.00%)
number of deaths (all causes)	2	2	0
number of deaths resulting from adverse events	2	2	0
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	0 / 10 (0.00%)	0 / 4 (0.00%)	1 / 6 (16.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fall			
subjects affected / exposed	0 / 10 (0.00%)	0 / 4 (0.00%)	1 / 6 (16.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Spinal cord compression			

subjects affected / exposed	0 / 10 (0.00%)	1 / 4 (25.00%)	0 / 6 (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
Blood and lymphatic system disorders			
B-cell lymphoma			
subjects affected / exposed	0 / 10 (0.00%)	0 / 4 (0.00%)	0 / 6 (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
Metastases to spine			
subjects affected / exposed	0 / 10 (0.00%)	0 / 4 (0.00%)	0 / 6 (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
NUT midline carcinoma			
subjects affected / exposed	0 / 10 (0.00%)	1 / 4 (25.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Thrombocytopenia			
subjects affected / exposed	0 / 10 (0.00%)	0 / 4 (0.00%)	1 / 6 (16.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tumour pain			
subjects affected / exposed	0 / 10 (0.00%)	1 / 4 (25.00%)	0 / 6 (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
Anaemia			
subjects affected / exposed	1 / 10 (10.00%)	0 / 4 (0.00%)	0 / 6 (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
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	1 / 10 (10.00%)	0 / 4 (0.00%)	0 / 6 (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

Pyrexia			
subjects affected / exposed	0 / 10 (0.00%)	0 / 4 (0.00%)	1 / 6 (16.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	1 / 10 (10.00%)	0 / 4 (0.00%)	0 / 6 (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 / 10 (10.00%)	0 / 4 (0.00%)	0 / 6 (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
Large intestine perforation			
subjects affected / exposed	0 / 10 (0.00%)	0 / 4 (0.00%)	0 / 6 (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
Lower gastrointestinal haemorrhage			
subjects affected / exposed	1 / 10 (10.00%)	0 / 4 (0.00%)	0 / 6 (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	0 / 10 (0.00%)	1 / 4 (25.00%)	0 / 6 (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
Pancreatitis necrotising			
subjects affected / exposed	0 / 10 (0.00%)	0 / 4 (0.00%)	0 / 6 (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
Vomiting			
subjects affected / exposed	0 / 10 (0.00%)	1 / 4 (25.00%)	1 / 6 (16.67%)
occurrences causally related to treatment / all	0 / 0	0 / 2	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal			

disorders			
Dyspnoea			
subjects affected / exposed	0 / 10 (0.00%)	2 / 4 (50.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Respiratory distress			
subjects affected / exposed	1 / 10 (10.00%)	0 / 4 (0.00%)	0 / 6 (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
Metabolism and nutrition disorders			
Hypokalaemia			
subjects affected / exposed	0 / 10 (0.00%)	0 / 4 (0.00%)	1 / 6 (16.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Cohort 1	Cohort 2	Cohort 3
Total subjects affected by non-serious adverse events			
subjects affected / exposed	3 / 3 (100.00%)	7 / 7 (100.00%)	5 / 5 (100.00%)
Vascular disorders			
Haematoma			
subjects affected / exposed	1 / 3 (33.33%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	2	0	0
Haemorrhage			
subjects affected / exposed	0 / 3 (0.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Hypertension			
subjects affected / exposed	1 / 3 (33.33%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Hypotension			
subjects affected / exposed	1 / 3 (33.33%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	2	0	0
Orthostatic hypotension			
subjects affected / exposed	0 / 3 (0.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0

General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 3 (0.00%)	2 / 7 (28.57%)	1 / 5 (20.00%)
occurrences (all)	0	2	1
Chest pain			
subjects affected / exposed	0 / 3 (0.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Chills			
subjects affected / exposed	1 / 3 (33.33%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Discomfort			
subjects affected / exposed	0 / 3 (0.00%)	0 / 7 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Fatigue			
subjects affected / exposed	1 / 3 (33.33%)	5 / 7 (71.43%)	2 / 5 (40.00%)
occurrences (all)	1	10	2
Mucosal haemorrhage			
subjects affected / exposed	0 / 3 (0.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Non-cardiac chest pain			
subjects affected / exposed	0 / 3 (0.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Oedema peripheral			
subjects affected / exposed	0 / 3 (0.00%)	1 / 7 (14.29%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Pain			
subjects affected / exposed	0 / 3 (0.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Pyrexia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Xerosis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Reproductive system and breast disorders			

Pelvic pain			
subjects affected / exposed	1 / 3 (33.33%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 3 (33.33%)	1 / 7 (14.29%)	0 / 5 (0.00%)
occurrences (all)	1	1	0
Dyspnoea			
subjects affected / exposed	0 / 3 (0.00%)	1 / 7 (14.29%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Dyspnoea exertional			
subjects affected / exposed	1 / 3 (33.33%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Epistaxis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Nasal congestion			
subjects affected / exposed	1 / 3 (33.33%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Pleural effusion			
subjects affected / exposed	0 / 3 (0.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Pleuritic pain			
subjects affected / exposed	0 / 3 (0.00%)	1 / 7 (14.29%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 3 (0.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Depression			
subjects affected / exposed	0 / 3 (0.00%)	2 / 7 (28.57%)	0 / 5 (0.00%)
occurrences (all)	0	3	0
Insomnia			
subjects affected / exposed	1 / 3 (33.33%)	1 / 7 (14.29%)	1 / 5 (20.00%)
occurrences (all)	1	1	1
Investigations			

Alanine aminotransferase increased			
subjects affected / exposed	0 / 3 (0.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 3 (0.00%)	0 / 7 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Blood creatine phosphokinase increased			
subjects affected / exposed	1 / 3 (33.33%)	0 / 7 (0.00%)	1 / 5 (20.00%)
occurrences (all)	2	0	2
Blood creatinine increased			
subjects affected / exposed	0 / 3 (0.00%)	0 / 7 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Blood sodium decreased			
subjects affected / exposed	0 / 3 (0.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
C-reactive protein increased			
subjects affected / exposed	0 / 3 (0.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Electrocardiogram QT prolonged			
subjects affected / exposed	0 / 3 (0.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Lipase increased			
subjects affected / exposed	0 / 3 (0.00%)	0 / 7 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Lymphocyte count decreased			
subjects affected / exposed	0 / 3 (0.00%)	1 / 7 (14.29%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Weight decreased			
subjects affected / exposed	3 / 3 (100.00%)	1 / 7 (14.29%)	0 / 5 (0.00%)
occurrences (all)	3	1	0
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	1 / 3 (33.33%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Fall			

subjects affected / exposed	2 / 3 (66.67%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	3	0	0
Laceration			
subjects affected / exposed	0 / 3 (0.00%)	1 / 7 (14.29%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Post procedural haematoma			
subjects affected / exposed	1 / 3 (33.33%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Tooth fracture			
subjects affected / exposed	0 / 3 (0.00%)	1 / 7 (14.29%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Wrist fracture			
subjects affected / exposed	1 / 3 (33.33%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Cardiac disorders			
Sinus tachycardia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 7 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Tachycardia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Nervous system disorders			
Ageusia			
subjects affected / exposed	0 / 3 (0.00%)	1 / 7 (14.29%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Dizziness			
subjects affected / exposed	0 / 3 (0.00%)	1 / 7 (14.29%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Dysgeusia			
subjects affected / exposed	0 / 3 (0.00%)	1 / 7 (14.29%)	0 / 5 (0.00%)
occurrences (all)	0	2	0
Headache			
subjects affected / exposed	0 / 3 (0.00%)	5 / 7 (71.43%)	2 / 5 (40.00%)
occurrences (all)	0	8	3
Hypotonia			

subjects affected / exposed	0 / 3 (0.00%)	0 / 7 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Myoclonus			
subjects affected / exposed	0 / 3 (0.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Presyncope			
subjects affected / exposed	0 / 3 (0.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Sciatica			
subjects affected / exposed	0 / 3 (0.00%)	1 / 7 (14.29%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Somnolence			
subjects affected / exposed	0 / 3 (0.00%)	1 / 7 (14.29%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Syncope			
subjects affected / exposed	0 / 3 (0.00%)	1 / 7 (14.29%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Tremor			
subjects affected / exposed	0 / 3 (0.00%)	1 / 7 (14.29%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Visual field defect			
subjects affected / exposed	0 / 3 (0.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 3 (0.00%)	1 / 7 (14.29%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Gastrointestinal melanoma			
subjects affected / exposed	0 / 3 (0.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Lymphopenia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Neutropenia			
subjects affected / exposed	0 / 3 (0.00%)	1 / 7 (14.29%)	0 / 5 (0.00%)
occurrences (all)	0	1	0

Neutrophilia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Thrombocytopenia			
subjects affected / exposed	0 / 3 (0.00%)	4 / 7 (57.14%)	2 / 5 (40.00%)
occurrences (all)	0	8	2
Tumour pain			
subjects affected / exposed	0 / 3 (0.00%)	0 / 7 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Ear and labyrinth disorders			
Ear discomfort			
subjects affected / exposed	0 / 3 (0.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Vertigo			
subjects affected / exposed	0 / 3 (0.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Eye disorders			
Dry eye			
subjects affected / exposed	0 / 3 (0.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Eye pain			
subjects affected / exposed	1 / 3 (33.33%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Eye swelling			
subjects affected / exposed	1 / 3 (33.33%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Ocular hyperaemia			
subjects affected / exposed	1 / 3 (33.33%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Optic nerve disorder			
subjects affected / exposed	0 / 3 (0.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Vision blurred			
subjects affected / exposed	0 / 3 (0.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorders			

Abdominal distension			
subjects affected / exposed	0 / 3 (0.00%)	1 / 7 (14.29%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Abdominal pain			
subjects affected / exposed	0 / 3 (0.00%)	0 / 7 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Abdominal pain lower			
subjects affected / exposed	1 / 3 (33.33%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Abdominal pain upper			
subjects affected / exposed	0 / 3 (0.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Aptyalism			
subjects affected / exposed	0 / 3 (0.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Constipation			
subjects affected / exposed	0 / 3 (0.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Diarrhoea			
subjects affected / exposed	1 / 3 (33.33%)	2 / 7 (28.57%)	3 / 5 (60.00%)
occurrences (all)	2	8	5
Dry mouth			
subjects affected / exposed	0 / 3 (0.00%)	1 / 7 (14.29%)	1 / 5 (20.00%)
occurrences (all)	0	1	1
Dysphagia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Gastritis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 3 (0.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Gingival bleeding			
subjects affected / exposed	0 / 3 (0.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0

Large intestinal haemorrhage			
subjects affected / exposed	0 / 3 (0.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Nausea			
subjects affected / exposed	2 / 3 (66.67%)	3 / 7 (42.86%)	3 / 5 (60.00%)
occurrences (all)	4	7	3
Vomiting			
subjects affected / exposed	3 / 3 (100.00%)	2 / 7 (28.57%)	0 / 5 (0.00%)
occurrences (all)	5	2	0
Hepatobiliary disorders			
Hyperbilirubinaemia			
subjects affected / exposed	0 / 3 (0.00%)	1 / 7 (14.29%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Skin and subcutaneous tissue disorders			
Dry skin			
subjects affected / exposed	0 / 3 (0.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Hyperhidrosis			
subjects affected / exposed	0 / 3 (0.00%)	1 / 7 (14.29%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Night sweats			
subjects affected / exposed	1 / 3 (33.33%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Rash			
subjects affected / exposed	0 / 3 (0.00%)	2 / 7 (28.57%)	0 / 5 (0.00%)
occurrences (all)	0	2	0
Rash erythematous			
subjects affected / exposed	0 / 3 (0.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Skin lesion			
subjects affected / exposed	0 / 3 (0.00%)	1 / 7 (14.29%)	0 / 5 (0.00%)
occurrences (all)	0	2	0
Solar dermatitis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 7 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Renal and urinary disorders			

Pollakiuria			
subjects affected / exposed	0 / 3 (0.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Urinary retention			
subjects affected / exposed	1 / 3 (33.33%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 3 (33.33%)	1 / 7 (14.29%)	1 / 5 (20.00%)
occurrences (all)	1	1	1
Flank pain			
subjects affected / exposed	1 / 3 (33.33%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Intervertebral disc protrusion			
subjects affected / exposed	0 / 3 (0.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Joint stiffness			
subjects affected / exposed	0 / 3 (0.00%)	1 / 7 (14.29%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Muscle contracture			
subjects affected / exposed	0 / 3 (0.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Muscle spasms			
subjects affected / exposed	1 / 3 (33.33%)	0 / 7 (0.00%)	1 / 5 (20.00%)
occurrences (all)	1	0	2
Musculoskeletal pain			
subjects affected / exposed	1 / 3 (33.33%)	0 / 7 (0.00%)	1 / 5 (20.00%)
occurrences (all)	1	0	1
Myalgia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Neck pain			
subjects affected / exposed	0 / 3 (0.00%)	1 / 7 (14.29%)	1 / 5 (20.00%)
occurrences (all)	0	1	1
Osteoarthritis			

subjects affected / exposed	0 / 3 (0.00%)	1 / 7 (14.29%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Pain in extremity			
subjects affected / exposed	0 / 3 (0.00%)	1 / 7 (14.29%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Trismus			
subjects affected / exposed	0 / 3 (0.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Infections and infestations			
Abdominal infection			
subjects affected / exposed	0 / 3 (0.00%)	0 / 7 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Bronchitis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Conjunctivitis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Infection			
subjects affected / exposed	0 / 3 (0.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Influenza			
subjects affected / exposed	0 / 3 (0.00%)	0 / 7 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Periodontitis			
subjects affected / exposed	1 / 3 (33.33%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Respiratory tract infection			
subjects affected / exposed	0 / 3 (0.00%)	1 / 7 (14.29%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Rhinitis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Upper respiratory tract infection			
subjects affected / exposed	0 / 3 (0.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0

Urinary tract infection			
subjects affected / exposed	0 / 3 (0.00%)	0 / 7 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	3
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	3 / 3 (100.00%)	6 / 7 (85.71%)	0 / 5 (0.00%)
occurrences (all)	7	9	0
Hypoalbuminaemia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Hypokalaemia			
subjects affected / exposed	1 / 3 (33.33%)	0 / 7 (0.00%)	1 / 5 (20.00%)
occurrences (all)	1	0	1
Hypomagnesaemia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Hyponatraemia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Hypophosphataemia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0

Non-serious adverse events	Cohort 5	Cohort 6	Cohort 4
Total subjects affected by non-serious adverse events			
subjects affected / exposed	10 / 10 (100.00%)	4 / 4 (100.00%)	6 / 6 (100.00%)
Vascular disorders			
Haematoma			
subjects affected / exposed	0 / 10 (0.00%)	0 / 4 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Haemorrhage			
subjects affected / exposed	0 / 10 (0.00%)	0 / 4 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Hypertension			
subjects affected / exposed	1 / 10 (10.00%)	0 / 4 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Hypotension			

subjects affected / exposed	1 / 10 (10.00%)	0 / 4 (0.00%)	2 / 6 (33.33%)
occurrences (all)	1	0	2
Orthostatic hypotension			
subjects affected / exposed	0 / 10 (0.00%)	0 / 4 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	3 / 10 (30.00%)	0 / 4 (0.00%)	2 / 6 (33.33%)
occurrences (all)	4	0	2
Chest pain			
subjects affected / exposed	1 / 10 (10.00%)	1 / 4 (25.00%)	0 / 6 (0.00%)
occurrences (all)	1	1	0
Chills			
subjects affected / exposed	0 / 10 (0.00%)	0 / 4 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Discomfort			
subjects affected / exposed	0 / 10 (0.00%)	0 / 4 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Fatigue			
subjects affected / exposed	4 / 10 (40.00%)	0 / 4 (0.00%)	3 / 6 (50.00%)
occurrences (all)	6	0	4
Mucosal haemorrhage			
subjects affected / exposed	0 / 10 (0.00%)	0 / 4 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Non-cardiac chest pain			
subjects affected / exposed	0 / 10 (0.00%)	1 / 4 (25.00%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Oedema peripheral			
subjects affected / exposed	0 / 10 (0.00%)	0 / 4 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Pain			
subjects affected / exposed	0 / 10 (0.00%)	1 / 4 (25.00%)	0 / 6 (0.00%)
occurrences (all)	0	2	0
Pyrexia			

subjects affected / exposed	0 / 10 (0.00%)	1 / 4 (25.00%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Xerosis			
subjects affected / exposed	0 / 10 (0.00%)	1 / 4 (25.00%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Reproductive system and breast disorders			
Pelvic pain			
subjects affected / exposed	0 / 10 (0.00%)	0 / 4 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	2 / 10 (20.00%)	1 / 4 (25.00%)	1 / 6 (16.67%)
occurrences (all)	2	1	1
Dyspnoea			
subjects affected / exposed	1 / 10 (10.00%)	2 / 4 (50.00%)	1 / 6 (16.67%)
occurrences (all)	1	2	1
Dyspnoea exertional			
subjects affected / exposed	0 / 10 (0.00%)	0 / 4 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Epistaxis			
subjects affected / exposed	2 / 10 (20.00%)	0 / 4 (0.00%)	0 / 6 (0.00%)
occurrences (all)	3	0	0
Nasal congestion			
subjects affected / exposed	0 / 10 (0.00%)	0 / 4 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Pleural effusion			
subjects affected / exposed	1 / 10 (10.00%)	0 / 4 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Pleuritic pain			
subjects affected / exposed	0 / 10 (0.00%)	0 / 4 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Psychiatric disorders			
Anxiety			
subjects affected / exposed	1 / 10 (10.00%)	1 / 4 (25.00%)	0 / 6 (0.00%)
occurrences (all)	1	1	0
Depression			

subjects affected / exposed	0 / 10 (0.00%)	0 / 4 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Insomnia			
subjects affected / exposed	0 / 10 (0.00%)	0 / 4 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 10 (10.00%)	0 / 4 (0.00%)	1 / 6 (16.67%)
occurrences (all)	1	0	1
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 10 (10.00%)	0 / 4 (0.00%)	1 / 6 (16.67%)
occurrences (all)	2	0	1
Blood creatine phosphokinase increased			
subjects affected / exposed	0 / 10 (0.00%)	1 / 4 (25.00%)	1 / 6 (16.67%)
occurrences (all)	0	1	1
Blood creatinine increased			
subjects affected / exposed	2 / 10 (20.00%)	0 / 4 (0.00%)	2 / 6 (33.33%)
occurrences (all)	2	0	3
Blood sodium decreased			
subjects affected / exposed	1 / 10 (10.00%)	0 / 4 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
C-reactive protein increased			
subjects affected / exposed	1 / 10 (10.00%)	0 / 4 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Electrocardiogram QT prolonged			
subjects affected / exposed	1 / 10 (10.00%)	0 / 4 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Lipase increased			
subjects affected / exposed	0 / 10 (0.00%)	0 / 4 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Lymphocyte count decreased			
subjects affected / exposed	0 / 10 (0.00%)	0 / 4 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Weight decreased			

subjects affected / exposed	2 / 10 (20.00%)	0 / 4 (0.00%)	2 / 6 (33.33%)
occurrences (all)	2	0	3
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	0 / 10 (0.00%)	0 / 4 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Fall			
subjects affected / exposed	0 / 10 (0.00%)	0 / 4 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Laceration			
subjects affected / exposed	0 / 10 (0.00%)	0 / 4 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Post procedural haematoma			
subjects affected / exposed	0 / 10 (0.00%)	0 / 4 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Tooth fracture			
subjects affected / exposed	0 / 10 (0.00%)	0 / 4 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Wrist fracture			
subjects affected / exposed	0 / 10 (0.00%)	0 / 4 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Cardiac disorders			
Sinus tachycardia			
subjects affected / exposed	0 / 10 (0.00%)	0 / 4 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Tachycardia			
subjects affected / exposed	0 / 10 (0.00%)	0 / 4 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Nervous system disorders			
Ageusia			
subjects affected / exposed	0 / 10 (0.00%)	0 / 4 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Dizziness			
subjects affected / exposed	0 / 10 (0.00%)	0 / 4 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Dysgeusia			

subjects affected / exposed	1 / 10 (10.00%)	1 / 4 (25.00%)	2 / 6 (33.33%)
occurrences (all)	1	1	4
Headache			
subjects affected / exposed	3 / 10 (30.00%)	0 / 4 (0.00%)	3 / 6 (50.00%)
occurrences (all)	4	0	5
Hypotonia			
subjects affected / exposed	0 / 10 (0.00%)	0 / 4 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Myoclonus			
subjects affected / exposed	1 / 10 (10.00%)	0 / 4 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Presyncope			
subjects affected / exposed	1 / 10 (10.00%)	0 / 4 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Sciatica			
subjects affected / exposed	1 / 10 (10.00%)	0 / 4 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Somnolence			
subjects affected / exposed	0 / 10 (0.00%)	0 / 4 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Syncope			
subjects affected / exposed	2 / 10 (20.00%)	0 / 4 (0.00%)	0 / 6 (0.00%)
occurrences (all)	2	0	0
Tremor			
subjects affected / exposed	0 / 10 (0.00%)	0 / 4 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Visual field defect			
subjects affected / exposed	0 / 10 (0.00%)	1 / 4 (25.00%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	4 / 10 (40.00%)	0 / 4 (0.00%)	3 / 6 (50.00%)
occurrences (all)	8	0	4
Gastrointestinal melanoma			
subjects affected / exposed	1 / 10 (10.00%)	0 / 4 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0

Lymphopenia			
subjects affected / exposed	1 / 10 (10.00%)	0 / 4 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Neutropenia			
subjects affected / exposed	0 / 10 (0.00%)	1 / 4 (25.00%)	1 / 6 (16.67%)
occurrences (all)	0	2	1
Neutrophilia			
subjects affected / exposed	1 / 10 (10.00%)	0 / 4 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Thrombocytopenia			
subjects affected / exposed	6 / 10 (60.00%)	0 / 4 (0.00%)	6 / 6 (100.00%)
occurrences (all)	14	0	11
Tumour pain			
subjects affected / exposed	1 / 10 (10.00%)	0 / 4 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Ear and labyrinth disorders			
Ear discomfort			
subjects affected / exposed	0 / 10 (0.00%)	1 / 4 (25.00%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Vertigo			
subjects affected / exposed	1 / 10 (10.00%)	0 / 4 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Eye disorders			
Dry eye			
subjects affected / exposed	1 / 10 (10.00%)	0 / 4 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Eye pain			
subjects affected / exposed	0 / 10 (0.00%)	0 / 4 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Eye swelling			
subjects affected / exposed	0 / 10 (0.00%)	0 / 4 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Ocular hyperaemia			
subjects affected / exposed	0 / 10 (0.00%)	0 / 4 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Optic nerve disorder			

subjects affected / exposed	0 / 10 (0.00%)	1 / 4 (25.00%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Vision blurred			
subjects affected / exposed	0 / 10 (0.00%)	1 / 4 (25.00%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	0 / 10 (0.00%)	0 / 4 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Abdominal pain			
subjects affected / exposed	3 / 10 (30.00%)	0 / 4 (0.00%)	0 / 6 (0.00%)
occurrences (all)	3	0	0
Abdominal pain lower			
subjects affected / exposed	0 / 10 (0.00%)	0 / 4 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Abdominal pain upper			
subjects affected / exposed	1 / 10 (10.00%)	0 / 4 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Aptyalism			
subjects affected / exposed	1 / 10 (10.00%)	0 / 4 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Constipation			
subjects affected / exposed	1 / 10 (10.00%)	0 / 4 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Diarrhoea			
subjects affected / exposed	3 / 10 (30.00%)	1 / 4 (25.00%)	4 / 6 (66.67%)
occurrences (all)	3	1	6
Dry mouth			
subjects affected / exposed	1 / 10 (10.00%)	0 / 4 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Dysphagia			
subjects affected / exposed	0 / 10 (0.00%)	1 / 4 (25.00%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Gastritis			
subjects affected / exposed	1 / 10 (10.00%)	0 / 4 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0

Gastrooesophageal reflux disease			
subjects affected / exposed	2 / 10 (20.00%)	0 / 4 (0.00%)	1 / 6 (16.67%)
occurrences (all)	2	0	1
Gingival bleeding			
subjects affected / exposed	1 / 10 (10.00%)	0 / 4 (0.00%)	0 / 6 (0.00%)
occurrences (all)	2	0	0
Large intestinal haemorrhage			
subjects affected / exposed	1 / 10 (10.00%)	0 / 4 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Nausea			
subjects affected / exposed	7 / 10 (70.00%)	4 / 4 (100.00%)	4 / 6 (66.67%)
occurrences (all)	9	4	7
Vomiting			
subjects affected / exposed	4 / 10 (40.00%)	1 / 4 (25.00%)	1 / 6 (16.67%)
occurrences (all)	4	1	1
Hepatobiliary disorders			
Hyperbilirubinaemia			
subjects affected / exposed	1 / 10 (10.00%)	0 / 4 (0.00%)	1 / 6 (16.67%)
occurrences (all)	1	0	1
Skin and subcutaneous tissue disorders			
Dry skin			
subjects affected / exposed	0 / 10 (0.00%)	0 / 4 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Hyperhidrosis			
subjects affected / exposed	0 / 10 (0.00%)	0 / 4 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Night sweats			
subjects affected / exposed	0 / 10 (0.00%)	0 / 4 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Rash			
subjects affected / exposed	2 / 10 (20.00%)	0 / 4 (0.00%)	0 / 6 (0.00%)
occurrences (all)	2	0	0
Rash erythematous			
subjects affected / exposed	0 / 10 (0.00%)	0 / 4 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Skin lesion			

subjects affected / exposed	0 / 10 (0.00%)	0 / 4 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Solar dermatitis			
subjects affected / exposed	0 / 10 (0.00%)	0 / 4 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Renal and urinary disorders			
Pollakiuria			
subjects affected / exposed	2 / 10 (20.00%)	0 / 4 (0.00%)	0 / 6 (0.00%)
occurrences (all)	2	0	0
Urinary retention			
subjects affected / exposed	0 / 10 (0.00%)	0 / 4 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 10 (0.00%)	2 / 4 (50.00%)	2 / 6 (33.33%)
occurrences (all)	0	2	2
Flank pain			
subjects affected / exposed	0 / 10 (0.00%)	0 / 4 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Intervertebral disc protrusion			
subjects affected / exposed	1 / 10 (10.00%)	0 / 4 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Joint stiffness			
subjects affected / exposed	0 / 10 (0.00%)	0 / 4 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Muscle contracture			
subjects affected / exposed	0 / 10 (0.00%)	0 / 4 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Muscle spasms			
subjects affected / exposed	1 / 10 (10.00%)	0 / 4 (0.00%)	0 / 6 (0.00%)
occurrences (all)	2	0	0
Musculoskeletal pain			
subjects affected / exposed	0 / 10 (0.00%)	0 / 4 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Myalgia			

subjects affected / exposed	1 / 10 (10.00%)	0 / 4 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Neck pain			
subjects affected / exposed	0 / 10 (0.00%)	0 / 4 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Osteoarthritis			
subjects affected / exposed	0 / 10 (0.00%)	0 / 4 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Pain in extremity			
subjects affected / exposed	1 / 10 (10.00%)	0 / 4 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Trismus			
subjects affected / exposed	1 / 10 (10.00%)	0 / 4 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Infections and infestations			
Abdominal infection			
subjects affected / exposed	0 / 10 (0.00%)	0 / 4 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Bronchitis			
subjects affected / exposed	1 / 10 (10.00%)	0 / 4 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Conjunctivitis			
subjects affected / exposed	1 / 10 (10.00%)	0 / 4 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Infection			
subjects affected / exposed	1 / 10 (10.00%)	0 / 4 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Influenza			
subjects affected / exposed	0 / 10 (0.00%)	0 / 4 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Periodontitis			
subjects affected / exposed	0 / 10 (0.00%)	0 / 4 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Respiratory tract infection			
subjects affected / exposed	0 / 10 (0.00%)	1 / 4 (25.00%)	0 / 6 (0.00%)
occurrences (all)	0	1	0

Rhinitis			
subjects affected / exposed	1 / 10 (10.00%)	0 / 4 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Upper respiratory tract infection			
subjects affected / exposed	0 / 10 (0.00%)	0 / 4 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Urinary tract infection			
subjects affected / exposed	0 / 10 (0.00%)	0 / 4 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	3 / 10 (30.00%)	1 / 4 (25.00%)	4 / 6 (66.67%)
occurrences (all)	3	1	7
Hypoalbuminaemia			
subjects affected / exposed	1 / 10 (10.00%)	0 / 4 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Hypokalaemia			
subjects affected / exposed	4 / 10 (40.00%)	0 / 4 (0.00%)	2 / 6 (33.33%)
occurrences (all)	6	0	3
Hypomagnesaemia			
subjects affected / exposed	1 / 10 (10.00%)	0 / 4 (0.00%)	2 / 6 (33.33%)
occurrences (all)	1	0	3
Hyponatraemia			
subjects affected / exposed	2 / 10 (20.00%)	0 / 4 (0.00%)	1 / 6 (16.67%)
occurrences (all)	2	0	1
Hypophosphataemia			
subjects affected / exposed	1 / 10 (10.00%)	0 / 4 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
17 February 2017	Evaluation of the effect of food on bioavailability of ODM-207 was added to the secondary objectives. 15 mg ODM-207 tablet was added for dose adjustment purpose. It was made possible to report the SAEs electronically in the EDC system. Minor adjustments in timings and instructions for assessments.
15 May 2017	Exclusion criterion 4 was modified to allow that 1 of the 3 measurements of BP is above the defined upper limit of eligibility as BP is known to fluctuate significantly within a short period of time. Exclusion criterion 5 was modified to allow concomitant use of fulvestrant if it's use had been started before the first dose of study treatment and the treatment related AEs were resolved to at least grade 1. Washout period of anticancer therapy in exclusion criterion 5 was reduced from 5 to 4 half-lives to shorten the period the patient needed to be without antineoplastic treatment.
27 October 2017	Flat dosing (mg) was changed to individual dosing (mg/kg). The lower age limit for eligible patients in Part 1B and Part 2 was reduced from 18 to 15 years in inclusion criterion 2. A 72-h PK cohort was added to Part 1B to study PK elimination. Patients were allowed to continue treatment with ODM-207 as long as it was considered benefical to the patient (as judged by the investigator) instead of until disease progression. A time window (within 4 weeks before the first dose of study treatment) for the requirement to have testosterone level < 50 mg/ml was added to inclusion criterion 12. The QTcF interval of 450 ms was changed to 470 ms in exclusion criterion 4. The list of drugs that cause QT prolongation or Torsades des Pointes was changed to an online 'QTDrugs list' in exclusion criterion 4. Prior exposure to BET inhibitors was modified in exclusion criterion 16 to allow patients with prior exposure to BET inhibitors to be considered eligible if they were considered to have a significantly greater likelihood of responding to ODM-207. Exclusion criterion 17 was added to exclude patients with glioma who had received radiotherapy or chemoradio therapy within the last 3 months before the first dose of study treatment or had a history of glioma-related bleeding as detected by MRI. The duration of ODM-207 treatment at the same dose level was changed to last for at least 8 weeks instead of until disease progression. New PK blood sampling timepoints were added to evaluate the long-term exposure and to follow-up compliance. A possibility to collect additional PK blood samples was added for patients who interrupted the ODM-207 treatment. It was possible to collect additional tumour samples if this was part of the clinical management of the patient.
12 February 2018	Eligibility criteria for patients with glioma were modified in inclusion criterion 6, removing restrictions on subtypes of the disease and providing more accurate definition of eligible patients' status and history of response. Exclusion criterion 17 for patients with glioma was modified to exclude patients with a more resistant disease who were less likely to respond with treatment. Modifications to schedules of ECG, PK sample and tumour biopsy.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported