Clinical trial results:
An Open-Label, Multicenter, Phase 1/2 Study of Poly(ADP-Ribose) Polymerase (PARP) Inhibitor E7449 as Single Agent in Subjects With Advanced Solid Tumours or With B-cell Malignancies and in Combination With Temozolomide(TMZ) or With Carboplatin and Paclitaxel in Subjects With Advanced Solid Tumors

Summary

EudraCT number	2011-001959-37
Trial protocol	GB
Global end of trial date	14 July 2015

Results information

Result version number	v1 (current)
This version publication date	23 May 2019
First version publication date	23 May 2019

Trial information

Trial identification

Sponsor protocol code	E7449-E044-101

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01618136
WHO universal trial number (UTN)	-
Other trial identifiers	PACT: E7449

Notes:

Sponsors

Sponsor organisation name	Eisai Ltd, European Knowledge Centre, Mosquito Way
Sponsor organisation address	AL10 9SN, Hatfield, Hertfordshire, United Kingdom,
Public contact	Medical Information, Eisai Limited, +44 2086001400, eumedinfo@eisai.net
Scientific contact	Medical Information, Eisai Limited, +44 2086001400, eumedinfo@eisai.net

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	14 July 2015
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	14 July 2015
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The Primary objective of the trial was to determine maximum tolerated dose (MTD) as single agent, administered once daily (QD) continuously in 28-day cycles in subjects with advanced solid tumors or B-cell lymphoma.

Protection of trial subjects:

This study was conducted in accordance with standard operating procedures (SOPs) of the sponsor (or designee), which are designed to ensure adherence to Good Clinical Practice (GCP) guidelines as required by the following:
- Principles of the World Medical Association Declaration of Helsinki (World Medical Association, 2008)
- International Council on Harmonisation (ICH) E6 Guideline for GCP (CPMP/ICH/135/95) of the European Agency for the Evaluation of Medicinal Products, Committee for Proprietary Medicinal Products, International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
- Title 21 of the United States (US) Code of Federal Regulations (US 21 CFR) regarding clinical studies, including Part 50 and Part 56 concerning informed subject consent and Institutional Review Board (IRB) regulations and applicable sections of US 21 CFR Part 312
- European Good Clinical Practice Directive 2005/28/EC and Clinical Trial Directive 2001/20/EC for studies conducted within any European Union (EU) country. All suspected unexpected serious adverse reactions were reported, as required, to the Competent Authorities of all involved EU member states.
- Article 14, Paragraph 3, and Article 80-2 of the Pharmaceutical Affairs Law (Law No. 145, 1960) for studies conducted in Japan, in addition to Japan’s GCP Subject Information and Informed Consent.

Background therapy: -
Evidence for comparator: -

Actual start date of recruitment	31 January 2012
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: 41
Worldwide total number of subjects	41
EEA total number of subjects	41

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)	20
From 65 to 84 years	21
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Enrollment to the study was stopped after Phase 1 single agent arm was completed and the Phase 1 combination arms and the Phase 2 part of the study were cancelled.

Pre-assignment

Screening details:

Extension Phase: of the 33 participants who completed the Treatment Phase, 32 entered the Extension Phase. Of these 32 participants; 27 discontinued due to disease progression (defined as treatment completion) and 5 discontinued due to; choice, withdrew consent, adverse event, physician choice, and biopsy procedure not done due to comorbidities.

Period 1

Period 1 title	Treatment Phase
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	50 mg E7449

Arm description:

E7449 (50 mg) was administered orally once on Day 2 in the single-dose pharmacokinetic (PK) period (dose escalation cohorts only) and once a day (QD) continuously starting on Cycle 1 Day 1 in 28-day treatment cycles until disease progression, development of unacceptable toxicity, or withdrawal of consent. E7449 had to be taken at least 2 hours before or 2 hours after food. Dose interruption, dose reduction, or treatment discontinuation was applied for participants who experienced E7449-related toxicity in accordance with protocol-specified instructions.

Arm type	Experimental
Investigational medicinal product name	Poly(ADP-Ribose) Polymerase (PARP) Inhibitor
Investigational medicinal product code	E7449
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

E7449 50 mg was administered as oral Capsule taken at least 2 hours before or 2 hours after food.

Arm title	100 mg E7449

Arm description:

E7449 (100 mg) was administered orally once on Day 2 in the single-dose PK period (dose escalation cohorts only) and QD continuously starting on Cycle 1 Day 1 in 28-day treatment cycles until disease progression, development of unacceptable toxicity, or withdrawal of consent. E7449 had to be taken at least 2 hours before or 2 hours after food. Dose interruption, dose reduction, or treatment discontinuation was applied for participants who experienced E7449-related toxicity in accordance with protocol-specified instructions.

Arm type	Experimental
Investigational medicinal product name	Poly(ADP-Ribose) Polymerase (PARP) Inhibitor
Investigational medicinal product code	E7449
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

E7449 100 mg was administered as oral Capsule taken at least 2 hours before or 2 hours after food.

Arm title	200 mg E7449

Arm description:

E7449 (200 mg) was administered orally once on Day 2 in the single-dose PK period (dose escalation cohorts only) and QD continuously starting on Cycle 1 Day 1 in 28-day treatment cycles until disease progression, development of unacceptable toxicity, or withdrawal of consent. E7449 had to be taken at least 2 hours before or 2 hours after food. Dose interruption, dose reduction, or treatment discontinuation was applied for participants who experienced E7449-related toxicity in accordance with protocol-specified instructions.

Arm type	Single agent
Investigational medicinal product name	Poly(ADP-Ribose) Polymerase (PARP) Inhibitor
Investigational medicinal product code	E7449
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

E7449 200 mg was administered as oral Capsule taken at least 2 hours before or 2 hours after food.

Arm title	400 mg E7449

Arm description:

E7449 (400 mg) was administered orally once on Day 2 in the single-dose PK period (dose escalation cohorts only) and QD continuously starting on Cycle 1 Day 1 in 28-day treatment cycles until disease progression, development of unacceptable toxicity, or withdrawal of consent. E7449 inhibitor had to be taken at least 2 hours before or 2 hours after food. Dose interruption, dose reduction, or treatment discontinuation was applied for participants who experienced E7449-related toxicity in accordance with protocol-specified instructions.

Arm type	Single agent
Investigational medicinal product name	Poly(ADP-Ribose) Polymerase (PARP) Inhibitor
Investigational medicinal product code	E7449
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

E7449 400 mg was administered as oral Capsule taken at least 2 hours before or 2 hours after food.

Arm title	600 mg E7449 Overall

Arm description:

E7449 (600 mg) was administered orally once on Day 2 in the single-dose PK period (dose escalation cohorts only) and QD continuously starting on Cycle 1 Day 1 in 28-day treatment cycles until disease progression, development of unacceptable toxicity, or withdrawal of consent. E7449 had to be taken at least 2 hours before or 2 hours after food. Also, participants in the MTD expansion cohort were randomized to receive E7449 either with or without food after an overnight fast on Cycle 1 Day 7. Participants randomized to fed condition received E7449 immediately after consuming a high fat breakfast. On Cycle 1 Day 15, participants crossed over to the other food regimen, according to the randomization scheme (with or without food). Dose interruption, dose reduction, or treatment discontinuation was applied for participants who experienced E7449-related toxicity in accordance with protocol-specified instructions.

Arm type	Single agent
Investigational medicinal product name	Poly(ADP-Ribose) Polymerase (PARP) Inhibitor
Investigational medicinal product code	E7449
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

E7449 600 mg was administered as oral Capsule taken at least 2 hours before or 2 hours after food.

Arm title	800 mg E7449

Arm description:

E7449 (800 mg) was administered orally once on Day 2 in the single-dose PK period (dose escalation cohorts only) and QD continuously starting on Cycle 1 Day 1 in 28-day treatment cycles until disease progression, development of unacceptable toxicity, or withdrawal of consent. E7449 had to be taken at least 2 hours before or 2 hours after food. Dose interruption, dose reduction, or treatment

discontinuation was applied for participants who experienced E7449-related toxicity in accordance with protocol-specified instructions.

Arm type	Single agent
Investigational medicinal product name	Poly(ADP-Ribose) Polymerase (PARP) Inhibitor
Investigational medicinal product code	E7449
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

E7449 800 mg was administered as oral Capsule taken at least 2 hours before or 2 hours after food.

Number of subjects in period 1	50 mg E7449	100 mg E7449	200 mg E7449
Started	3	3	4
Completed	3	3	4
Not completed	0	0	0
Participant choice	-	-	-
Consent withdrawn by subject	-	-	-
Adverse event, non-fatal	-	-	-
Not specified	-	-	-
Lost to follow-up	-	-	-

Number of subjects in period 1	400 mg E7449	600 mg E7449 Overall	800 mg E7449
Started	4	21	6
Completed	3	15	5
Not completed	1	6	1
Participant choice	-	2	-
Consent withdrawn by subject	-	1	-
Adverse event, non-fatal	-	1	-
Not specified	-	2	1
Lost to follow-up	1	-	-

Period 2

Period 2 title	Extension Phase
Is this the baseline period?	No
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes

Arm title	50 mg E7449

Arm description:

E7449 (50 mg) was administered orally once on Day 2 in the single-dose pharmacokinetic (PK) period (dose escalation cohorts only) and once a day (QD) continuously starting on Cycle 1 Day 1 in 28-day treatment cycles until disease progression, development of unacceptable toxicity, or withdrawal of consent. E7449 had to be taken at least 2 hours before or 2 hours after food. Dose interruption, dose reduction, or treatment discontinuation was applied for participants who experienced E7449-related toxicity in accordance with protocol-specified instructions.

Arm type	Experimental
Investigational medicinal product name	Poly(ADP-Ribose) Polymerase (PARP) Inhibitor
Investigational medicinal product code	E7449
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

E7449 50 mg was administered as oral Capsule taken at least 2 hours before or 2 hours after food.

Arm title	100 mg E7449

Arm description:

E7449 (100 mg) was administered orally once on Day 2 in the single-dose PK period (dose escalation cohorts only) and QD continuously starting on Cycle 1 Day 1 in 28-day treatment cycles until disease progression, development of unacceptable toxicity, or withdrawal of consent. E7449 had to be taken at least 2 hours before or 2 hours after food. Dose interruption, dose reduction, or treatment discontinuation was applied for participants who experienced E7449-related toxicity in accordance with protocol-specified instructions.

Arm type	Experimental
Investigational medicinal product name	Poly(ADP-Ribose) Polymerase (PARP) Inhibitor
Investigational medicinal product code	E7449
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

E7449 100 mg was administered as oral Capsule taken at least 2 hours before or 2 hours after food.

Arm title	200 mg E7449

Arm description:

E7449 (200 mg) was administered orally once on Day 2 in the single-dose PK period (dose escalation cohorts only) and QD continuously starting on Cycle 1 Day 1 in 28-day treatment cycles until disease progression, development of unacceptable toxicity, or withdrawal of consent. E7449 had to be taken at least 2 hours before or 2 hours after food. Dose interruption, dose reduction, or treatment discontinuation was applied for participants who experienced E7449-related toxicity in accordance with protocol-specified instructions.

Arm type	Single agent
Investigational medicinal product name	Poly(ADP-Ribose) Polymerase (PARP) Inhibitor
Investigational medicinal product code	E7449
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

E7449 200 mg was administered as oral Capsule taken at least 2 hours before or 2 hours after food.

Arm title	400 mg E7449

Arm description:

E7449 (400 mg) was administered orally once on Day 2 in the single-dose PK period (dose escalation cohorts only) and QD continuously starting on Cycle 1 Day 1 in 28-day treatment cycles until disease progression, development of unacceptable toxicity, or withdrawal of consent. E7449 inhibitor had to be taken at least 2 hours before or 2 hours after food. Dose interruption, dose reduction, or treatment discontinuation was applied for participants who experienced E7449-related toxicity in accordance with protocol-specified instructions.

Arm type	Single agent
Investigational medicinal product name	Poly(ADP-Ribose) Polymerase (PARP) Inhibitor
Investigational medicinal product code	E7449
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

E7449 400 mg was administered as oral Capsule taken at least 2 hours before or 2 hours after food.

Arm title	600 mg E7449 Overall

Arm description:

E7449 (600 mg) was administered orally once on Day 2 in the single-dose PK period (dose escalation cohorts only) and QD continuously starting on Cycle 1 Day 1 in 28-day treatment cycles until disease progression, development of unacceptable toxicity, or withdrawal of consent. E7449 had to be taken at least 2 hours before or 2 hours after food. Also, participants in the MTD expansion cohort were randomized to receive E7449 either with or without food after an overnight fast on Cycle 1 Day 7. Participants randomized to fed condition received E7449 immediately after consuming a high fat breakfast. On Cycle 1 Day 15, participants crossed over to the other food regimen, according to the randomization scheme (with or without food). Dose interruption, dose reduction, or treatment discontinuation was applied for participants who experienced E7449-related toxicity in accordance with protocol-specified instructions.

Arm type	Single agent
Investigational medicinal product name	Poly(ADP-Ribose) Polymerase (PARP) Inhibitor
Investigational medicinal product code	E7449
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

E7449 600 mg was administered as oral Capsule taken at least 2 hours before or 2 hours after food.

Arm title	800 mg E7449

Arm description:

E7449 (800 mg) was administered orally once on Day 2 in the single-dose PK period (dose escalation cohorts only) and QD continuously starting on Cycle 1 Day 1 in 28-day treatment cycles until disease progression, development of unacceptable toxicity, or withdrawal of consent. E7449 had to be taken at least 2 hours before or 2 hours after food. Dose interruption, dose reduction, or treatment discontinuation was applied for participants who experienced E7449-related toxicity in accordance with protocol-specified instructions.

Arm type	Single agent
Investigational medicinal product name	Poly(ADP-Ribose) Polymerase (PARP) Inhibitor
Investigational medicinal product code	E7449
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

E7449 800 mg was administered as oral Capsule taken at least 2 hours before or 2 hours after food.

Number of subjects in period 2[1]	50 mg E7449	100 mg E7449	200 mg E7449
Started	3	3	4
Completed	2	3	4
Not completed	1	0	0
withdrawal of consent from study	-	-	-

Adverse event, non-fatal	-	-	-
Other	1	-	-
Subject choice	-	-	-

Number of subjects in period 2[1]	400 mg E7449	600 mg E7449 Overall	800 mg E7449
Started	3	14	5
Completed	3	11	4
Not completed	0	3	1
withdrawal of consent from study	-	-	1
Adverse event, non-fatal	-	1	-
Other	-	1	-
Subject choice	-	1	-

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: Not all subjects who completed treatment period in 600 mg E7449 overall arm entered in the extension phase.

Baseline characteristics

Reporting groups

Reporting group title	50 mg E7449

Reporting group description:

E7449 (50 mg) was administered orally once on Day 2 in the single-dose pharmacokinetic (PK) period (dose escalation cohorts only) and once a day (QD) continuously starting on Cycle 1 Day 1 in 28-day treatment cycles until disease progression, development of unacceptable toxicity, or withdrawal of consent. E7449 had to be taken at least 2 hours before or 2 hours after food. Dose interruption, dose reduction, or treatment discontinuation was applied for participants who experienced E7449-related toxicity in accordance with protocol-specified instructions.

Reporting group title	100 mg E7449

Reporting group description:

E7449 (100 mg) was administered orally once on Day 2 in the single-dose PK period (dose escalation cohorts only) and QD continuously starting on Cycle 1 Day 1 in 28-day treatment cycles until disease progression, development of unacceptable toxicity, or withdrawal of consent. E7449 had to be taken at least 2 hours before or 2 hours after food. Dose interruption, dose reduction, or treatment discontinuation was applied for participants who experienced E7449-related toxicity in accordance with protocol-specified instructions.

Reporting group title	200 mg E7449

Reporting group description:

E7449 (200 mg) was administered orally once on Day 2 in the single-dose PK period (dose escalation cohorts only) and QD continuously starting on Cycle 1 Day 1 in 28-day treatment cycles until disease progression, development of unacceptable toxicity, or withdrawal of consent. E7449 had to be taken at least 2 hours before or 2 hours after food. Dose interruption, dose reduction, or treatment discontinuation was applied for participants who experienced E7449-related toxicity in accordance with protocol-specified instructions.

Reporting group title	400 mg E7449

Reporting group description:

E7449 (400 mg) was administered orally once on Day 2 in the single-dose PK period (dose escalation cohorts only) and QD continuously starting on Cycle 1 Day 1 in 28-day treatment cycles until disease progression, development of unacceptable toxicity, or withdrawal of consent. E7449 inhibitor had to be taken at least 2 hours before or 2 hours after food. Dose interruption, dose reduction, or treatment discontinuation was applied for participants who experienced E7449-related toxicity in accordance with protocol-specified instructions.

Reporting group title	600 mg E7449 Overall

Reporting group description:

E7449 (600 mg) was administered orally once on Day 2 in the single-dose PK period (dose escalation cohorts only) and QD continuously starting on Cycle 1 Day 1 in 28-day treatment cycles until disease progression, development of unacceptable toxicity, or withdrawal of consent. E7449 had to be taken at least 2 hours before or 2 hours after food. Also, participants in the MTD expansion cohort were randomized to receive E7449 either with or without food after an overnight fast on Cycle 1 Day 7. Participants randomized to fed condition received E7449 immediately after consuming a high fat breakfast. On Cycle 1 Day 15, participants crossed over to the other food regimen, according to the randomization scheme (with or without food). Dose interruption, dose reduction, or treatment discontinuation was applied for participants who experienced E7449-related toxicity in accordance with protocol-specified instructions.

Reporting group title	800 mg E7449

Reporting group description:

E7449 (800 mg) was administered orally once on Day 2 in the single-dose PK period (dose escalation cohorts only) and QD continuously starting on Cycle 1 Day 1 in 28-day treatment cycles until disease progression, development of unacceptable toxicity, or withdrawal of consent. E7449 had to be taken at least 2 hours before or 2 hours after food. Dose interruption, dose reduction, or treatment discontinuation was applied for participants who experienced E7449-related toxicity in accordance with protocol-specified instructions.

Reporting group values	50 mg E7449	100 mg E7449	200 mg E7449
Number of subjects	3	3	4
Age categorical			
Units: Subjects			
In utero			
Preterm newborn infants (gestational age < 37 wks)			
Newborns (0-27 days)			
Infants and toddlers (28 days-23 months)			
Children (2-11 years)			
Adolescents (12-17 years)			
Adults (18-64 years)			
From 65-84 years			
85 years and over			
Age continuous			
Units: years			
arithmetic mean	62	64.3	56.8
standard deviation	± 11.36	± 11.06	± 14.2
Gender categorical			
Units: Subjects			
Female	1	1	2
Male	2	2	2
Race			
Units: Subjects			
White	3	3	4
Asian	0	0	0

Reporting group values	400 mg E7449	600 mg E7449 Overall	800 mg E7449
Number of subjects	4	21	6
Age categorical			
Units: Subjects			
In utero			
Preterm newborn infants (gestational age < 37 wks)			
Newborns (0-27 days)			
Infants and toddlers (28 days-23 months)			
Children (2-11 years)			
Adolescents (12-17 years)			
Adults (18-64 years)			
From 65-84 years			
85 years and over			
Age continuous			
Units: years			
arithmetic mean	58	60.7	61.2
standard deviation	± 22.67	± 9.5	± 15.66
Gender categorical			
Units: Subjects			
Female	2	10	3
Male	2	11	3

Race Units: Subjects			
White	4	21	5
Asian	0	0	1

Reporting group values	Total		
Number of subjects	41		
Age categorical Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	0		
Newborns (0-27 days)	0		
Infants and toddlers (28 days-23 months)	0		
Children (2-11 years)	0		
Adolescents (12-17 years)	0		
Adults (18-64 years)	0		
From 65-84 years	0		
85 years and over	0		
Age continuous Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical Units: Subjects			
Female	19		
Male	22		
Race Units: Subjects			
White	40		
Asian	1		

End points

End points reporting groups

Reporting group title	50 mg E7449

Reporting group description:

E7449 (50 mg) was administered orally once on Day 2 in the single-dose pharmacokinetic (PK) period (dose escalation cohorts only) and once a day (QD) continuously starting on Cycle 1 Day 1 in 28-day treatment cycles until disease progression, development of unacceptable toxicity, or withdrawal of consent. E7449 had to be taken at least 2 hours before or 2 hours after food. Dose interruption, dose reduction, or treatment discontinuation was applied for participants who experienced E7449-related toxicity in accordance with protocol-specified instructions.

Reporting group title	100 mg E7449

Reporting group description:

E7449 (100 mg) was administered orally once on Day 2 in the single-dose PK period (dose escalation cohorts only) and QD continuously starting on Cycle 1 Day 1 in 28-day treatment cycles until disease progression, development of unacceptable toxicity, or withdrawal of consent. E7449 had to be taken at least 2 hours before or 2 hours after food. Dose interruption, dose reduction, or treatment discontinuation was applied for participants who experienced E7449-related toxicity in accordance with protocol-specified instructions.

Reporting group title	200 mg E7449

Reporting group description:

E7449 (200 mg) was administered orally once on Day 2 in the single-dose PK period (dose escalation cohorts only) and QD continuously starting on Cycle 1 Day 1 in 28-day treatment cycles until disease progression, development of unacceptable toxicity, or withdrawal of consent. E7449 had to be taken at least 2 hours before or 2 hours after food. Dose interruption, dose reduction, or treatment discontinuation was applied for participants who experienced E7449-related toxicity in accordance with protocol-specified instructions.

Reporting group title	400 mg E7449

Reporting group description:

E7449 (400 mg) was administered orally once on Day 2 in the single-dose PK period (dose escalation cohorts only) and QD continuously starting on Cycle 1 Day 1 in 28-day treatment cycles until disease progression, development of unacceptable toxicity, or withdrawal of consent. E7449 inhibitor had to be taken at least 2 hours before or 2 hours after food. Dose interruption, dose reduction, or treatment discontinuation was applied for participants who experienced E7449-related toxicity in accordance with protocol-specified instructions.

Reporting group title	600 mg E7449 Overall

Reporting group description:

E7449 (600 mg) was administered orally once on Day 2 in the single-dose PK period (dose escalation cohorts only) and QD continuously starting on Cycle 1 Day 1 in 28-day treatment cycles until disease progression, development of unacceptable toxicity, or withdrawal of consent. E7449 had to be taken at least 2 hours before or 2 hours after food. Also, participants in the MTD expansion cohort were randomized to receive E7449 either with or without food after an overnight fast on Cycle 1 Day 7. Participants randomized to fed condition received E7449 immediately after consuming a high fat breakfast. On Cycle 1 Day 15, participants crossed over to the other food regimen, according to the randomization scheme (with or without food). Dose interruption, dose reduction, or treatment discontinuation was applied for participants who experienced E7449-related toxicity in accordance with protocol-specified instructions.

Reporting group title	800 mg E7449

Reporting group description:

E7449 (800 mg) was administered orally once on Day 2 in the single-dose PK period (dose escalation cohorts only) and QD continuously starting on Cycle 1 Day 1 in 28-day treatment cycles until disease progression, development of unacceptable toxicity, or withdrawal of consent. E7449 had to be taken at least 2 hours before or 2 hours after food. Dose interruption, dose reduction, or treatment discontinuation was applied for participants who experienced E7449-related toxicity in accordance with protocol-specified instructions.

Reporting group title	50 mg E7449

Reporting group description:

E7449 (50 mg) was administered orally once on Day 2 in the single-dose pharmacokinetic (PK) period (dose escalation cohorts only) and once a day (QD) continuously starting on Cycle 1 Day 1 in 28-day treatment cycles until disease progression, development of unacceptable toxicity, or withdrawal of consent. E7449 had to be taken at least 2 hours before or 2 hours after food. Dose interruption, dose

reduction, or treatment discontinuation was applied for participants who experienced E7449-related toxicity in accordance with protocol-specified instructions.

Reporting group title	100 mg E7449

Reporting group description:

E7449 (100 mg) was administered orally once on Day 2 in the single-dose PK period (dose escalation cohorts only) and QD continuously starting on Cycle 1 Day 1 in 28-day treatment cycles until disease progression, development of unacceptable toxicity, or withdrawal of consent. E7449 had to be taken at least 2 hours before or 2 hours after food. Dose interruption, dose reduction, or treatment discontinuation was applied for participants who experienced E7449-related toxicity in accordance with protocol-specified instructions.

Reporting group title	200 mg E7449

Reporting group description:

E7449 (200 mg) was administered orally once on Day 2 in the single-dose PK period (dose escalation cohorts only) and QD continuously starting on Cycle 1 Day 1 in 28-day treatment cycles until disease progression, development of unacceptable toxicity, or withdrawal of consent. E7449 had to be taken at least 2 hours before or 2 hours after food. Dose interruption, dose reduction, or treatment discontinuation was applied for participants who experienced E7449-related toxicity in accordance with protocol-specified instructions.

Reporting group title	400 mg E7449

Reporting group description:

E7449 (400 mg) was administered orally once on Day 2 in the single-dose PK period (dose escalation cohorts only) and QD continuously starting on Cycle 1 Day 1 in 28-day treatment cycles until disease progression, development of unacceptable toxicity, or withdrawal of consent. E7449 inhibitor had to be taken at least 2 hours before or 2 hours after food. Dose interruption, dose reduction, or treatment discontinuation was applied for participants who experienced E7449-related toxicity in accordance with protocol-specified instructions.

Reporting group title	600 mg E7449 Overall

Reporting group description:

E7449 (600 mg) was administered orally once on Day 2 in the single-dose PK period (dose escalation cohorts only) and QD continuously starting on Cycle 1 Day 1 in 28-day treatment cycles until disease progression, development of unacceptable toxicity, or withdrawal of consent. E7449 had to be taken at least 2 hours before or 2 hours after food. Also, participants in the MTD expansion cohort were randomized to receive E7449 either with or without food after an overnight fast on Cycle 1 Day 7. Participants randomized to fed condition received E7449 immediately after consuming a high fat breakfast. On Cycle 1 Day 15, participants crossed over to the other food regimen, according to the randomization scheme (with or without food). Dose interruption, dose reduction, or treatment discontinuation was applied for participants who experienced E7449-related toxicity in accordance with protocol-specified instructions.

Reporting group title	800 mg E7449

Reporting group description:

E7449 (800 mg) was administered orally once on Day 2 in the single-dose PK period (dose escalation cohorts only) and QD continuously starting on Cycle 1 Day 1 in 28-day treatment cycles until disease progression, development of unacceptable toxicity, or withdrawal of consent. E7449 had to be taken at least 2 hours before or 2 hours after food. Dose interruption, dose reduction, or treatment discontinuation was applied for participants who experienced E7449-related toxicity in accordance with protocol-specified instructions.

Subject analysis set title	E7449 (single agent)
Subject analysis set type	Intention-to-treat

Subject analysis set description:

During dose escalation, sequential cohorts of 3 to 6 participants (dose escalation cohorts) were administered increasing doses (starting at 50 mg) of E7449 orally, once daily in 28-day cycles to determine the MTD of E7449 as a single agent. Dose escalation proceeded in 100% increments (i.e. 100 mg, 200 mg, 400 mg, etc.) in subsequent cohorts unless 2 Grade 2 toxicities were assessed as related to the study drug. After which, dose escalation had to follow a modified scheme increasing in 50%, 33%, and 25% dose increments in subsequent cohorts.

Subject analysis set title	600 mg E7449 (Fed)
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants in the MTD expansion cohort were randomized to receive E7449 with food after an overnight fast on Cycle 1 Day 7. Participants randomized to fed condition received PARP immediately after consuming a high fat breakfast. On Cycle 1 Day 15, participants crossed over to the other food regimen, according to the randomization scheme (with food).

Subject analysis set title	600 mg E7449 (Fasted)
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants in the MTD expansion cohort were randomized to receive E7449 without food after an overnight fast on Cycle 1 Day 7. On Cycle 1 Day 15, participants crossed over to the other food regimen, according to the randomization scheme (without food).

Primary: Phase 1: Maximum Tolerated Dose (MTD) and Recommended Phase 2 (RP2) Dose of E7449 when Administered as a Single Agent

End point title	Phase 1: Maximum Tolerated Dose (MTD) and Recommended Phase 2 (RP2) Dose of E7449 when Administered as a Single Agent[1]

End point description:

The MTD was defined as the highest dose level at which no more than 1 out of 6 participants experienced dose-limiting toxicity (DLT). A DLT was assessed according to the Common Terminology Criteria for Adverse Events (CTCAE v4.03): Any Grade 4 neutropenia for >=7 days or Grade 3 neutropenia with fever; Grade 4 thrombocytopenia or Grade 3 thrombocytopenia with bleeding or lasting >7 days. Grade 3 fatigue, or a 2 point decline in Eastern Cooperative Oncology Group (ECOG) performance status that persists for >7days; Nausea, vomiting or diarrhea that persists at Grade 3 or 4 despite maximal medical therapy; Any Grade 3 or higher non-hematological laboratory abnormalities that require hospitalization. The RP2 dose was the same as the confirmed MTD and was to be used for the Phase 2 part of this study, however enrollment was stopped after Phase 1 was completed and the Phase 2 part of the study was cancelled.

End point type	Primary

End point timeframe:

First dose of study drug (Day -2) to end of first 4 weeks of therapy (Cycle 1) (1 cycle = 28 days)

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: Only descriptive analysis was planned to be reported for this outcome measure.

End point values	E7449 (single agent)			
Subject group type	Subject analysis set			
Number of subjects analysed	41[2]			
Units: milligrams				
number (not applicable)	600			

Notes:

[2] - Total participants treated in Arm 1 including all dose escalation cohorts and MTD expansion cohort.

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 1: Number of Participants with DLT

End point title	Phase 1: Number of Participants with DLT

End point description:

A DLT was assessed according to the CTCAE v4.03: Any Grade 4 neutropenia for >=7 days or Grade 3 neutropenia with fever; Grade 4 thrombocytopenia or Grade 3 thrombocytopenia with bleeding or lasting >7 days; Grade 3 fatigue, or a 2 point decline in ECOG performance status that persists for >7days; Nausea, vomiting or diarrhea that persists at Grade 3 or 4 despite maximal medical therapy; Any Grade 3 or higher non-hematological laboratory abnormalities that require hospitalization. DLT was assessed during the first 4 weeks of therapy (Cycle 1) for dose escalation purposes. Participants who failed to take at least 75% of the daily doses of E7449 during Cycle 1 (first 4 weeks of treatment), for reasons not related to toxicity, were not evaluable for DLTs and were replaced by a new participant in the same dose group.

End point type	Secondary

End point timeframe:

First dose of study drug (Day -2) to end of first 4 weeks of therapy (Cycle 1) (1 cycle = 28 days)

End point values	50 mg E7449	100 mg E7449	200 mg E7449	400 mg E7449
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3	3	4	4
Units: Percentage of participants				
number (not applicable)				
Any DLT during 1st Cycle	0	0	0	0
Treatment-related non-hematological AE Grade ≥3	0	0	0	0
Treatment-related toxicity	0	0	0	0

End point values	600 mg E7449 Overall	800 mg E7449		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8	6		
Units: Percentage of participants				
number (not applicable)				
Any DLT during 1st Cycle	1	4		
Treatment-related non-hematological AE Grade ≥3	1	1		
Treatment-related toxicity	0	4		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects with Treatment-emergent Adverse Events (TEAEs) and Serious Adverse Events (SAEs)

End point title	Percentage of Subjects with Treatment-emergent Adverse Events (TEAEs) and Serious Adverse Events (SAEs)

End point description:

TEAEs were defined as AEs that occurred after the first dose of treatment on Cycle 1 Day 1 and up to 30 days after the last dose of treatment. Participants with 2 or more TEAEs in a specific category were counted only once. Safety was assessed by monitoring and recording all AEs, including all CTCAE version 4.03 grades (both increasing and decreasing severity) and SAEs, regular monitoring of hematology, clinical chemistry, and urine values, measurement of weight, vital signs, and electrocardiograms. Treatment-related TEAEs included TEAEs that were considered by the investigatory to be possible or probably related to study treatment. Participants reporting AEs with different CTCAE grades were counted only once using the highest CTCAE grade. Participants may be counted in more than one category. Safety analysis set included all participants who received at least 1 dose of the study drug and had at least 1 postbaseline safety evaluation.

End point type	Secondary

End point timeframe:

From date of administration of first dose up to 30 days after the last dose, or up to approximately 3 years 8 months.

End point values	50 mg E7449	100 mg E7449	200 mg E7449	400 mg E7449
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3	3	4	4
Units: Percentage of participants				
number (not applicable)				
All TEAEs	100	100	100	100
Treatment-related TEAEs	100	100	75	75
TEAEs with CTCAE grade 3 or 4	66.7	0	100	50
Treatment-related TEAEs with CTCAE Grade 3 or 4	33.3	0	0	25
Serious Adverse Events	33.3	0	100	50
TEAEs leading to treatment withdrawal	33.3	0	0	0
TEAEs leading to dose reduction	0	0	0	25
TEAEs leading to dose interruption	33.3	33.3	75	75
TEAEs associated with skin rash	0	33.3	25	25

End point values	600 mg E7449 Overall	800 mg E7449		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	21	6		
Units: Percentage of participants				
number (not applicable)				
All TEAEs	100	100		
Treatment-related TEAEs	100	100		
TEAEs with CTCAE grade 3 or 4	76.2	66.7		
Treatment-related TEAEs with CTCAE Grade 3 or 4	28.6	50		
Serious Adverse Events	57.1	83.3		
TEAEs leading to treatment withdrawal	19	33.3		
TEAEs leading to dose reduction	9.5	50		
TEAEs leading to dose interruption	47.6	100		
TEAEs associated with skin rash	47.6	66.7		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects with Best Overall Response (BOR) for E7449

End point title	Percentage of Subjects with Best Overall Response (BOR) for E7449

End point description:

BOR was the best confirmed response of partial response (PR), progressive disease (PD), or stable disease (SD), recorded from the start of E7449 until disease progression/recurrence or death. Analysis was based on investigator review of computed tomography (CT) scans, magnetic resonance imaging (MRI) scans, photographs, and bone scans, as appropriate to tumor type, utilizing Response Evaluation

Criteria in Solid Tumors (RECIST) 1.1. PR; at least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters. PD; 20% or greater increase in the sum of the longest diameter of measured lesions, taking as reference the smallest sum longest diameter recorded since treatment started or the appearance of one or more new lesions. SD; PR failed to be achieved in the overall response assessment and there was no PD observed at 7 weeks or later after starting E7449. 95% confidence interval was constructed using exact method of binomial distribution.

End point type	Secondary

End point timeframe:

Baseline to first date of documented CR, PR, SD, or PD, assessed up to approximately 3 years 7 months

End point values	50 mg E7449	100 mg E7449	200 mg E7449	400 mg E7449
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3	3	4	4
Units: Percentage of participants				
number (not applicable)				
Complete response	0	0	0	0
Partial response	0	0	0	0
Stable disease	66.7	33.3	25.0	50.0
Progressive disease	33.3	66.7	75.0	25.0

End point values	600 mg E7449 Overall	800 mg E7449		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	21	6		
Units: Percentage of participants				
number (not applicable)				
Complete response	0	0		
Partial response	4.8	16.7		
Stable disease	23.8	33.3		
Progressive disease	52.4	33.3		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects with Objective Response Rate (ORR) for E7449

End point title	Percentage of Subjects with Objective Response Rate (ORR) for E7449

End point description:

ORR was the percentage of participants with best overall response (BOR) of complete response (CR) and PR based on modified RECIST 1.1 for target lesions using MRI/CT scans, as determined by Independent Imaging Review (IIR). CR was defined as disappearance of all target lesions. PR was defined as at least a 30% decrease in the sum of the longest diameter of target lesions, taking as reference the baseline sum of the longest diameter. ORR=CR+PR.
The safety analysis set included all participants who received at least 1 dose of study drug and had at least 1 postbaseline safety evaluation. Here '99999' represents that none of the participants achieved ORR.

End point type	Secondary

End point timeframe:

From date of treatment start until disease progression, development of unacceptable toxicity, withdrawal of consent, participant's choice to stop study treatment, for up to approximately 3 years 7 months.

End point values	50 mg E7449	100 mg E7449	200 mg E7449	400 mg E7449
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3	3	4	4
Units: Percentage of participants				
number (not applicable)	99999	99999	99999	99999

End point values	600 mg E7449 Overall	800 mg E7449		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	21	6		
Units: Percentage of participants				
number (not applicable)	4.8	16.7		

Statistical analyses

No statistical analyses for this end point

Secondary: Preliminary Efficacy Assessment of Disease Control Rate (DCR) for E7449 when Administered as a Single Agent

End point title	Preliminary Efficacy Assessment of Disease Control Rate (DCR) for E7449 when Administered as a Single Agent

End point description:

DCR was the percentage of the participants who had BOR of CR, PR, and SD with the minimum duration of SD lasting greater than or equal to 7 weeks, based on assessments by IIR. The 95% CI was calculated using exact method of binomial distribution. DCR = CR + PR + SD greater than or equal to 23 weeks. The safety analysis set included all participants who received at least 1 dose of study drug and had at least 1 postbaseline safety evaluation.

End point type	Secondary

End point timeframe:

From date of treatment start until disease progression, development of unacceptable toxicity, withdrawal of consent, participant's choice to stop study treatment, for up to approximately 3 years 7 months

End point values	50 mg E7449	100 mg E7449	200 mg E7449	400 mg E7449
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3	3	4	4
Units: Percentage of participants				
number (not applicable)	33.3	33.3	0	50

End point values	600 mg E7449 Overall	800 mg E7449		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	21	6		
Units: Percentage of participants				
number (not applicable)	19	33.3		

Statistical analyses

No statistical analyses for this end point

Secondary: Preliminary Efficacy Assessment of Duration of Response (DoR) for E7449 when Administered as a Single Agent

End point title	Preliminary Efficacy Assessment of Duration of Response (DoR) for E7449 when Administered as a Single Agent

End point description:

DoR was calculated as 'end date minus date of first CR or PR plus 1', based on assessments by IIR. Participants without Progressive disease or death were censored at the date of last adequate tumor assessment according to the progression free survival (PFS) censoring rule. The safety analysis set included all participants who received at least 1 dose of study drug and had at least 1 postbaseline safety evaluation.

End point type	Secondary

End point timeframe:

From date of treatment start until disease progression, development of unacceptable toxicity, withdrawal of consent, participant's choice to stop study treatment, for up to approximately 3 years 7 months

End point values	50 mg E7449	100 mg E7449	200 mg E7449	400 mg E7449
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	0[3]	0[4]	0[5]	0[6]
Units: Days				
median (confidence interval 95%)	(to)	(to)	(to)	(to)

Notes:

[3] - None of the participants achieved a complete or partial response.

[4] - None of the participants achieved a complete or partial response.

[5] - None of the participants achieved a complete or partial response.

[6] - None of the participants achieved a complete or partial response.

End point values	600 mg E7449 Overall	800 mg E7449		

Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1[7]	1[8]		
Units: Days				
median (confidence interval 95%)	281 (281 to 281)	208 (208 to 208)		

Notes:

[7] - n=1

[8] - n=1

Statistical analyses

No statistical analyses for this end point

Secondary: Preliminary Efficacy Assessment of Duration of Stable Disease for E7449 when Administered as a Single Agent

End point title	Preliminary Efficacy Assessment of Duration of Stable Disease for E7449 when Administered as a Single Agent

End point description:

Tumor assessment was based on RECIST 1.1 criteria. Safety analysis set included Only participants with SD as their BOR were included. The safety analysis set included all participants who received at least 1 dose of study drug and had at least 1 postbaseline safety evaluation. Here '-99999' and '99999' represents lower and upper limit of the CI as only a single participant was analyzed and CI could not be estimated.

End point type	Secondary

End point timeframe:

Date of first dose of study treatment until disease progression or death, whichever occurs first, or up to approximately 3 years 7 months.

End point values	50 mg E7449	100 mg E7449	200 mg E7449	400 mg E7449
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	2	1	1	2
Units: Weeks				
median (confidence interval 95%)	184 (106 to 262)	332 (-99999 to 99999)	52 (-99999 to 99999)	190.5 (163 to 218)

End point values	600 mg E7449 Overall	800 mg E7449		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5	2		
Units: Weeks				
median (confidence interval 95%)	148 (42 to 266)	109.5 (57 to 162)		

Statistical analyses

No statistical analyses for this end point

Secondary: Preliminary Efficacy Assessment of Time to First Response for E7449 when Administered as a Single Agent

End point title	Preliminary Efficacy Assessment of Time to First Response for E7449 when Administered as a Single Agent

End point description:

Tumor assessment based on RECIST 1.1 criteria. Time to first response is defined as the time from first dose until the first documented evidence of CR or PR (whichever status is recorded first). For participants in the subset of non-responders, time to first response was censored. The safety analysis set included all participants who received at least 1 dose of study drug and had at least 1 postbaseline safety evaluation.

End point type	Secondary

End point timeframe:

Date of first dose of study treatment until the first dose of documented evidence of CR or PR (whichever status is recorded first), up to approximately 3 years 7 months

End point values	50 mg E7449	100 mg E7449	200 mg E7449	400 mg E7449
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	0[9]	0[10]	0[11]	0[12]
Units: Weeks				
median (confidence interval 95%)	(to)	(to)	(to)	(to)

Notes:

[9] - no responders

[10] - no responders

[11] - no responders

[12] - no responders

End point values	600 mg E7449 Overall	800 mg E7449		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1	1		
Units: Weeks				
median (confidence interval 95%)	51 (51 to 51)	108 (108 to 108)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Maximum Observed Concentration (Tmax) for E7449 when Administered as a Single Agent

End point title	Time to Maximum Observed Concentration (Tmax) for E7449 when Administered as a Single Agent

End point description:

Tmax for E7449 was the time it took after administration of study treatment on Day -2 and Cycle 1 Day 15 to reach the maximum concentration of E7449 in plasma. The PK analysis set included all participants who received at least one dose of E7449 and had at least one evaluable plasma concentration.

End point type	Secondary

End point timeframe:

Day -2 (predose, 0 to 2 hours, 2 to 4 hours, 4 to 10 hours, 10 to 24 hours) and Cycle 1 Day 15 (0 to 4,

8, and 12 hours)

End point values	50 mg E7449	100 mg E7449	200 mg E7449	400 mg E7449
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3	3	4[13]	4[14]
Units: Hours				
median (full range (min-max))				
Day -2	2 (0.58 to 2.03)	2.05 (1.08 to 3)	3.1 (1.03 to 4.18)	2.04 (1.03 to 4.05)
Cycle 1 Day 15	1 (0.5 to 2)	3 (1 to 4)	1 (1 to 2)	4 (0.5 to 4)

Notes:

[13] - Cycle 1 Day 15 (n=3)

[14] - Cycle 1 Day 15 (n=3)

End point values	600 mg E7449 Overall	800 mg E7449		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8[15]	6[16]		
Units: Hours				
median (full range (min-max))				
Day -2	2.12 (0.5 to 24.3)	0.79 (0.5 to 2)		
Cycle 1 Day 15	1.14 (0.5 to 4.05)	0.5 (0 to 1.97)		

Notes:

[15] - Cycle 1 Day 15 (n=6)

[16] - Cycle 1 Day 15 (n=5)

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum Concentration (Cmax) of E7449 in Plasma when Administered as a Single Agent

End point title	Maximum Concentration (Cmax) of E7449 in Plasma when Administered as a Single Agent

End point description:

Cmax for E7449 was defined as the maximum observed concentration of E7449 in plasma following administration of study treatment on Day -2 and Cycle 1 Day 15 and was obtained directly from the measured plasma concentration-time curves. The PK analysis set included all participants who received at least one dose of E7449 and had at least one evaluable plasma concentration.

End point type	Secondary

End point timeframe:

Day -2 (predose, 0 to 2 hours, 2 to 4 hours, 4 to 10 hours, 10 to 24 hours)and Cycle 1 Day 15 (0 to 4, 8, and 12 hours)

End point values	50 mg E7449	100 mg E7449	200 mg E7449	400 mg E7449
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3	3	4[17]	4[18]
Units: nanograms per millilitre (ng/mL)				
arithmetic mean (standard deviation)				
Day -2	265 (± 99.8)	284 (± 112)	996 (± 676)	999 (± 619)
Cycle 1 Day 15	264 (± 227)	404 (± 175)	1430 (± 1080)	1130 (± 1030)

Notes:

[17] - Cycle 1 Day 15 (n=3)

[18] - Cycle 1 Day 15 (n=3)

End point values	600 mg E7449 Overall	800 mg E7449		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8[19]	6[20]		
Units: nanograms per millilitre (ng/mL)				
arithmetic mean (standard deviation)				
Day -2	2250 (± 1330)	4430 (± 2470)		
Cycle 1 Day 15	2230 (± 1570)	4120 (± 2160)		

Notes:

[19] - Cycle 1 Day 15 (n=6)

[20] - Cycle 1 Day 15 (n=5)

Statistical analyses

No statistical analyses for this end point

Secondary: Area Under the Plasma Concentration-Time Curve From 0 to 24 Hours AUC(0-24) for E7449 when Administered as a Single Agent

End point title	Area Under the Plasma Concentration-Time Curve From 0 to 24 Hours AUC(0-24) for E7449 when Administered as a Single Agent

End point description:

The PK analysis set included all participants who received at least one dose of E7449 and had at least one evaluable plasma concentration.

End point type	Secondary

End point timeframe:

Day -2 (predose, 0 to 2 hours, 2 to 4 hours, 4 to 10 hours, 10 to 24 hours)and Cycle 1 Day 15 (0 to 4, 8, and 12 hours)

End point values	50 mg E7449	100 mg E7449	200 mg E7449	400 mg E7449
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3[21]	3	4[22]	4[23]
Units: nanogram*hour per milliliter (ng·h/mL)				
arithmetic mean (standard deviation)				
Day -2	768 (± 99999)	879 (± 104)	3670 (± 1170)	4690 (± 2400)
Cycle 1 Day 15	714 (± 193)	1100 (± 244)	3690 (± 2230)	4730 (± 2730)

Notes:

[21] - Day -2 (n=1)

[22] - Cycle 1 Day 15 (n = 3)

[23] - Cycle 1 Day 15 (n = 3)

End point values	600 mg E7449 Overall	800 mg E7449		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	21[24]	6[25]		
Units: nanogram*hour per milliliter (ng·h/mL)				
arithmetic mean (standard deviation)				
Day -2	7930 (± 4990)	11300 (± 3230)		
Cycle 1 Day 15	7900 (± 4730)	12400 (± 5230)		

Notes:

[24] - Cycle 1 Day 15 (n = 6)

[25] - Cycle 1 Day 15 (n = 5)

Statistical analyses

No statistical analyses for this end point

Secondary: Effect of Food on Time to Maximum Concentration (Tmax) of E7449 when Administered as a Single Agent

End point title	Effect of Food on Time to Maximum Concentration (Tmax) of E7449 when Administered as a Single Agent

End point description:

The bioavailability of E7449 when administered as a single agent was explored under fast/fed conditions at the MTD during Cycle 1. The effect of food was estimated using a mixed linear model of logarithmically transformed values of the primary PK parameters (Cmax, AUC(0-24)) with fixed effects for treatment, period and sequence and a random effect of participant. Ratios of geometric means and associated 2-sided 90% CIs were presented. The PK analysis set included all participants who received at least one dose of E7449 and had at least one evaluable plasma concentration.

End point type	Secondary

End point timeframe:

Cycle 1 Day 7 (predose) and Cycle 1 Day 15 (predose, 0.5 hours, 1 to 4 hours, 4, 6, 8, 10, 12, and 24 hours (Day 16)

End point values	600 mg E7449 (Fed)	600 mg E7449 (Fasted)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	11	10		
Units: Hours				
median (full range (min-max))	4.05 (1.07 to 8.18)	2.01 (0.97 to 3)		

Statistical analyses

No statistical analyses for this end point

Secondary: Effect of Food on the Maximum Plasma Concentration (Cmax) of E7449 when Administered as a Single Agent

End point title	Effect of Food on the Maximum Plasma Concentration (Cmax) of E7449 when Administered as a Single Agent

End point description:

The bioavailability of E7449 when administered as a single agent was explored under fast/fed conditions at the MTD during Cycle 1. The effect of food was estimated using a mixed linear model of logarithmically transformed values of the primary PK parameters (Cmax, AUC(0-24)) with fixed effects for treatment, period and sequence and a random effect of participant. Ratios of geometric means and associated 2-sided 90% confidence intervals (CIs) were presented. The PK analysis set included all participants who received at least one dose of E7449 and had at least one evaluable plasma concentration.

End point type	Secondary

End point timeframe:

Cycle 1 Day 7 (predose) and Cycle 1 Day 15 (predose, 0.5 hours, 1 to 4 hours, 4, 6, 8, 10, 12, and 24 hours (Day 16)

End point values	600 mg E7449 (Fed)	600 mg E7449 (Fasted)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	11	10		
Units: ng/mL				
arithmetic mean (standard deviation)	863 (± 563)	1470 (± 697)		

Statistical analyses

No statistical analyses for this end point

Secondary: Effect of Food on the Area Under the Plasma Concentration-Time Curve from 0 to 24 Hours (AUC(0-24)) for E7449 when Administered as a Single Agent

End point title	Effect of Food on the Area Under the Plasma Concentration-Time Curve from 0 to 24 Hours (AUC(0-24)) for E7449 when Administered as a Single Agent

End point description:

The bioavailability of E7449 when administered as a single agent was explored under fast/fed conditions at the MTD during Cycle 1. The effect of food was estimated using a mixed linear model of logarithmically transformed values of the primary PK parameters (Cmax, AUC(0-24)) with fixed effects for treatment, period and sequence and a random effect of participant. Ratios of geometric means and associated 2-sided 90% confidence intervals (CIs) were presented. The PK analysis set included all participants who received at least one dose of E7449 and had at least one evaluable plasma concentration.

End point type	Secondary

End point timeframe:

Cycle 1 Day 7 (predose) and Cycle 1 Day 15 (predose, 0.5 hours, 1 to 4 hours, 4, 6, 8, 10, 12, and 24 hours (Day 16)

End point values	600 mg E7449 (Fed)	600 mg E7449 (Fasted)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	11	9		
Units: ng·hr/mL				
median (standard deviation)	6150 (± 3280)	5510 (± 1730)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From date of administration of first dose up to 30 days after the last dose, or up to approximately 3 years 8 months.

Adverse event reporting additional description:

Treatment-emergent adverse events were reported and were defined as AEs that occurred after the first dose of treatment on Cycle 1 Day 1 and up to 30 days after the last dose of study treatment. Adverse events were graded using CTCAE version 4.03.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.1

Reporting groups

Reporting group title	50 mg E7449

Reporting group description:

E7449 (50 mg) was administered orally once on Day 2 in the single-dose pharmacokinetic (PK) period (dose escalation cohorts only) and once a day (QD) continuously starting on Cycle 1 Day 1 in 28-day treatment cycles. E7449 had to be taken at least 2 hours before or 2 hours after food. Dose interruption, dose reduction, or treatment discontinuation was applied for participants who experienced E7449-related toxicity in accordance with protocol-specified instructions.

Reporting group title	100 mg E7449

Reporting group description:

E7449 (100 mg) was administered orally once on Day 2 in the single-dose PK period (dose escalation cohorts only) and QD continuously starting on Cycle 1 Day 1 in 28-day treatment cycles. E7449 had to be taken at least 2 hours before or 2 hours after food. Dose interruption, dose reduction, or treatment discontinuation was applied for participants who experienced E7449-related toxicity in accordance with protocol-specified instructions.

Reporting group title	200 mg E7449

Reporting group description:

E7449 (200 mg) was administered orally once on Day 2 in the single-dose PK period (dose escalation cohorts only) and QD continuously starting on Cycle 1 Day 1 in 28-day treatment cycles. E7449 had to be taken at least 2 hours before or 2 hours after food. Dose interruption, dose reduction, or treatment discontinuation was applied for participants who experienced E7449-related toxicity in accordance with protocol-specified instructions.

Reporting group title	400 mg E7449

Reporting group description:

E7449 (400 mg) was administered orally once on Day 2 in the single-dose PK period (dose escalation cohorts only) and QD continuously starting on Cycle 1 Day 1 in 28-day treatment cycles. E7449 inhibitor had to be taken at least 2 hours before or 2 hours after food. Dose interruption, dose reduction, or treatment discontinuation was applied for participants who experienced E7449-related toxicity in accordance with protocol-specified instructions.

Reporting group title	600 mg E7449

Reporting group description:

E7449 (600 mg) was administered orally once on Day 2 in the single-dose PK period (dose escalation cohorts only) and QD continuously starting on Cycle 1 Day 1 in 28-day treatment cycles. E7449 had to be taken at least 2 hours before or 2 hours after food. Also, participants in the MTD expansion cohort were randomized to receive E7449 either with or without food after an overnight fast on Cycle 1 Day 7. Participants randomized to fed condition received E7449 immediately after consuming a high fat breakfast. On Cycle 1 Day 15, participants crossed over to the other food regimen, according to the randomization scheme (with or without food). Dose interruption, dose reduction, or treatment discontinuation was applied for participants who experienced E7449-related toxicity in accordance with protocol-specified instructions.

Reporting group title	800 mg E7449

Reporting group description:

E7449 (800 mg) was administered orally once on Day 2 in the single-dose PK period (dose escalation cohorts only) and QD continuously starting on Cycle 1 Day 1 in 28-day treatment cycles. E7449 had to

be taken at least 2 hours before or 2 hours after food. Dose interruption, dose reduction, or treatment discontinuation was applied for participants who experienced E7449-related toxicity in accordance with protocol-specified instructions.

Serious adverse events	50 mg E7449	100 mg E7449	200 mg E7449
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	4 / 4 (100.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Investigations			
Transaminases increased			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
Anaphylactic reaction			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Drug hypersensitivity			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Dysphagia			

subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal obstruction			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 4 (25.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 4 (25.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oesophageal spasm			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 4 (25.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fatigue			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 5	0 / 5	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain lower			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 4 (25.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Female genital tract fistula			

subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vaginal haemorrhage			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholangitis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 3	0 / 3
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 / 3 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cancer pain			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Malignant ascites			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 4 (25.00%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleuritic pain			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Depression			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Renal and urinary disorders			
Nephrolithiasis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 4 (25.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Musculoskeletal chest pain			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bile duct obstruction			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal pain			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain in extremity			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Lower respiratory tract infection			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 3	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Catheter site infection			

subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Escherichia bacteraemia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Klebsiella bacteraemia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oral candidiasis			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pelvic abscess			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 4 (25.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 4 (25.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colonic fistula			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 4 (25.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Constipation			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 4 (25.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Duodenal obstruction			

subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	400 mg E7449	600 mg E7449	800 mg E7449
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 4 (50.00%)	12 / 21 (57.14%)	5 / 6 (83.33%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Investigations			
Transaminases increased			
subjects affected / exposed	1 / 4 (25.00%)	0 / 21 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	0 / 4 (0.00%)	1 / 21 (4.76%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 21 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
Anaphylactic reaction			
subjects affected / exposed	0 / 4 (0.00%)	1 / 21 (4.76%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Drug hypersensitivity			
subjects affected / exposed	0 / 4 (0.00%)	1 / 21 (4.76%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Dysphagia			

subjects affected / exposed	0 / 4 (0.00%)	1 / 21 (4.76%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal obstruction			
subjects affected / exposed	0 / 4 (0.00%)	0 / 21 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			
subjects affected / exposed	0 / 4 (0.00%)	0 / 21 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oesophageal spasm			
subjects affected / exposed	0 / 4 (0.00%)	1 / 21 (4.76%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	0 / 4 (0.00%)	0 / 21 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fatigue			
subjects affected / exposed	0 / 4 (0.00%)	1 / 21 (4.76%)	2 / 6 (33.33%)
occurrences causally related to treatment / all	0 / 5	0 / 5	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 21 (0.00%)	1 / 6 (16.67%)
occurrences causally related to treatment / all	1 / 1	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain lower			
subjects affected / exposed	0 / 4 (0.00%)	0 / 21 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Female genital tract fistula			

subjects affected / exposed	0 / 4 (0.00%)	1 / 21 (4.76%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vaginal haemorrhage			
subjects affected / exposed	0 / 4 (0.00%)	1 / 21 (4.76%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholangitis			
subjects affected / exposed	0 / 4 (0.00%)	2 / 21 (9.52%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 3	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	0 / 4 (0.00%)	1 / 21 (4.76%)	1 / 6 (16.67%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cancer pain			
subjects affected / exposed	0 / 4 (0.00%)	0 / 21 (0.00%)	1 / 6 (16.67%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Malignant ascites			
subjects affected / exposed	0 / 4 (0.00%)	0 / 21 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleuritic pain			
subjects affected / exposed	0 / 4 (0.00%)	1 / 21 (4.76%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Depression			
subjects affected / exposed	0 / 4 (0.00%)	0 / 21 (0.00%)	1 / 6 (16.67%)
occurrences causally related to treatment / all	1 / 1	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Renal and urinary disorders			
Nephrolithiasis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 21 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Musculoskeletal chest pain			
subjects affected / exposed	0 / 4 (0.00%)	1 / 21 (4.76%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bile duct obstruction			
subjects affected / exposed	0 / 4 (0.00%)	1 / 21 (4.76%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal pain			
subjects affected / exposed	0 / 4 (0.00%)	1 / 21 (4.76%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain in extremity			
subjects affected / exposed	0 / 4 (0.00%)	1 / 21 (4.76%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Lower respiratory tract infection			
subjects affected / exposed	0 / 4 (0.00%)	2 / 21 (9.52%)	1 / 6 (16.67%)
occurrences causally related to treatment / all	0 / 3	0 / 3	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	1 / 4 (25.00%)	0 / 21 (0.00%)	1 / 6 (16.67%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Catheter site infection			

subjects affected / exposed	0 / 4 (0.00%)	1 / 21 (4.76%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Escherichia bacteraemia			
subjects affected / exposed	0 / 4 (0.00%)	1 / 21 (4.76%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Klebsiella bacteraemia			
subjects affected / exposed	0 / 4 (0.00%)	1 / 21 (4.76%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oral candidiasis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 21 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pelvic abscess			
subjects affected / exposed	0 / 4 (0.00%)	0 / 21 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain			
subjects affected / exposed	0 / 4 (0.00%)	0 / 21 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colonic fistula			
subjects affected / exposed	0 / 4 (0.00%)	0 / 21 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Constipation			
subjects affected / exposed	0 / 4 (0.00%)	0 / 21 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Duodenal obstruction			

subjects affected / exposed	0 / 4 (0.00%)	1 / 21 (4.76%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	50 mg E7449	100 mg E7449	200 mg E7449
Total subjects affected by non-serious adverse events			
subjects affected / exposed	3 / 3 (100.00%)	3 / 3 (100.00%)	4 / 4 (100.00%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Malignant ascites			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 4 (25.00%)
occurrences (all)	8	8	8
Cancer pain			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	1	1
Vascular disorders			
Hypotension			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 4 (25.00%)
occurrences (all)	4	4	4
Hypertension			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	2	2	2
Hot flush			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	1	1
Superior vena cava stenosis			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	1	1
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	2 / 3 (66.67%)	2 / 3 (66.67%)	3 / 4 (75.00%)
occurrences (all)	85	85	85
Oedema peripheral			

subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	3	3	3
Pain			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	4	4	4
Catheter site erythema			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	1	1
Catheter site swelling			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	1	1
Chills			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	2	2	2
Early satiety			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 4 (25.00%)
occurrences (all)	1	1	1
Local swelling			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	2	2	2
Malaise			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	1	1
Non-cardiac chest pain			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	1	1
Performance status decreased			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	1	1
Pyrexia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	3	3	3
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	1	1

Reproductive system and breast disorders			
Benign prostatic hyperplasia			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	0 / 4 (0.00%)
occurrences (all)	1	1	1
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	2 / 3 (66.67%)	1 / 3 (33.33%)	0 / 4 (0.00%)
occurrences (all)	14	14	14
Cough			
subjects affected / exposed	1 / 3 (33.33%)	1 / 3 (33.33%)	1 / 4 (25.00%)
occurrences (all)	10	10	10
Pleural effusion			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	0 / 4 (0.00%)
occurrences (all)	2	2	2
Pleuritic pain			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	0 / 4 (0.00%)
occurrences (all)	2	2	2
Haemoptysis			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	1	1
Nasal congestion			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	0 / 4 (0.00%)
occurrences (all)	1	1	1
Psychiatric disorders			
Depression			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	1 / 4 (25.00%)
occurrences (all)	13	13	13
Insomnia			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	0 / 4 (0.00%)
occurrences (all)	6	6	6
Anxiety			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 4 (25.00%)
occurrences (all)	4	4	4
Confusional state			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	3	3	3

Agitation			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	0 / 4 (0.00%)
occurrences (all)	1	1	1
Depressed mood			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	2	2	2
Abnormal dreams			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	0 / 4 (0.00%)
occurrences (all)	1	1	1
Euphoric mood			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	1	1
Hallucination			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	1	1
Panic disorder			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	1	1
Sleep disorder			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	0 / 4 (0.00%)
occurrences (all)	1	1	1
Investigations			
Weight decreased			
subjects affected / exposed	1 / 3 (33.33%)	1 / 3 (33.33%)	3 / 4 (75.00%)
occurrences (all)	13	13	13
Blood alkaline phosphatase increased			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	8	8	8
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	4	4	4
Blood bilirubin increased			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 4 (25.00%)
occurrences (all)	5	5	5
Alanine aminotransferase increased			

subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	5	5	5
Blood creatinine increased			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	3	3	3
Body temperature increased			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	1 / 4 (25.00%)
occurrences (all)	3	3	3
Blood cholesterol increased			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 4 (25.00%)
occurrences (all)	1	1	1
Blood glucose increased			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	0 / 4 (0.00%)
occurrences (all)	2	2	2
Blood lactate dehydrogenase increased			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	0 / 4 (0.00%)
occurrences (all)	3	3	3
Transaminases increased			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	2	2	2
White blood cell count increased			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	1	1
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	1	1
Muscle strain			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	1	1
Wound			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 4 (25.00%)
occurrences (all)	1	1	1
Cardiac disorders			

Tachycardia			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	1 / 4 (25.00%)
occurrences (all)	5	5	5
Atrial flutter			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	1	1
Nervous system disorders			
Dizziness			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	0 / 4 (0.00%)
occurrences (all)	8	8	8
Paraesthesia			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	7	7	7
Dysgeusia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	3	3	3
Headache			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	1 / 4 (25.00%)
occurrences (all)	4	4	4
Aphasia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	2	2	2
Lethargy			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	1 / 4 (25.00%)
occurrences (all)	2	2	2
Balance disorder			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	0 / 4 (0.00%)
occurrences (all)	1	1	1
Dysarthria			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	1	1
Migraine			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	1	1
Myoclonus			

subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 4 (25.00%)
occurrences (all)	1	1	1
Restless legs syndrome			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	1	1
Speech disorder			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	1	1
Tremor			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	1	1
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 3 (66.67%)	0 / 3 (0.00%)	2 / 4 (50.00%)
occurrences (all)	22	22	22
Eye disorders			
Periorbital oedema			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	6	6	6
Dry eye			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	2	2	2
Eyelid oedema			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	2	2	2
Eye pain			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	0 / 4 (0.00%)
occurrences (all)	1	1	1
Pinguecula			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	1	1
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	1 / 3 (33.33%)	1 / 3 (33.33%)	2 / 4 (50.00%)
occurrences (all)	29	29	29
Diarrhoea			

subjects affected / exposed	1 / 3 (33.33%)	1 / 3 (33.33%)	2 / 4 (50.00%)
occurrences (all)	23	23	23
Constipation			
subjects affected / exposed	1 / 3 (33.33%)	3 / 3 (100.00%)	3 / 4 (75.00%)
occurrences (all)	20	20	20
Vomiting			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	2 / 4 (50.00%)
occurrences (all)	19	19	19
Abdominal pain			
subjects affected / exposed	0 / 3 (0.00%)	2 / 3 (66.67%)	2 / 4 (50.00%)
occurrences (all)	19	19	19
Abdominal distension			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	2 / 4 (50.00%)
occurrences (all)	5	5	5
Dyspepsia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 4 (25.00%)
occurrences (all)	4	4	4
Dysphagia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	3	3	3
Abdominal pain upper			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	3	3	3
Dry mouth			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 4 (25.00%)
occurrences (all)	2	2	2
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	3	3	3
Stomatitis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	3	3	3
Abdominal pain lower			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 4 (25.00%)
occurrences (all)	2	2	2
Intestinal obstruction			

subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 4 (25.00%)
occurrences (all)	1	1	1
Toothache			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	1	1
Skin and subcutaneous tissue disorders			
Rash maculo-papular			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	1 / 4 (25.00%)
occurrences (all)	20	20	20
Photosensitivity reaction			
subjects affected / exposed	1 / 3 (33.33%)	1 / 3 (33.33%)	0 / 4 (0.00%)
occurrences (all)	20	20	20
Pruritus			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	1 / 4 (25.00%)
occurrences (all)	7	7	7
Skin hyperpigmentation			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	0 / 4 (0.00%)
occurrences (all)	10	10	10
Dry skin			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	0 / 4 (0.00%)
occurrences (all)	5	5	5
Rash erythematous			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	8	8	8
Night sweats			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	5	5	5
Onycholysis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	3	3	3
Dermatitis acneiform			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	2	2	2
Skin discolouration			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	2	2	2

Acne			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	1	1
Blister			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	1	1
Dermatitis contact			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	1	1
Erythema			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	1	1
Nail discolouration			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	1	1
Nail disorder			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	1	1
Nail ridging			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	1	1
Swelling face			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	1	1
Renal and urinary disorders			
Chromaturia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	25	25	25
Nephrolithiasis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 4 (25.00%)
occurrences (all)	1	1	1
Nocturia			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	0 / 4 (0.00%)
occurrences (all)	1	1	1
Proteinuria			

subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	0 / 4 (0.00%)
occurrences (all)	1	1	1
Musculoskeletal and connective tissue disorders			
Musculoskeletal chest pain			
subjects affected / exposed	2 / 3 (66.67%)	0 / 3 (0.00%)	1 / 4 (25.00%)
occurrences (all)	10	10	10
Back pain			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	1 / 4 (25.00%)
occurrences (all)	5	5	5
Musculoskeletal pain			
subjects affected / exposed	1 / 3 (33.33%)	1 / 3 (33.33%)	0 / 4 (0.00%)
occurrences (all)	4	4	4
Muscular weakness			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	6	6	6
Arthralgia			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	0 / 4 (0.00%)
occurrences (all)	7	7	7
Pain in extremity			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	1	1
Joint swelling			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	1	1
Muscle spasms			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	0 / 4 (0.00%)
occurrences (all)	1	1	1
Musculoskeletal stiffness			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	1	1
Myalgia			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	1	1
Neck mass			

subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	0 / 4 (0.00%)
occurrences (all)	1	1	1
Infections and infestations			
Lower respiratory tract infection			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	1 / 4 (25.00%)
occurrences (all)	10	10	10
Oral candidiasis			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	7	7	7
Urinary tract infection			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 4 (25.00%)
occurrences (all)	4	4	4
Nasopharyngitis			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	2	2	2
Tooth infection			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	1	1
Viral infection			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	1	1
Wound infection			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 4 (25.00%)
occurrences (all)	1	1	1
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	3 / 3 (100.00%)	0 / 3 (0.00%)	2 / 4 (50.00%)
occurrences (all)	33	33	33
Dehydration			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 4 (25.00%)
occurrences (all)	2	2	2
Hypercalcaemia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	2	2	2
Hypokalaemia			

subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 4 (25.00%)
occurrences (all)	5	5	5
Hyponatraemia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 4 (25.00%)
occurrences (all)	2	2	2
Hypophosphataemia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 4 (25.00%)
occurrences (all)	2	2	2
Fluid overload			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	1	1
Hypoalbuminaemia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 4 (25.00%)
occurrences (all)	1	1	1
Hypomagnesaemia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	1	1

Non-serious adverse events	400 mg E7449	600 mg E7449	800 mg E7449
Total subjects affected by non-serious adverse events			
subjects affected / exposed	4 / 4 (100.00%)	21 / 21 (100.00%)	6 / 6 (100.00%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Malignant ascites			
subjects affected / exposed	1 / 4 (25.00%)	1 / 21 (4.76%)	0 / 6 (0.00%)
occurrences (all)	8	8	8
Cancer pain			
subjects affected / exposed	0 / 4 (0.00%)	1 / 21 (4.76%)	1 / 6 (16.67%)
occurrences (all)	1	1	1
Vascular disorders			
Hypotension			
subjects affected / exposed	0 / 4 (0.00%)	1 / 21 (4.76%)	2 / 6 (33.33%)
occurrences (all)	4	4	4
Hypertension			
subjects affected / exposed	0 / 4 (0.00%)	2 / 21 (9.52%)	0 / 6 (0.00%)
occurrences (all)	2	2	2
Hot flush			

subjects affected / exposed	0 / 4 (0.00%)	0 / 21 (0.00%)	1 / 6 (16.67%)
occurrences (all)	1	1	1
Superior vena cava stenosis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 21 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	1	1
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	4 / 4 (100.00%)	17 / 21 (80.95%)	6 / 6 (100.00%)
occurrences (all)	85	85	85
Oedema peripheral			
subjects affected / exposed	0 / 4 (0.00%)	3 / 21 (14.29%)	0 / 6 (0.00%)
occurrences (all)	3	3	3
Pain			
subjects affected / exposed	0 / 4 (0.00%)	0 / 21 (0.00%)	1 / 6 (16.67%)
occurrences (all)	4	4	4
Catheter site erythema			
subjects affected / exposed	0 / 4 (0.00%)	0 / 21 (0.00%)	1 / 6 (16.67%)
occurrences (all)	1	1	1
Catheter site swelling			
subjects affected / exposed	0 / 4 (0.00%)	0 / 21 (0.00%)	1 / 6 (16.67%)
occurrences (all)	1	1	1
Chills			
subjects affected / exposed	0 / 4 (0.00%)	0 / 21 (0.00%)	1 / 6 (16.67%)
occurrences (all)	2	2	2
Early satiety			
subjects affected / exposed	0 / 4 (0.00%)	0 / 21 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	1	1
Local swelling			
subjects affected / exposed	0 / 4 (0.00%)	0 / 21 (0.00%)	0 / 6 (0.00%)
occurrences (all)	2	2	2
Malaise			
subjects affected / exposed	0 / 4 (0.00%)	0 / 21 (0.00%)	1 / 6 (16.67%)
occurrences (all)	1	1	1
Non-cardiac chest pain			

subjects affected / exposed	0 / 4 (0.00%)	0 / 21 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	1	1
Performance status decreased			
subjects affected / exposed	0 / 4 (0.00%)	0 / 21 (0.00%)	1 / 6 (16.67%)
occurrences (all)	1	1	1
Pyrexia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 21 (0.00%)	1 / 6 (16.67%)
occurrences (all)	3	3	3
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	0 / 4 (0.00%)	2 / 21 (9.52%)	0 / 6 (0.00%)
occurrences (all)	1	1	1
Reproductive system and breast disorders			
Benign prostatic hyperplasia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 21 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	1	1
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	0 / 4 (0.00%)	5 / 21 (23.81%)	2 / 6 (33.33%)
occurrences (all)	14	14	14
Cough			
subjects affected / exposed	1 / 4 (25.00%)	1 / 21 (4.76%)	1 / 6 (16.67%)
occurrences (all)	10	10	10
Pleural effusion			
subjects affected / exposed	0 / 4 (0.00%)	1 / 21 (4.76%)	0 / 6 (0.00%)
occurrences (all)	2	2	2
Pleuritic pain			
subjects affected / exposed	0 / 4 (0.00%)	1 / 21 (4.76%)	0 / 6 (0.00%)
occurrences (all)	2	2	2
Haemoptysis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 21 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	1	1
Nasal congestion			
subjects affected / exposed	0 / 4 (0.00%)	0 / 21 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	1	1
Psychiatric disorders			

Depression			
subjects affected / exposed	2 / 4 (50.00%)	1 / 21 (4.76%)	1 / 6 (16.67%)
occurrences (all)	13	13	13
Insomnia			
subjects affected / exposed	0 / 4 (0.00%)	3 / 21 (14.29%)	2 / 6 (33.33%)
occurrences (all)	6	6	6
Anxiety			
subjects affected / exposed	0 / 4 (0.00%)	1 / 21 (4.76%)	2 / 6 (33.33%)
occurrences (all)	4	4	4
Confusional state			
subjects affected / exposed	1 / 4 (25.00%)	1 / 21 (4.76%)	0 / 6 (0.00%)
occurrences (all)	3	3	3
Agitation			
subjects affected / exposed	0 / 4 (0.00%)	1 / 21 (4.76%)	0 / 6 (0.00%)
occurrences (all)	1	1	1
Depressed mood			
subjects affected / exposed	0 / 4 (0.00%)	1 / 21 (4.76%)	0 / 6 (0.00%)
occurrences (all)	2	2	2
Abnormal dreams			
subjects affected / exposed	0 / 4 (0.00%)	0 / 21 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	1	1
Euphoric mood			
subjects affected / exposed	0 / 4 (0.00%)	0 / 21 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	1	1
Hallucination			
subjects affected / exposed	0 / 4 (0.00%)	0 / 21 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	1	1
Panic disorder			
subjects affected / exposed	0 / 4 (0.00%)	0 / 21 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	1	1
Sleep disorder			
subjects affected / exposed	0 / 4 (0.00%)	0 / 21 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	1	1
Investigations			
Weight decreased			

subjects affected / exposed	2 / 4 (50.00%)	0 / 21 (0.00%)	0 / 6 (0.00%)
occurrences (all)	13	13	13
Blood alkaline phosphatase increased			
subjects affected / exposed	1 / 4 (25.00%)	3 / 21 (14.29%)	0 / 6 (0.00%)
occurrences (all)	8	8	8
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 4 (0.00%)	3 / 21 (14.29%)	0 / 6 (0.00%)
occurrences (all)	4	4	4
Blood bilirubin increased			
subjects affected / exposed	0 / 4 (0.00%)	2 / 21 (9.52%)	0 / 6 (0.00%)
occurrences (all)	5	5	5
Alanine aminotransferase increased			
subjects affected / exposed	0 / 4 (0.00%)	2 / 21 (9.52%)	0 / 6 (0.00%)
occurrences (all)	5	5	5
Blood creatinine increased			
subjects affected / exposed	0 / 4 (0.00%)	0 / 21 (0.00%)	1 / 6 (16.67%)
occurrences (all)	3	3	3
Body temperature increased			
subjects affected / exposed	0 / 4 (0.00%)	0 / 21 (0.00%)	0 / 6 (0.00%)
occurrences (all)	3	3	3
Blood cholesterol increased			
subjects affected / exposed	0 / 4 (0.00%)	0 / 21 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	1	1
Blood glucose increased			
subjects affected / exposed	0 / 4 (0.00%)	0 / 21 (0.00%)	0 / 6 (0.00%)
occurrences (all)	2	2	2
Blood lactate dehydrogenase increased			
subjects affected / exposed	0 / 4 (0.00%)	0 / 21 (0.00%)	0 / 6 (0.00%)
occurrences (all)	3	3	3
Transaminases increased			
subjects affected / exposed	1 / 4 (25.00%)	0 / 21 (0.00%)	0 / 6 (0.00%)
occurrences (all)	2	2	2
White blood cell count increased			

subjects affected / exposed	0 / 4 (0.00%)	1 / 21 (4.76%)	0 / 6 (0.00%)
occurrences (all)	1	1	1
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	1 / 4 (25.00%)	0 / 21 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	1	1
Muscle strain			
subjects affected / exposed	1 / 4 (25.00%)	0 / 21 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	1	1
Wound			
subjects affected / exposed	0 / 4 (0.00%)	0 / 21 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	1	1
Cardiac disorders			
Tachycardia			
subjects affected / exposed	0 / 4 (0.00%)	2 / 21 (9.52%)	1 / 6 (16.67%)
occurrences (all)	5	5	5
Atrial flutter			
subjects affected / exposed	0 / 4 (0.00%)	0 / 21 (0.00%)	1 / 6 (16.67%)
occurrences (all)	1	1	1
Nervous system disorders			
Dizziness			
subjects affected / exposed	0 / 4 (0.00%)	4 / 21 (19.05%)	2 / 6 (33.33%)
occurrences (all)	8	8	8
Paraesthesia			
subjects affected / exposed	1 / 4 (25.00%)	2 / 21 (9.52%)	0 / 6 (0.00%)
occurrences (all)	7	7	7
Dysgeusia			
subjects affected / exposed	0 / 4 (0.00%)	3 / 21 (14.29%)	0 / 6 (0.00%)
occurrences (all)	3	3	3
Headache			
subjects affected / exposed	0 / 4 (0.00%)	0 / 21 (0.00%)	1 / 6 (16.67%)
occurrences (all)	4	4	4
Aphasia			
subjects affected / exposed	0 / 4 (0.00%)	2 / 21 (9.52%)	0 / 6 (0.00%)
occurrences (all)	2	2	2
Lethargy			

subjects affected / exposed	0 / 4 (0.00%)	0 / 21 (0.00%)	0 / 6 (0.00%)
occurrences (all)	2	2	2
Balance disorder			
subjects affected / exposed	0 / 4 (0.00%)	0 / 21 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	1	1
Dysarthria			
subjects affected / exposed	1 / 4 (25.00%)	0 / 21 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	1	1
Migraine			
subjects affected / exposed	1 / 4 (25.00%)	0 / 21 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	1	1
Myoclonus			
subjects affected / exposed	0 / 4 (0.00%)	0 / 21 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	1	1
Restless legs syndrome			
subjects affected / exposed	1 / 4 (25.00%)	0 / 21 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	1	1
Speech disorder			
subjects affected / exposed	0 / 4 (0.00%)	0 / 21 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	1	1
Tremor			
subjects affected / exposed	0 / 4 (0.00%)	0 / 21 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	1	1
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 4 (0.00%)	4 / 21 (19.05%)	1 / 6 (16.67%)
occurrences (all)	22	22	22
Eye disorders			
Periorbital oedema			
subjects affected / exposed	1 / 4 (25.00%)	4 / 21 (19.05%)	0 / 6 (0.00%)
occurrences (all)	6	6	6
Dry eye			
subjects affected / exposed	1 / 4 (25.00%)	1 / 21 (4.76%)	0 / 6 (0.00%)
occurrences (all)	2	2	2
Eyelid oedema			

subjects affected / exposed	0 / 4 (0.00%)	2 / 21 (9.52%)	0 / 6 (0.00%)
occurrences (all)	2	2	2
Eye pain			
subjects affected / exposed	0 / 4 (0.00%)	0 / 21 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	1	1
Pinguecula			
subjects affected / exposed	0 / 4 (0.00%)	0 / 21 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	1	1
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	3 / 4 (75.00%)	9 / 21 (42.86%)	2 / 6 (33.33%)
occurrences (all)	29	29	29
Diarrhoea			
subjects affected / exposed	2 / 4 (50.00%)	6 / 21 (28.57%)	4 / 6 (66.67%)
occurrences (all)	23	23	23
Constipation			
subjects affected / exposed	1 / 4 (25.00%)	5 / 21 (23.81%)	2 / 6 (33.33%)
occurrences (all)	20	20	20
Vomiting			
subjects affected / exposed	3 / 4 (75.00%)	5 / 21 (23.81%)	3 / 6 (50.00%)
occurrences (all)	19	19	19
Abdominal pain			
subjects affected / exposed	1 / 4 (25.00%)	1 / 21 (4.76%)	1 / 6 (16.67%)
occurrences (all)	19	19	19
Abdominal distension			
subjects affected / exposed	0 / 4 (0.00%)	0 / 21 (0.00%)	1 / 6 (16.67%)
occurrences (all)	5	5	5
Dyspepsia			
subjects affected / exposed	1 / 4 (25.00%)	0 / 21 (0.00%)	1 / 6 (16.67%)
occurrences (all)	4	4	4
Dysphagia			
subjects affected / exposed	0 / 4 (0.00%)	2 / 21 (9.52%)	1 / 6 (16.67%)
occurrences (all)	3	3	3
Abdominal pain upper			
subjects affected / exposed	1 / 4 (25.00%)	1 / 21 (4.76%)	0 / 6 (0.00%)
occurrences (all)	3	3	3

Dry mouth			
subjects affected / exposed	0 / 4 (0.00%)	1 / 21 (4.76%)	0 / 6 (0.00%)
occurrences (all)	2	2	2
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 4 (0.00%)	2 / 21 (9.52%)	0 / 6 (0.00%)
occurrences (all)	3	3	3
Stomatitis			
subjects affected / exposed	0 / 4 (0.00%)	2 / 21 (9.52%)	0 / 6 (0.00%)
occurrences (all)	3	3	3
Abdominal pain lower			
subjects affected / exposed	0 / 4 (0.00%)	0 / 21 (0.00%)	0 / 6 (0.00%)
occurrences (all)	2	2	2
Intestinal obstruction			
subjects affected / exposed	0 / 4 (0.00%)	0 / 21 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	1	1
Toothache			
subjects affected / exposed	0 / 4 (0.00%)	0 / 21 (0.00%)	1 / 6 (16.67%)
occurrences (all)	1	1	1
Skin and subcutaneous tissue disorders			
Rash maculo-papular			
subjects affected / exposed	1 / 4 (25.00%)	7 / 21 (33.33%)	1 / 6 (16.67%)
occurrences (all)	20	20	20
Photosensitivity reaction			
subjects affected / exposed	1 / 4 (25.00%)	5 / 21 (23.81%)	2 / 6 (33.33%)
occurrences (all)	20	20	20
Pruritus			
subjects affected / exposed	0 / 4 (0.00%)	4 / 21 (19.05%)	0 / 6 (0.00%)
occurrences (all)	7	7	7
Skin hyperpigmentation			
subjects affected / exposed	0 / 4 (0.00%)	2 / 21 (9.52%)	2 / 6 (33.33%)
occurrences (all)	10	10	10
Dry skin			
subjects affected / exposed	0 / 4 (0.00%)	1 / 21 (4.76%)	2 / 6 (33.33%)
occurrences (all)	5	5	5
Rash erythematous			

subjects affected / exposed	0 / 4 (0.00%)	3 / 21 (14.29%)	1 / 6 (16.67%)
occurrences (all)	8	8	8
Night sweats			
subjects affected / exposed	0 / 4 (0.00%)	2 / 21 (9.52%)	0 / 6 (0.00%)
occurrences (all)	5	5	5
Onycholysis			
subjects affected / exposed	1 / 4 (25.00%)	2 / 21 (9.52%)	0 / 6 (0.00%)
occurrences (all)	3	3	3
Dermatitis acneiform			
subjects affected / exposed	0 / 4 (0.00%)	1 / 21 (4.76%)	1 / 6 (16.67%)
occurrences (all)	2	2	2
Skin discolouration			
subjects affected / exposed	0 / 4 (0.00%)	2 / 21 (9.52%)	0 / 6 (0.00%)
occurrences (all)	2	2	2
Acne			
subjects affected / exposed	0 / 4 (0.00%)	0 / 21 (0.00%)	1 / 6 (16.67%)
occurrences (all)	1	1	1
Blister			
subjects affected / exposed	0 / 4 (0.00%)	0 / 21 (0.00%)	1 / 6 (16.67%)
occurrences (all)	1	1	1
Dermatitis contact			
subjects affected / exposed	1 / 4 (25.00%)	0 / 21 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	1	1
Erythema			
subjects affected / exposed	0 / 4 (0.00%)	0 / 21 (0.00%)	1 / 6 (16.67%)
occurrences (all)	1	1	1
Nail discolouration			
subjects affected / exposed	0 / 4 (0.00%)	0 / 21 (0.00%)	1 / 6 (16.67%)
occurrences (all)	1	1	1
Nail disorder			
subjects affected / exposed	1 / 4 (25.00%)	0 / 21 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	1	1
Nail ridging			
subjects affected / exposed	0 / 4 (0.00%)	0 / 21 (0.00%)	1 / 6 (16.67%)
occurrences (all)	1	1	1
Swelling face			

subjects affected / exposed	0 / 4 (0.00%)	0 / 21 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	1	1
Renal and urinary disorders			
Chromaturia			
subjects affected / exposed	2 / 4 (50.00%)	14 / 21 (66.67%)	5 / 6 (83.33%)
occurrences (all)	25	25	25
Nephrolithiasis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 21 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	1	1
Nocturia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 21 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	1	1
Proteinuria			
subjects affected / exposed	0 / 4 (0.00%)	0 / 21 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	1	1
Musculoskeletal and connective tissue disorders			
Musculoskeletal chest pain			
subjects affected / exposed	0 / 4 (0.00%)	3 / 21 (14.29%)	0 / 6 (0.00%)
occurrences (all)	10	10	10
Back pain			
subjects affected / exposed	1 / 4 (25.00%)	2 / 21 (9.52%)	0 / 6 (0.00%)
occurrences (all)	5	5	5
Musculoskeletal pain			
subjects affected / exposed	0 / 4 (0.00%)	1 / 21 (4.76%)	2 / 6 (33.33%)
occurrences (all)	4	4	4
Muscular weakness			
subjects affected / exposed	1 / 4 (25.00%)	2 / 21 (9.52%)	0 / 6 (0.00%)
occurrences (all)	6	6	6
Arthralgia			
subjects affected / exposed	0 / 4 (0.00%)	1 / 21 (4.76%)	1 / 6 (16.67%)
occurrences (all)	7	7	7
Pain in extremity			
subjects affected / exposed	0 / 4 (0.00%)	1 / 21 (4.76%)	0 / 6 (0.00%)
occurrences (all)	1	1	1
Joint swelling			

subjects affected / exposed	0 / 4 (0.00%)	0 / 21 (0.00%)	1 / 6 (16.67%)
occurrences (all)	1	1	1
Muscle spasms			
subjects affected / exposed	0 / 4 (0.00%)	0 / 21 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	1	1
Musculoskeletal stiffness			
subjects affected / exposed	0 / 4 (0.00%)	0 / 21 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	1	1
Myalgia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 21 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	1	1
Neck mass			
subjects affected / exposed	0 / 4 (0.00%)	0 / 21 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	1	1
Infections and infestations			
Lower respiratory tract infection			
subjects affected / exposed	2 / 4 (50.00%)	5 / 21 (23.81%)	2 / 6 (33.33%)
occurrences (all)	10	10	10
Oral candidiasis			
subjects affected / exposed	1 / 4 (25.00%)	3 / 21 (14.29%)	1 / 6 (16.67%)
occurrences (all)	7	7	7
Urinary tract infection			
subjects affected / exposed	1 / 4 (25.00%)	2 / 21 (9.52%)	1 / 6 (16.67%)
occurrences (all)	4	4	4
Nasopharyngitis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 21 (0.00%)	1 / 6 (16.67%)
occurrences (all)	2	2	2
Tooth infection			
subjects affected / exposed	0 / 4 (0.00%)	0 / 21 (0.00%)	1 / 6 (16.67%)
occurrences (all)	1	1	1
Viral infection			
subjects affected / exposed	0 / 4 (0.00%)	0 / 21 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	1	1
Wound infection			
subjects affected / exposed	0 / 4 (0.00%)	0 / 21 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	1	1

Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	2 / 4 (50.00%)	7 / 21 (33.33%)	4 / 6 (66.67%)
occurrences (all)	33	33	33
Dehydration			
subjects affected / exposed	0 / 4 (0.00%)	1 / 21 (4.76%)	0 / 6 (0.00%)
occurrences (all)	2	2	2
Hypercalcaemia			
subjects affected / exposed	0 / 4 (0.00%)	1 / 21 (4.76%)	1 / 6 (16.67%)
occurrences (all)	2	2	2
Hypokalaemia			
subjects affected / exposed	0 / 4 (0.00%)	1 / 21 (4.76%)	0 / 6 (0.00%)
occurrences (all)	5	5	5
Hyponatraemia			
subjects affected / exposed	0 / 4 (0.00%)	1 / 21 (4.76%)	0 / 6 (0.00%)
occurrences (all)	2	2	2
Hypophosphataemia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 21 (0.00%)	1 / 6 (16.67%)
occurrences (all)	2	2	2
Fluid overload			
subjects affected / exposed	0 / 4 (0.00%)	1 / 21 (4.76%)	0 / 6 (0.00%)
occurrences (all)	1	1	1
Hypoalbuminaemia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 21 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	1	1
Hypomagnesaemia			
subjects affected / exposed	0 / 4 (0.00%)	1 / 21 (4.76%)	0 / 6 (0.00%)
occurrences (all)	1	1	1

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
14 September 2011	Addition of a communication strategy among the study sites so that the drug escalation rules can be followed to comply with the local regulatory and health authority based on a request from the Medicines and Healthcare products Regulatory Agency (MHRA).
08 October 2012	• Clarified the type of B-cell malignancy (ie, B-cell lymphoma) for subject who will be enrolled in Phase 1 Arm 1. • Revised inclusion criteria: to include radiotherapy (5b) and update contraceptive use language (12) • Revised Exclusion Criterion 5 to allow subjects with squamous cell carcinoma of the skin, carcinoma in situ cervix, adequately treated Stage I or II cancer currently in complete remission, or any other cancer from which the subject has been disease-free for 5 years. • Revised dose reduction and interruption instructions table to exclude Grade 2 and Grade 3 laboratory abnormalities that are considered to be not clinically relevant by the investigator, and to discontinue E7449 and discuss with the sponsor any Grade 4 occurrences. • PK sampling schedule was revised to omit time points that were considered unnecessary without compromising results.
08 July 2013	• Added advisory to avoid sunlight, information to minimize sunlight exposure, and instructions on what to do in the event of a rash. • Revised alcohol and caffeine restrictions to allow for moderate use. Added advice regarding what constitutes moderate use.
20 September 2013	Amendment 04 was approved internally by the sponsor; however it was not implemented at the study sites due to logistical challenges associated with the proposed changes to explore BID dosing. Hence, BID dosing was not explored in this study. Not implemented.
30 October 2013	• Added information pertaining to the reporting of skin rash as an AE of special interest to allow collection of information related to skin rash.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

Study was terminated early by the sponsor.

Notes: