



Clinical trial results:

Phase I/II trial of S 81694 administered intravenously in combination with paclitaxel to evaluate the safety, pharmacokinetic and efficacy in metastatic breast cancer.

Summary

EudraCT number	2017-002459-27
Trial protocol	BE NL FR
Global end of trial date	08 June 2020

Results information

Result version number	v1 (current)
This version publication date	12 March 2021
First version publication date	12 March 2021

Trial information

Trial identification

Sponsor protocol code	CL1-81694-003
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03411161
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Institut de Recherches Internationales Servier
Sponsor organisation address	50 rue Carnot, Suresnes Cedex, France, 92284
Public contact	Center for Therapeutic Innovation in Oncology, Institut de Recherches Internationales Servier, +33 155724366, clinicaltrials@servier.com
Scientific contact	Center for Therapeutic Innovation in Oncology, Institut de Recherches Internationales Servier, +33 155724366, clinicaltrials@servier.com

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	28 July 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	08 June 2020
Global end of trial reached?	Yes
Global end of trial date	08 June 2020
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

For Phase I:

- To determine the safety profile and tolerability of S 81694 given in combination with paclitaxel by assessment of the Dose-Limiting Toxicities (DLT) and the Maximum Tolerated Dose (MTD) based on safety data described using Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4.03 in patients with metastatic Breast Cancer (mBC).
- To establish the recommended phase II dose (RP2D) of S 81694 in combination with paclitaxel.

For phase II:

- To evaluate Progression Free Survival (PFS).

Phase II was not initiated and is not described here.

Protection of trial subjects:

This study was conducted in accordance with Good Practice standards, ethical principles stated in the Declaration of Helsinki and applicable regulatory requirements. After the subject has ended his/her participation in the trial, the investigator provided appropriate medication and/or arranged access to appropriate care for the patient.

Background therapy:

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Evidence for comparator:

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Actual start date of recruitment	04 January 2018
Long term follow-up planned	Yes
Long term follow-up rationale	Efficacy
Long term follow-up duration	6 Months
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Netherlands: 3
Country: Number of subjects enrolled	Belgium: 7
Country: Number of subjects enrolled	France: 8
Country: Number of subjects enrolled	Japan: 4
Worldwide total number of subjects	22
EEA total number of subjects	18

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	2
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The investigators were specialists in Medical Oncology

Pre-assignment

Screening details:

Male or female patient aged ≥ 18 years old, with metastatic Breast Cancer, refractory to any standard therapy. Patient had at least one evaluable or measurable metastatic lesion, ECOG ≤ 1 , estimated life expectancy of at least 3 months, adequate haematological, renal, hepatic functions.

Period 1

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

Arms

Arm title	S81694 + Paclitaxel
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Arm description:

The dose escalation phase I part was a single arm, non-randomised and non-comparative study in patient with mBC, guided by a Bayesian dose-finding design for drug combination trials.

Arm type	Experimental
Investigational medicinal product name	S81694 + Paclitaxel
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder and solvent for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

A range of six provisional dose for S81694 was defined (13.5, 20, 30, 60, 80 and 150 mg/m²).

The investigational medicinal product S81694 was given in combination with paclitaxel 80mg/m²/W. S81694 administration was first scheduled on D1, D8 and D15 of a 28-day cycle until the approval of Amendment No. 4; then only two administrations on D1 and D15 of a 28-day cycle were done. Paclitaxel was administered IV as a one-hour infusion on D1, D8 and D15 of a 28-day cycle.

Number of subjects in period 1	S81694 + Paclitaxel
Started	22
Completed	0
Not completed	22
Adverse event, serious fatal	1
Physician decision	4
Adverse event, non-fatal	3
Progressive disease	14

Baseline characteristics

Reporting groups

Reporting group title	Phase I period (overall period)
Reporting group description: -	

Reporting group values	Phase I period (overall period)	Total	
Number of subjects	22	22	
Age categorical Units: Subjects			
Adults (18-64 years)	20	20	
From 65-84 years	2	2	
Age continuous Units: years			
arithmetic mean	52.4		
standard deviation	± 8.2	-	
Gender categorical Units: Subjects			
Female	22	22	
Male	0	0	

Subject analysis sets

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

Subject analysis set description:

The safety set consisted of all included patients who took at least one dose of IMP (either S81694 or paclitaxel).

Subject analysis set title	DLT evaluable set
Subject analysis set type	Safety analysis

Subject analysis set description:

The DLT evaluable set consisted of all patients of the Safety Set who were evaluable for DLT according to the DLT assessment at end of cycle 1.

A patient was not considered evaluable if :

- he/she discontinued treatment during DLTs assessment period for reasons other than DLT, or
- he/she did not undergo a DLT assessment at C1D28 or on C2D1, or
- he/she did not receive at least 90% (90% of paclitaxel and 90% of S81694) of associated agent prescribed doses from study entry to DLTs assessment visit (on C1D28 or on C2D1), unless treatment was stopped for a DLT, or
- he/she did receive more than 110% of associated agent prescribed doses from study entry to DLT occurrence during the DLT assessment period.

Reporting group values	Safety set	DLT evaluable set	
Number of subjects	22	16	
Age categorical Units: Subjects			
Adults (18-64 years)	20		
From 65-84 years	2		

Age continuous			
Units: years			
arithmetic mean	52.4		
standard deviation	± 8.2	\pm	
Gender categorical			
Units: Subjects			
Female	22	16	
Male	0	0	

End points

End points reporting groups

Reporting group title	S81694 + Paclitaxel
Reporting group description: The dose escalation phase I part was a single arm, non-randomised and non-comparative study in patient with mBC , guided by a Bayesian dose-finding design for drug combination trials.	
Subject analysis set title	Safety set
Subject analysis set type	Safety analysis
Subject analysis set description: The safety set consisted of all included patients who took at least one dose of IMP (either S81694 or paclitaxel).	
Subject analysis set title	DLT evaluable set
Subject analysis set type	Safety analysis
Subject analysis set description: The DLT evaluable set consisted of all patients of the Safety Set who were evaluable for DLT according to the DLT assessment at end of cycle 1. A patient was not considered evaluable if : -he/she discontinued treatment during DLTs assessment period for reasons other than DLT, or -he/she did not undergo a DLT assessment at C1D28 or on C2D1, or -he/she did not receive at least 90% (90% of paclitaxel and 90% of S81694) of associated agent prescribed doses from study entry to DLTs assessment visit (on C1D28 or on C2D1), unless treatment was stopped for a DLT, or -he/she did receive more than 110% of associated agent prescribed doses from study entry to DLT occurrence during the DLT assessment period.	

Primary: Recommended Phase II Dose

End point title	Recommended Phase II Dose ^[1]
End point description: During the dose-escalation, four S81694 dose levels were tested (13.5 mg/m ² /W; 20 mg/m ² /W; 30 mg/m ² /EOW; 45 mg/m ² /EOW) in combination with fixed dose paclitaxel (80 mg/m ² /W). Dose limiting Toxicity (DLT) was assessed during cycle 1 according to a Bayesian Logistic Regression Model for drug combination trials. One DLT at 20 mg/m ² /W (grade 3 acute kidney injury, grade 3 anaemia, grade 3 hyperkalaemia and grade 4 hyperuricaemia) was observed in one patient of the third cohort (20 mg/m ² /W of S81694 on D1, D8 and D15 in combination with paclitaxel 80 mg/m ² /W). Five successive cohorts were observed during C1. With the fifth cohort, following the sponsor's decision to discontinue the study, no Maximum Tolerated Dose (MTD) was reached. The highest combination tested, i.e. 45mg/m ² /EOW of S81694 (D1, D15) in combination with paclitaxel 80 mg/m ² /W (D1, D8, D15) had a median toxicity rate of 12% and a probability of being in the toxicity interval of 27%.	
End point type	Primary
End point timeframe: See description above.	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No statistical analysis for this endpoint.

End point values	DLT evaluable set			
Subject group type	Subject analysis set			
Number of subjects analysed	16 ^[2]			
Units: number of patients at risk	1			

Notes:

[2] - 16 patients were evaluable for DLT according to the DLT assessment at end of C1, 1 DLT identified.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were reported as follows:

Serious adverse events (SAE) during the study

Emergent adverse event (EAE) under treatment

Non-Emergent adverse events after treatment period

Death during the treatment and/or follow-up period

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	22
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Reporting groups

Reporting group title	S81694 13.5 mg/m2/W + Paclitaxel 80 mg/m2/W
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Reporting group description:

The investigational medicinal product S81694 was given in combination with paclitaxel 80mg/m2/W.

Reporting group title	S81694 30 mg/m2/EOW + Paclitaxel 80 mg/m2/W
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Reporting group description:

The investigational medicinal product S81694 was given in combination with paclitaxel 80mg/m2/W.

Reporting group title	S81694 45 mg/m2/EOW + Paclitaxel 80 mg/m2/W
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Reporting group description:

The investigational medicinal product S81694 was given in combination with paclitaxel 80mg/m2/W.

Reporting group title	S81694 20 mg/m2/W + Paclitaxel 80 mg/m2/W
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Reporting group description:

The investigational medicinal product S81694 was given in combination with paclitaxel 80mg/m2/W.

Serious adverse events	S81694 13.5 mg/m2/W + Paclitaxel 80 mg/m2/W	S81694 30 mg/m2/EOW + Paclitaxel 80 mg/m2/W	S81694 45 mg/m2/EOW + Paclitaxel 80 mg/m2/W
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 4 (25.00%)	1 / 4 (25.00%)	1 / 5 (20.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Malignant neoplasm progression			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metastases to central nervous system			

subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Malignant pleural effusion			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Pelvic venous thrombosis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	1 / 5 (20.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutropenia			
subjects affected / exposed	1 / 4 (25.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Pulmonary embolism			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	1 / 5 (20.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Delirium			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute kidney injury			

subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Osteonecrosis of jaw			
subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Pneumonia			
subjects affected / exposed	1 / 4 (25.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Hyperkalaemia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperuricaemia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	S81694 20 mg/m2/W + Paclitaxel 80 mg/m2/W		
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 9 (22.22%)		
number of deaths (all causes)	1		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Malignant neoplasm progression			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Metastases to central nervous			

system			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Malignant pleural effusion			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Pelvic venous thrombosis			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Neutropenia			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Pulmonary embolism			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Delirium			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Acute kidney injury			

subjects affected / exposed	1 / 9 (11.11%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Osteonecrosis of jaw			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Pneumonia			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Hyperkalaemia			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Hyperuricaemia			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	S81694 13.5 mg/m2/W + Paclitaxel 80 mg/m2/W	S81694 30 mg/m2/EOW + Paclitaxel 80 mg/m2/W	S81694 45 mg/m2/EOW + Paclitaxel 80 mg/m2/W
Total subjects affected by non-serious adverse events			
subjects affected / exposed	4 / 4 (100.00%)	4 / 4 (100.00%)	5 / 5 (100.00%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Cancer pain			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Malignant neoplasm progression			

subjects affected / exposed occurrences (all)	1 / 4 (25.00%) 1	0 / 4 (0.00%) 0	0 / 5 (0.00%) 0
Tumour associated fever subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	1 / 4 (25.00%) 1	0 / 5 (0.00%) 0
Vascular disorders			
Hot flush subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 4 (0.00%) 0	1 / 5 (20.00%) 1
Hypertension subjects affected / exposed occurrences (all)	1 / 4 (25.00%) 1	1 / 4 (25.00%) 1	0 / 5 (0.00%) 0
Lymphoedema subjects affected / exposed occurrences (all)	1 / 4 (25.00%) 1	0 / 4 (0.00%) 0	1 / 5 (20.00%) 1
Peripheral coldness subjects affected / exposed occurrences (all)	1 / 4 (25.00%) 1	0 / 4 (0.00%) 0	0 / 5 (0.00%) 0
General disorders and administration site conditions			
Fatigue subjects affected / exposed occurrences (all)	3 / 4 (75.00%) 3	1 / 4 (25.00%) 1	3 / 5 (60.00%) 3
Influenza like illness subjects affected / exposed occurrences (all)	2 / 4 (50.00%) 2	0 / 4 (0.00%) 0	0 / 5 (0.00%) 0
Malaise subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	1 / 4 (25.00%) 1	0 / 5 (0.00%) 0
Mucosal dryness subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	1 / 4 (25.00%) 1	0 / 5 (0.00%) 0
Oedema peripheral subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 4 (0.00%) 0	2 / 5 (40.00%) 4
Pain			

subjects affected / exposed occurrences (all)	1 / 4 (25.00%) 1	0 / 4 (0.00%) 0	0 / 5 (0.00%) 0
Pyrexia subjects affected / exposed occurrences (all)	1 / 4 (25.00%) 1	1 / 4 (25.00%) 1	2 / 5 (40.00%) 2
Immune system disorders Contrast media reaction subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 4 (0.00%) 0	1 / 5 (20.00%) 1
Reproductive system and breast disorders Vulvovaginal dryness subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 4 (0.00%) 0	1 / 5 (20.00%) 1
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	1 / 4 (25.00%) 1	1 / 5 (20.00%) 2
Dysphonia subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 4 (0.00%) 0	0 / 5 (0.00%) 0
Dyspnoea subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	1 / 4 (25.00%) 1	1 / 5 (20.00%) 3
Epistaxis subjects affected / exposed occurrences (all)	1 / 4 (25.00%) 1	0 / 4 (0.00%) 0	0 / 5 (0.00%) 0
Haemoptysis subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 4 (0.00%) 0	1 / 5 (20.00%) 1
Nasal crusting subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 4 (0.00%) 0	1 / 5 (20.00%) 1
Oropharyngeal pain subjects affected / exposed occurrences (all)	1 / 4 (25.00%) 1	0 / 4 (0.00%) 0	0 / 5 (0.00%) 0
Pleural effusion			

subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	1 / 4 (25.00%) 1	0 / 5 (0.00%) 0
Rhinitis allergic subjects affected / exposed occurrences (all)	1 / 4 (25.00%) 1	0 / 4 (0.00%) 0	0 / 5 (0.00%) 0
Vocal cord disorder subjects affected / exposed occurrences (all)	1 / 4 (25.00%) 1	0 / 4 (0.00%) 0	0 / 5 (0.00%) 0
Psychiatric disorders Anxiety subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	1 / 4 (25.00%) 1	1 / 5 (20.00%) 1
Insomnia subjects affected / exposed occurrences (all)	1 / 4 (25.00%) 1	0 / 4 (0.00%) 0	1 / 5 (20.00%) 1
Sleep disorder due to general medical condition, insomnia type subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	1 / 4 (25.00%) 1	0 / 5 (0.00%) 0
Investigations Alanine aminotransferase increased subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	1 / 4 (25.00%) 1	1 / 5 (20.00%) 1
Aspartate aminotransferase increased subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 4 (0.00%) 0	1 / 5 (20.00%) 1
Blood alkaline phosphatase increased subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 4 (0.00%) 0	1 / 5 (20.00%) 1
Blood phosphorus decreased subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 4 (0.00%) 0	1 / 5 (20.00%) 2
Electrocardiogram QT prolonged subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	1 / 4 (25.00%) 1	0 / 5 (0.00%) 0
Gamma-glutamyltransferase increased			

subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Lymphocyte count decreased			
subjects affected / exposed	1 / 4 (25.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	2	0	0
Neutrophil count decreased			
subjects affected / exposed	1 / 4 (25.00%)	1 / 4 (25.00%)	4 / 5 (80.00%)
occurrences (all)	2	2	4
Weight decreased			
subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Weight increased			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
White blood cell count decreased			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Infusion related reaction			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Joint injury			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Postmastectomy lymphoedema syndrome			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Skin injury			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Upper limb fracture			

subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 4 (0.00%) 0	1 / 5 (20.00%) 1
Nervous system disorders			
Ageusia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Brachial plexopathy			
subjects affected / exposed	1 / 4 (25.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Dysgeusia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	2 / 5 (40.00%)
occurrences (all)	0	0	2
Headache			
subjects affected / exposed	0 / 4 (0.00%)	2 / 4 (50.00%)	0 / 5 (0.00%)
occurrences (all)	0	2	0
Memory impairment			
subjects affected / exposed	1 / 4 (25.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Neuralgia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Neuropathy peripheral			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	2
Paraesthesia			
subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	2 / 5 (40.00%)
occurrences (all)	0	1	2
Peripheral sensory neuropathy			
subjects affected / exposed	1 / 4 (25.00%)	0 / 4 (0.00%)	1 / 5 (20.00%)
occurrences (all)	1	0	1
Sciatica			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Somnolence			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0

Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 4 (50.00%)	3 / 4 (75.00%)	2 / 5 (40.00%)
occurrences (all)	3	4	3
Iron deficiency anaemia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Lymphopenia			
subjects affected / exposed	1 / 4 (25.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Neutropenia			
subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Ear and labyrinth disorders			
Tinnitus			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Eye disorders			
Dry eye			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Keratitis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Lacrimation increased			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Vision blurred			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	2 / 5 (40.00%)
occurrences (all)	0	0	2
Abdominal pain upper			
subjects affected / exposed	1 / 4 (25.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0

Anal incontinence			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Cheilitis			
subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Constipation			
subjects affected / exposed	1 / 4 (25.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Diarrhoea			
subjects affected / exposed	2 / 4 (50.00%)	2 / 4 (50.00%)	3 / 5 (60.00%)
occurrences (all)	2	2	7
Dry mouth			
subjects affected / exposed	1 / 4 (25.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Dyspepsia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Epigastric discomfort			
subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Haemorrhoids			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Nausea			
subjects affected / exposed	2 / 4 (50.00%)	0 / 4 (0.00%)	1 / 5 (20.00%)
occurrences (all)	2	0	2
Odynophagia			
subjects affected / exposed	1 / 4 (25.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Stomatitis			
subjects affected / exposed	1 / 4 (25.00%)	0 / 4 (0.00%)	1 / 5 (20.00%)
occurrences (all)	2	0	1

Tooth discolouration subjects affected / exposed occurrences (all)	1 / 4 (25.00%) 1	0 / 4 (0.00%) 0	0 / 5 (0.00%) 0
Vomiting subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	2 / 4 (50.00%) 2	0 / 5 (0.00%) 0
Hepatobiliary disorders Hepatocellular injury subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 4 (0.00%) 0	1 / 5 (20.00%) 2
Skin and subcutaneous tissue disorders Alopecia subjects affected / exposed occurrences (all)	1 / 4 (25.00%) 1	2 / 4 (50.00%) 2	3 / 5 (60.00%) 3
Dry skin subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 4 (0.00%) 0	1 / 5 (20.00%) 1
Erythema subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 4 (0.00%) 0	1 / 5 (20.00%) 1
Hand dermatitis subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 4 (0.00%) 0	0 / 5 (0.00%) 0
Nail discolouration subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	1 / 4 (25.00%) 1	0 / 5 (0.00%) 0
Onychoclasia subjects affected / exposed occurrences (all)	1 / 4 (25.00%) 1	0 / 4 (0.00%) 0	0 / 5 (0.00%) 0
Onycholysis subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 4 (0.00%) 0	2 / 5 (40.00%) 2
Palmar-plantar erythrodysaesthesia syndrome subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 4 (0.00%) 0	0 / 5 (0.00%) 0
Pruritus generalised			

subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Rash			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	7
Rash erythematous			
subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Rash maculo-papular			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	2
Skin reaction			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Urinary incontinence			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 4 (25.00%)	1 / 4 (25.00%)	0 / 5 (0.00%)
occurrences (all)	2	1	0
Arthritis			
subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Back pain			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Bone pain			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Joint stiffness			

subjects affected / exposed	1 / 4 (25.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Muscle spasms			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	2
Musculoskeletal discomfort			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Myalgia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	3
Neck pain			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Pain in extremity			
subjects affected / exposed	1 / 4 (25.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Periarthritis			
subjects affected / exposed	1 / 4 (25.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Infections and infestations			
Conjunctivitis			
subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Gastroenteritis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Lung infection			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Nasopharyngitis			
subjects affected / exposed	1 / 4 (25.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Paronychia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0

Rhinitis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Sinusitis			
subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Tooth infection			
subjects affected / exposed	1 / 4 (25.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Upper respiratory tract infection			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Urinary tract infection			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	4
Viral upper respiratory tract infection			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	0 / 4 (0.00%)	2 / 4 (50.00%)	3 / 5 (60.00%)
occurrences (all)	0	2	4
Fluid retention			
subjects affected / exposed	1 / 4 (25.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Hyperglycaemia			
subjects affected / exposed	1 / 4 (25.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Hypocalcaemia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Hypokalaemia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	2
Hypophosphataemia			

subjects affected / exposed	1 / 4 (25.00%)	2 / 4 (50.00%)	0 / 5 (0.00%)
occurrences (all)	1	2	0

Non-serious adverse events	S81694 20 mg/m2/W + Paclitaxel 80 mg/m2/W		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	8 / 9 (88.89%)		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Cancer pain			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Malignant neoplasm progression			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Tumour associated fever			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Vascular disorders			
Hot flush			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Hypertension			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Lymphoedema			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Peripheral coldness			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	6 / 9 (66.67%)		
occurrences (all)	8		
Influenza like illness			

subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Malaise			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Mucosal dryness			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Oedema peripheral			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Pain			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Pyrexia			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Immune system disorders			
Contrast media reaction			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Reproductive system and breast disorders			
Vulvovaginal dryness			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Dysphonia			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Dyspnoea			
subjects affected / exposed	2 / 9 (22.22%)		
occurrences (all)	2		
Epistaxis			

subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Haemoptysis			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Nasal crusting			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Oropharyngeal pain			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Pleural effusion			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Rhinitis allergic			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Vocal cord disorder			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Insomnia			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Sleep disorder due to general medical condition, insomnia type			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Aspartate aminotransferase increased			

subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Blood alkaline phosphatase increased			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Blood phosphorus decreased			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Electrocardiogram QT prolonged			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Gamma-glutamyltransferase increased			
subjects affected / exposed	2 / 9 (22.22%)		
occurrences (all)	2		
Lymphocyte count decreased			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Neutrophil count decreased			
subjects affected / exposed	4 / 9 (44.44%)		
occurrences (all)	12		
Weight decreased			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Weight increased			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
White blood cell count decreased			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	2 / 9 (22.22%)		
occurrences (all)	2		
Infusion related reaction			

subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Joint injury			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Postmastectomy lymphoedema syndrome			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Skin injury			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Upper limb fracture			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Nervous system disorders			
Ageusia			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Brachial plexopathy			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Dysgeusia			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Headache			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Memory impairment			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Neuralgia			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Neuropathy peripheral			

subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Paraesthesia			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Peripheral sensory neuropathy			
subjects affected / exposed	3 / 9 (33.33%)		
occurrences (all)	3		
Sciatica			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Somnolence			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	4 / 9 (44.44%)		
occurrences (all)	6		
Iron deficiency anaemia			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Lymphopenia			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Neutropenia			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Ear and labyrinth disorders			
Tinnitus			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Eye disorders			
Dry eye			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Keratitis			

subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Lacrimation increased			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Vision blurred			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Abdominal pain upper			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Anal incontinence			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Cheilitis			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Constipation			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	2		
Diarrhoea			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Dry mouth			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Dyspepsia			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Epigastric discomfort			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		

Gastrooesophageal reflux disease subjects affected / exposed occurrences (all)	1 / 9 (11.11%) 1		
Haemorrhoids subjects affected / exposed occurrences (all)	1 / 9 (11.11%) 1		
Nausea subjects affected / exposed occurrences (all)	1 / 9 (11.11%) 2		
Odynophagia subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0		
Stomatitis subjects affected / exposed occurrences (all)	1 / 9 (11.11%) 1		
Tooth discolouration subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0		
Vomiting subjects affected / exposed occurrences (all)	1 / 9 (11.11%) 2		
Hepatobiliary disorders Hepatocellular injury subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0		
Skin and subcutaneous tissue disorders Alopecia subjects affected / exposed occurrences (all)	3 / 9 (33.33%) 3		
Dry skin subjects affected / exposed occurrences (all)	1 / 9 (11.11%) 1		
Erythema subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0		
Hand dermatitis			

subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Nail discolouration			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Onychoclasia			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Onycholysis			
subjects affected / exposed	3 / 9 (33.33%)		
occurrences (all)	3		
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Pruritus generalised			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Rash			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Rash erythematous			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Rash maculo-papular			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Skin reaction			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Urinary incontinence			

subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Arthritis			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Back pain			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Bone pain			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Joint stiffness			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Muscle spasms			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Musculoskeletal discomfort			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Myalgia			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Neck pain			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Pain in extremity			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Periarthritis			

subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Infections and infestations			
Conjunctivitis			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Gastroenteritis			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Lung infection			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Nasopharyngitis			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Paronychia			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Rhinitis			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Sinusitis			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Tooth infection			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Upper respiratory tract infection			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Urinary tract infection			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Viral upper respiratory tract infection			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		

Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Fluid retention			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Hyperglycaemia			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Hypocalcaemia			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Hypokalaemia			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Hypophosphataemia			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
24 July 2017	Following the requests from the Competent Authority in Japan, it mainly concerned the definition of the initial dose of S81694 and added a check for HIV and HCV antibodies and HBs antigen.
15 January 2018	It mainly concerned the possibility of dose modification for paclitaxel in case of occurrence of toxicity, the patient authorisation when benefiting from treatment to continue on study despite a criterion for discontinuation, recommendations in case of extravasation of S81694 during infusion or contact of the study drug with the eye, and the requirement for a pregnancy test.
08 June 2018	It mainly concerned the extent of the range of doses of S81694 and the associated dose escalation design, the number of patients needed for the phase I-part, contraindicated drugs and concomitant treatments to be used with caution and the inclusion/exclusion criteria accordingly, the urinary pregnancy test, the table related to S81694 "dose reduction applied in case of toxicity".
14 December 2018	It mainly concerned the change of S81694 administration schedule: two administrations on D1 and D15 of a 28-day cycle instead of three administrations on days 1, 8 and 15 of a 28-day cycle. This new administration schedule of S81694 at D1/D15 was applied from cohort 4.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
02 December 2019	The sponsor decided to discontinue the study CL1-81694-003, with S81694 in combination with paclitaxel in mBC. This decision was related to the likely narrow therapeutic margin of S81694 in combination with paclitaxel and the emergence of effective immune therapies in mTNBC (very recent changes in competitive environment).	-

Notes:

Limitations and caveats

None reported