



## Clinical trial results:

### Phase II study for the evaluation of neoadjuvant treatment with cabozantinib prior to cytoreductive nephrectomy in patients with locally advanced or metastatic renal cell carcinoma

#### Summary

EudraCT number	2018-001201-93
Trial protocol	ES
Global end of trial date	09 August 2022

#### Results information

Result version number	v1 (current)
This version publication date	04 November 2022
First version publication date	04 November 2022
Summary attachment (see zip file)	Summary CABOPRE study 2018-001201-93 (Summary_CABOPREstudy.docx)

#### Trial information

##### Trial identification

Sponsor protocol code	CABOPRE
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##### Additional study identifiers

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

Notes:

#### Sponsors

Sponsor organisation name	Fundación ONCOSUR
Sponsor organisation address	Gran Via del Marqués del Túria, Valencia, Spain, 46005
Public contact	PLATAFORMA DE ENSAYOS CLÍNICOS, Fundación ONCOSUR, 34 628 88 64 20, secretaria_tecnica@oncosur.org
Scientific contact	PLATAFORMA DE ENSAYOS CLÍNICOS, Fundación ONCOSUR, 34 628 88 64 20, secretaria_tecnica@oncosur.org

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:

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## Results analysis stage

Analysis stage	Final
Date of interim/final analysis	02 May 2022
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	09 August 2022
Was the trial ended prematurely?	No

Notes:

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## General information about the trial

Main objective of the trial:

This Phase II study was designed to evaluate the effectiveness of preoperative treatment with cabozantinib (Cabometyx), measured by the radiological response rate prior to cytoreductive nephrectomy, in patients with advanced or metastatic renal cell carcinoma who are candidates for cytoreductive nephrectomy .

Protection of trial subjects:

This study was conducted in accordance with the basic ethical principles contained in the Declaration of Helsinki (version of Fortaleza, Brazil, October 2013), and with the Spanish regulations (Royal Decree 1090/2015, of 4 December, regulating clinical trials with medicinal products, Research Ethics Committees with medicinal products and the Spanish Clinical Studies Registry). Participation of the investigators in this study was free, voluntary and independent. Both the principal investigators and the rest of the personnel engaged in the study were bound to comply with GCP standards, as described in the ICH Tripartite and Harmonized GCP guideline (2016 revision).

All patients provided written informed consent to participate in the study prior to being screened.

The patient information sheet detailed the procedures involved in the study (objectives, methodology, potential risks, anticipated benefits) and the investigator explained these to each patient. The patient signed the consent form to indicate that the information had been explained and understood. The patient was then allowed time to consider the information presented before signing and dating the informed consent form to indicate that they fully understood the information, and willingly volunteered to participate in the study. The patient was given a copy of the informed consent form for their information. The original copy of the informed consent was kept in a confidential file in the Investigators' site records.

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Background therapy:

The rest of the treatments other than treatment with cabozantinib during the trial are considered concomitant treatments and were collected in the medical record.

Participating patients were reminded not to take any concomitant treatments without informing the investigator, subject to their authorization.

Prohibited medications

- Oral anticoagulants (e.g., warfarin, direct thrombin and Factor Xa) inhibitors and antiplatelet agents (although low dose aspirin is allowed).
- VEGF growth factor targeted therapy

Medications to use with caution

- CYP3A4 inhibitors: Caution should be exercised when administering cabozantinib concomitantly with strong inhibitors of CYP3A4 (for example, ketoconazole, ritonavir, itraconazole, erythromycin, clarithromycin, grapefruit juice)
- CYP3A4 inducers: chronic administration of strong inducers of CYP3A4 should be avoided with cabozantinib (e.g., phenytoin, carbamazepine, rifampicin, phenobarbital or natural remedies with St. John's wort [Hypericum perforatum])
- P-glycoprotein substrates. Subjects should be warned about the use of Pgp substrates (e.g., fexofenadine, aliskiren, ambrisentan, dabigatran etexilate, digoxin, colchicine, maraviroc, posaconazole, ranolazine, saxagliptin, sitagliptin, talinolol, tolvaptan)
- MRP2 inhibitors: Caution should be exercised when administering concomitantly with MRP2 inhibitors (such as cyclosporin, efavirenz or emtricitabine)
- Drugs that can prolong the QT should be avoided (and used with caution in patients with a

history of QT interval prolongation), patients who are on anti-arrhythmia medication, or patients with relevant pre-existing heart disease, bradycardia or electrolyte disorders)

- Bile salt chelates

Evidence for comparator:

Not applicable

Actual start date of recruitment	01 October 2018
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	Spain: 18
Worldwide total number of subjects	18
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)	18
From 65 to 84 years	0
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details:

Patients with advanced or metastatic renal cell carcinoma who were candidates for primary tumor CN were recruited in eight centers in Spain.

### Pre-assignment

Screening details:

Twenty patients with advanced or metastatic renal cell carcinoma who were candidates for primary tumor CN fulfilling selection criteria were pre-screened, of which 3 did not receive the study medication.

### Period 1

Period 1 title	Overall Trial (overall period)
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

### Arms

<b>Arm title</b>	Cabozantinib
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	Cabozantinib 60 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Patients took a daily pill for 12 weeks. The tablets should be swallowed whole without crushing. Patients should be directed not to eat anything for at least 2 hours before taking cabozantinib and one hour after doing so.

Number of subjects in period 1	Cabozantinib
Started	18
Completed	15
Not completed	3
Protocol deviation	3

## Baseline characteristics

### Reporting groups

Reporting group title	Overall Trial
Reporting group description: -	

Reporting group values	Overall Trial	Total	
Number of subjects	18	18	
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	57.1		
standard deviation	± 10.9	-	
Gender categorical			
Units: Subjects			
Female	6	6	
Male	12	12	
Comorbidities			
Previous comorbidities of interest			
Units: Subjects			
Yes	17	17	
No	1	1	
Smoking status			
Units: Subjects			
Current smoker	5	5	
Former smoker	5	5	
Never smoke	8	8	
Previous surgery			
Previous surgery of interest			
Units: Subjects			
Yes	10	10	
No	8	8	
ECOG status			
Units: Subjects			
ECOG 0	5	5	
ECOG 1	11	11	
Missing	2	2	

Karnofsky Performance Status			
Units: Subjects			
Rating 70 %	0	0	
Rating 80%	7	7	
Rating 90%	4	4	
Rating 100%	5	5	
Missing	2	2	
Metastasis			
Units: Subjects			
Yes	18	18	
No	0	0	
Number of metastatic location			
Units: Subjects			
One	6	6	
Two	8	8	
Three	2	2	
Four	1	1	
Five	1	1	
Metastatic location			
Units: Subjects			
Bone	2	2	
Liver	2	2	
Other	14	14	
TNM Classification of Malignant Tumors (TNM)-T			
Tumor extent			
Units: Subjects			
T1	1	1	
T2	2	2	
T3	1	1	
T3a	1	1	
T3b	2	2	
T3c	2	2	
T4	8	8	
Missing	1	1	
TNM Classification of Malignant Tumors (TNM)-N			
Lymph node status			
Units: Subjects			
N0	7	7	
N1	7	7	
Missing	4	4	
TNM Classification of Malignant Tumors (TNM)-M			
Metastasis			
Units: Subjects			
M0	0	0	
M1	18	18	
IMDC Risk score			
IMDC (International Metastatic RCC Database Consortium) Risk Model for Metastatic Renal Cell Carcinoma			
Units: Subjects			

Favorable risk	0	0	
Intermediate risk	14	14	
Poor risk	4	4	
MSKCC/Motzer risk score			
Memorial Sloan-Kettering Cancer Center (MSKCC) prognostic model			
Units: Subjects			
Favorable risk	0	0	
Intermediate risk	14	14	
Poor risk	4	4	
Height			
Units: cm			
arithmetic mean	167.8		
standard deviation	± 9.4	-	
BMI			
Body Mass INDEX			
Units: KG/M2			
arithmetic mean	25.5		
standard deviation	± 5.9	-	
Weight			
Units: kg			
arithmetic mean	74.1		
standard deviation	± 18.3	-	
Respiratory rate			
Units: breaths/min			
arithmetic mean	16.2		
standard deviation	± 1.5	-	
Heart rate			
Units: beats/min			
arithmetic mean	81.9		
standard deviation	± 17.8	-	
Systolic Blood Pressure			
Units: mmHg			
arithmetic mean	123.7		
standard deviation	± 16.1	-	
Diastolic Blood Pressure			
Units: mmHg			
arithmetic mean	72.6		
standard deviation	± 12.8	-	
Temperature			
Units: celsius temperature			
arithmetic mean	36.2		
standard deviation	± 0.5	-	
Time smoking			
Units: months			
arithmetic mean	334.5		
standard deviation	± 205.3	-	
Number of cigarretes			
Units: Cigarretes/day			
arithmetic mean	22.5		
standard deviation	± 2.9	-	
Time between diagnosis of the primary tumor and inclusion of the patient in the			

study			
Units: days			
arithmetic mean	25.41		
standard deviation	± 24.30	-	
Time between diagnosis of metastatic/advanced disease and inclusion of the patient in the study			
Units: days			
arithmetic mean	27.82		
standard deviation	± 23.99	-	
Time between primary tumor diagnosis and the start of cabozatinib treatment			
Units: days			
arithmetic mean	34.7		
standard deviation	± 24.7	-	
Time between advanced/metastatic disease diagnosis-initiation of cabozatinib treatment			
Units: days			
arithmetic mean	36.3		
standard deviation	± 24.6	-	
LDH			
Units: UI/L			
arithmetic mean	439.2		
standard deviation	± 538.1	-	
Calcium			
Units: mg/dL			
arithmetic mean	9.9		
standard deviation	± 0.8	-	
Hemoglobin			
Units: g/dl			
arithmetic mean	12.1		
standard deviation	± 2.4	-	
Neutrophils			
Units: cells per microliter			
arithmetic mean	6.9		
standard deviation	± 4.9	-	
Platelets			
Units: cells per microliter			
arithmetic mean	377.5		
standard deviation	± 126.5	-	

### Subject analysis sets

Subject analysis set title	FAS population
Subject analysis set type	Full analysis
Subject analysis set description:	
Patients who have received at least one dose of the study medication.	
Subject analysis set title	SAF
Subject analysis set type	Safety analysis
Subject analysis set description:	
Safety analysis population	



Reporting group values	FAS population	SAF	
Number of subjects	18	18	
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	57.1		
standard deviation	± 10.9	±	
Gender categorical Units: Subjects			
Female	6		
Male	12		
Comorbidities			
Previous comorbidities of interest			
Units: Subjects			
Yes	17		
No	1		
Smoking status Units: Subjects			
Current smoker	5		
Former smoker	5		
Never smoke	8		
Previous surgery			
Previous surgery of interest			
Units: Subjects			
Yes	10		
No	8		
ECOG status Units: Subjects			
ECOG 0	5		
ECOG 1	11		
Missing	2		
Karnofsky Performance Status Units: Subjects			
Rating 70 %	0		
Rating 80%	7		
Rating 90%	4		
Rating 100%	5		
Missing	2		
Metastasis Units: Subjects			

Yes	18		
No	0		
Number of metastatic location Units: Subjects			
One	6		
Two	8		
Three	2		
Four	1		
Five	1		
Metastatic location Units: Subjects			
Bone	2		
Liver	2		
Other	14		
TNM Classification of Malignant Tumors (TNM)-T			
Tumor extent			
Units: Subjects			
T1	1		
T2	2		
T3	1		
T3a	1		
T3b	2		
T3c	2		
T4	8		
Missing	1		
TNM Classification of Malignant Tumors (TNM)-N			
Lymph node status			
Units: Subjects			
N0	7		
N1	7		
Missing	4		
TNM Classification of Malignant Tumors (TNM)-M			
Metastasis			
Units: Subjects			
M0	0		
M1	18		
IMDC Risk score			
IMDC (International Metastatic RCC Database Consortium) Risk Model for Metastatic Renal Cell Carcinoma			
Units: Subjects			
Favorable risk	0		
Intermediate risk	14		
Poor risk	4		
MSKCC/Motzer risk score			
Memorial Sloan-Kettering Cancer Center (MSKCC) prognostic model			
Units: Subjects			
Favorable risk	0		
Intermediate risk	14		
Poor risk	4		

Height Units: cm arithmetic mean standard deviation	167.8 ± 9.4	±	
BMI			
Body Mass iNDEX			
Units: KG/M2 arithmetic mean standard deviation	25.5 ± 5.9	±	
Weight Units: kg arithmetic mean standard deviation	74.1 ± 18.3	±	
Respiratory rate Units: breaths/min arithmetic mean standard deviation	16.2 ± 1.5	±	
Heart rate Units: beats/min arithmetic mean standard deviation	81.9 ± 17.8	±	
Systolic Blood Pressure Units: mmHg arithmetic mean standard deviation	123.7 ± 16.1	±	
Diastolic Blood Pressure Units: mmHg arithmetic mean standard deviation	72.6 ± 12.8	±	
Temperature Units: celsius temperature arithmetic mean standard deviation	36.2 ± 0.5	±	
Time smoking Units: months arithmetic mean standard deviation	334.5 ± 205.3	±	
Number of cigarretes Units: Cigarretes/day arithmetic mean standard deviation	22.5 ± 2.9	±	
Time between diagnosis of the primary tumor and inclusion of the patient in the study Units: days arithmetic mean standard deviation	25.41 ± 24.30	±	
Time between diagnosis of metastatic/advanced disease and inclusion of the patient in the study Units: days arithmetic mean standard deviation	27.82 ± 23.99	±	

Time between primary tumor diagnosis and the start of cabozatinib treatment Units: days arithmetic mean standard deviation	34.7 ± 24.7	±	
Time between advanced/metastatic disease diagnosis-initiation of cabozatinib treatment Units: days arithmetic mean standard deviation	36.3 ± 24.6	±	
LDH Units: UI/L arithmetic mean standard deviation	439.2 ± 538.1	±	
Calcium Units: mg/dL arithmetic mean standard deviation	9.9 ± 0.8	±	
Hemoglobin Units: g/dl arithmetic mean standard deviation	12.1 ± 2.4	±	
Neutrophils Units: cells per microliter arithmetic mean standard deviation	6.9 ± 4.9	±	
Platelets Units: cells per microliter arithmetic mean standard deviation	377.5 ± 126.5	±	

## End points

### End points reporting groups

Reporting group title	Cabozantinib
Reporting group description: -	
Subject analysis set title	FAS population
Subject analysis set type	Full analysis
Subject analysis set description:	
Patients who have received at least one dose of the study medication.	
Subject analysis set title	SAF
Subject analysis set type	Safety analysis
Subject analysis set description:	
Safety analysis population	

### Primary: Radiological response rate prior to cytoreductive nephrectomy (CN)

End point title	Radiological response rate prior to cytoreductive nephrectomy (CN) <sup>[1]</sup>
End point description:	
Objective response to preoperative treatment with cabozantinib, defined as the percentage of patients that reach complete or partial radiological response after a 12-week cycle of treatment with cabozantinib, defined according to the RECIST 1.1 criteria (Eisenhauer et al. 2009)	
End point type	Primary
End point timeframe:	
At 12 weeks following the start of the treatment.	

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: Due to the sample size limitations, results are mainly descriptive.

<b>End point values</b>	FAS population			
Subject group type	Subject analysis set			
Number of subjects analysed	15			
Units: subjects				
Partial response	4			
Stable disease	10			
Progression	1			

<b>Attachments (see zip file)</b>	Radiological response rate prior to CN (FAS)/Figure Radiological
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### Statistical analyses

No statistical analyses for this end point

### Secondary: Complete or partial radiological response (CR + PR)

End point title	Complete or partial radiological response (CR + PR)
End point description:	
Best objective response during treatment with cabozantinib, defined as the percentage of patients that reach complete or partial radiological response during treatment with cabozantinib.	
End point type	Secondary

End point timeframe:  
During treatment with cabozantinib

<b>End point values</b>	FAS population			
Subject group type	Subject analysis set			
Number of subjects analysed	12			
Units: subjects				
Complete response (CP)	1			
Partial response (PR)	2			
Stable disease	4			
Progression	5			
CP+PR	3			

### Statistical analyses

No statistical analyses for this end point

### Secondary: Progression free survival (PFS)

End point title	Progression free survival (PFS)
End point description: Free Survival, defined as the time (in months) elapsed since the start of treatment with cabozantinib until progression of the disease (according to the RECIST criteria 1.1).	
End point type	Secondary
End point timeframe: In patients undergoing CN after treatment with cabozantinib.	

<b>End point values</b>	FAS population			
Subject group type	Subject analysis set			
Number of subjects analysed				
Units: months				
median (confidence interval 95%)	7.8 (5.1 to )			

<b>Attachments (see zip file)</b>	PFS (FAS)/Figure Progression-free Survival - FAS.docx
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### Statistical analyses

No statistical analyses for this end point

### Secondary: Overall survival (OS)

End point title	Overall survival (OS)
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End point description:

Overall Survival, defined as the time (in months) elapsed since the start of treatment with cabozantinib until the death of the patient.

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End point type	Secondary
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End point timeframe:

In patients undergoing CN after a 12-month treatment with cabozantinib.

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<b>End point values</b>	FAS population			
Subject group type	Subject analysis set			
Number of subjects analysed				
Units: months				
median (confidence interval 95%)	12.0 (1.4 to )			

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<b>Attachments (see zip file)</b>	OS (FAS)/Figure Overall Survival-FAS.docx
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### Statistical analyses

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No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

The safety and tolerability of cabozantinib have been assessed based on the total number of adverse events recorded during patient follow-up.

Assessment type	Non-systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	27
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### Reporting groups

Reporting group title	SAF population
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Reporting group description:

Safety assessment population

Serious adverse events	SAF population		
Total subjects affected by serious adverse events			
subjects affected / exposed	8 / 18 (44.44%)		
number of deaths (all causes)	4		
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Neoplasm progression			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Surgical and medical procedures			
Hospitalisation			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Cervical cord compression			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Asthenia			



subjects affected / exposed	1 / 18 (5.56%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Death			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Gastrointestinal disorders			
Intestinal pseudo-obstruction			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Reproductive system and breast disorders			
Prostatic obstruction			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pulmonary thrombosis			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Fracture			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Oral candidiasis			

subjects affected / exposed	1 / 18 (5.56%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Superinfection			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infection	Additional description: Post-surgical infection		
subjects affected / exposed	1 / 18 (5.56%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	SAF population		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	17 / 18 (94.44%)		
Cardiac disorders			
Hypertension			
subjects affected / exposed	10 / 18 (55.56%)		
occurrences (all)	10		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	12 / 18 (66.67%)		
occurrences (all)	12		
Decreased appetite			
subjects affected / exposed	6 / 18 (33.33%)		
occurrences (all)	6		
Dysgeusia			
subjects affected / exposed	3 / 18 (16.67%)		
occurrences (all)	3		
Weight loss			
subjects affected / exposed	2 / 18 (11.11%)		
occurrences (all)	2		
Gastrointestinal disorders			

Diarrhoea subjects affected / exposed occurrences (all)	11 / 18 (61.11%) 11		
Nausea subjects affected / exposed occurrences (all)	7 / 18 (38.89%) 7		
Hepatobiliary disorders Hypertransaminasaemia subjects affected / exposed occurrences (all)	6 / 18 (33.33%) 6		
Skin and subcutaneous tissue disorders Mucositis subjects affected / exposed occurrences (all)	7 / 18 (38.89%) 7		
Hand and foot syndrome subjects affected / exposed occurrences (all)	4 / 18 (22.22%) 4		
Renal and urinary disorders Renal impairment subjects affected / exposed occurrences (all)	2 / 18 (11.11%) 2		
Endocrine disorders Hypothyroidism subjects affected / exposed occurrences (all)	3 / 18 (16.67%) 3		

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

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### 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.

The achieved sample has been smaller than the planned 50 thus, a mainly descriptive final result analysis was conducted, as presented herein.
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Notes: