

**Clinical trial results:****A single arm Pharmacokinetic/Pharmacodynamic Study of Sunitinib and Pazopanib in Patients with Metastasized Renal Cell Carcinoma****Summary**

EudraCT number	2012-001415-23
Trial protocol	DE
Global end of trial date	01 July 2015

Results information

Result version number	v1 (current)
This version publication date	04 October 2018
First version publication date	04 October 2018

Trial information**Trial identification**

Sponsor protocol code	C-IV-001
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Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Central European Society for Anticancer Drug Research
Sponsor organisation address	Hanglössgasse, 4/1-3, Vienna, Austria, 1150
Public contact	CESAR, Central European Society for Anticancer Drug Research - EWIV, 0043 6765273814, max.roessler@cesar.or.at
Scientific contact	CESAR, Central European Society for Anticancer Drug Research - EWIV, 6765273814 6765273814, max.roessler@cesar.or.at

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 December 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	01 July 2015
Global end of trial reached?	Yes
Global end of trial date	01 July 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Develop PK/PD models for sunitinib and pazopanib including biomarker response (blood pressure, sVEGFR2, sVEGFR3) as PD marker

Protection of trial subjects:

Patient are treated in accordance with clinical routine. Additional blood draws for PK/PD analysis are performed in course of routine needle puncture if possible.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	21 March 2013
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	Netherlands: 10
Country: Number of subjects enrolled	Germany: 34
Worldwide total number of subjects	44
EEA total number of subjects	44

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)	19
From 65 to 84 years	25
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Recruitment of patients was performed on 9 study sites in Germany and 2 study sites in the Netherlands

Pre-assignment

Screening details:

The screening criteria were defined by the inclusion and exclusion criteria as defined in the study protocol.

Period 1

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

Arms

Arm title	Treatment Arm
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Arm description:

Patient which were being treated with Pazopanib or Sunitinib as standard of care treatment against their Metastasized Renal Cell Carcinoma and fulfilling all inclusion criteria where eligible for the the study. Participants were treated according to dosing regimens described in current guidelines and the SmPC for Sutent® and Votrient® or a respective generic drug as well as to the physician's discretion. Patients remained on study until a total of three sunitinib-cycles (4 weeks on/2-weeks off treatment) or in case of pazopanib for 18 weeks of daily administration or until withdrawal of patient's consent or withdrawal by the treating physician for safety reasons or due tumor progression, whatever happened first. Following study completion, patients received further treatment according to best local practice and remain in the EuroTARGET non-interventional study.

Arm type	Experimental
Investigational medicinal product name	Pazopanib
Investigational medicinal product code	L01XE11
Other name	votrient
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Participants were treated according to dosing regimens described in current guidelines and the SmPC for Votrient® or a respective generic drug as well as to the physician's discretion.

Investigational medicinal product name	Sunitinib
Investigational medicinal product code	L01XE04
Other name	Sutent
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Sunitinib was administered according to SmPC

Number of subjects in period 1	Treatment Arm
Started	44
Completed	44

Baseline characteristics

Reporting groups

Reporting group title	Overall trial
Reporting group description:	
Complete study population including sunitinib and pazopanib patients	

Reporting group values	Overall trial	Total	
Number of subjects	44	44	
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	65.16		
standard deviation	± 9.35	-	
Gender categorical			
Patients in ITT			
Units: Subjects			
Female	11	11	
Male	33	33	

End points

End points reporting groups

Reporting group title	Treatment Arm
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Reporting group description:

Patient which were being treated with Pazopanib or Sunitinib as standard of care treatment against their Metastasized Renal Cell Carcinoma and fulfilling all inclusion criteria where eligible for the the study. Participants were treated according to dosing regimens described in current guidelines and the SmPC for Sutent® and Votrient® or a respective generic drug as well as to the physician's discretion. Patients remained on study until a total of three sunitinib-cycles (4 weeks on/2-weeks off treatment) or in case of pazopanib for 18 weeks of daily administration or until withdrawal of patient's consent or withdrawal by the treating physician for safety reasons or due tumor progression, whatever happened first. Following study completion, patients received further treatment according to best local practice and remain in the EuroTARGET non-interventional study.

Subject analysis set title	ITT Sutent + Pazopanib
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Subject analysis set type	Full analysis
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Subject analysis set description:

All patient treated with Sutent or Pazopanib were included in this analysis set

Subject analysis set title	ITT Sutent
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Subject analysis set type	Full analysis
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Subject analysis set description:

All patient treated with Sutent or Pazopanib were included in this analysis set

Primary: sVEGFR2 in plasma (sunitinib subgroup)

End point title	sVEGFR2 in plasma (sunitinib subgroup)
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End point description:

sVEGFR-2 plasma concentration was measured at baseline before the first drug intake and over the course of the therapy

End point type	Primary
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End point timeframe:

Patients remained on study until a total of three sunitinib-cycles (4 weeks on/2-weeks off treatment) or until withdrawal of patient's consent or withdrawal by the treating physician for safety reasons or due tumor progression, whatever happened first.

End point values	Treatment Arm	ITT Sutent + Pazopanib		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	27 ^[1]	44		
Units: Concentration				
number (not applicable)	27	44		

Notes:

[1] - Sunitinib only, three subjects were not applicable for endpoint analysis, only for PK/PD modeling

Statistical analyses

Statistical analysis title	Model based TTE analysis sVEGFR-2 baseline
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Statistical analysis description:

Relationship between sVEGFR-2 baseline values and progression-free survival in the sunitinib cohort was analyzed in a model based time-to-event (TTE) analysis using NONMEM 7.3 (Hazard model)

Comparison groups	Treatment Arm v ITT Sutent + Pazopanib
Number of subjects included in analysis	71
Analysis specification	Pre-specified
Analysis type	other ^[2]
P-value	≤ 0.05 ^[3]
Method	Chi-squared
Parameter estimate	Beta
Point estimate	1.45
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.71
upper limit	2.68
Variability estimate	Standard error of the mean
Dispersion value	43.3

Notes:

[2] - Biomarker Analysis

Comment to "Subjects in this analysis": Only 44 patients were analyzed in this group and there was no control group, but the EudraCT-DB does not accept this entry.

[3] - As the objective function (OF) of NONMEM the OF value must reach at least 3.84 in order to be considered as significant ($p < 0,05$).

Primary: sVEGFR-2 in plasma (sunitinib + pazopanib)

End point title	sVEGFR-2 in plasma (sunitinib + pazopanib)
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End point description:

sVEGFR-2 plasma concentration was measured at baseline before the first drug intake and over the course of the therapy

End point type	Primary
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End point timeframe:

Patients remained on study until a total of three sunitinib-cycles or 18 weeks with pazopanib or until withdrawal of patient's consent or withdrawal by the treating physician for safety reasons or due tumor progression, whatever happened first.

End point values	Treatment Arm	ITT Sutent + Pazopanib		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	44 ^[4]	27		
Units: Concentration				
number (not applicable)	44	27		

Notes:

[4] - total study, four subjects were not applicable for endpoint analysis, only for PK/PD modeling

Statistical analyses

Statistical analysis title	Model based TTE analysis sVEGFR-2 over time
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Statistical analysis description:

Relationship between pharmacokinetic/pharmacodynamic models for sVEGFR-2 and progression-free survival in the sunitinib and pazopanib cohorts was analyzed in a model based time-to-event (TTE) analysis using NONMEM 7.3

(Hazard model)

Comparison groups	Treatment Arm v ITT Sutent + Pazopanib
Number of subjects included in analysis	71
Analysis specification	Pre-specified
Analysis type	other ^[5]
Method	Chi-squared
Parameter estimate	Beta
Point estimate	0.292
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.153
upper limit	0.458
Variability estimate	Standard error of the mean
Dispersion value	30.9

Notes:

[5] - Biomarker Analysis

Comment to "Subjects in this analysis": Only 27 patients were analyzed in this group and there was no control group, but the EudraCT-DB does not accept this entry.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All adverse events, which are observed during and 28-35 days after study drug administration will be recorded.

Assessment type	Non-systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	15.1
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Reporting groups

Reporting group title	Sunitinib
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Reporting group description:

Participants are treated according to dosing regimens described in current guidelines and the SmPC for Sutent as well as to the physician's discretion.

Usually a 4/2 therapy cycle is applied. Patients take a defined dose of sunitinib (usually 50 mg) per day for four weeks followed by an off-phase of two weeks without an antiangiogenic treatment.

Reporting group title	Pazopanib
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Reporting group description:

Participants are treated according to dosing regimens described in current guidelines and the SmPC for Pazopanib as well as to the physician's discretion.

Typically pazopanib is administered once daily continuously.

Serious adverse events	Sunitinib	Pazopanib	
Total subjects affected by serious adverse events			
subjects affected / exposed	12 / 27 (44.44%)	5 / 17 (29.41%)	
number of deaths (all causes)	5	1	
number of deaths resulting from adverse events	1	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Neoplasm malignant			
subjects affected / exposed	1 / 27 (3.70%)	0 / 17 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Vascular disorders			
Circulatory collapse			
subjects affected / exposed	1 / 27 (3.70%)	0 / 17 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Surgical and medical procedures			
Tumour excision			

subjects affected / exposed	1 / 27 (3.70%)	0 / 17 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	1 / 27 (3.70%)	0 / 17 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain			
subjects affected / exposed	1 / 27 (3.70%)	0 / 17 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical health deterioration			
subjects affected / exposed	5 / 27 (18.52%)	1 / 17 (5.88%)	
occurrences causally related to treatment / all	0 / 6	1 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Pleural effusion			
subjects affected / exposed	1 / 27 (3.70%)	0 / 17 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 27 (3.70%)	0 / 17 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 27 (3.70%)	0 / 17 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
C-reactive protein increased			

subjects affected / exposed	1 / 27 (3.70%)	0 / 17 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Procalcitonin increased			
subjects affected / exposed	1 / 27 (3.70%)	0 / 17 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Laceration			
subjects affected / exposed	1 / 27 (3.70%)	0 / 17 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Myocardial infarction			
subjects affected / exposed	1 / 27 (3.70%)	0 / 17 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure			
subjects affected / exposed	0 / 27 (0.00%)	1 / 17 (5.88%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Epilepsy			
subjects affected / exposed	1 / 27 (3.70%)	0 / 17 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Haemorrhage intracranial			
subjects affected / exposed	1 / 27 (3.70%)	0 / 17 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Speech disorder			
subjects affected / exposed	1 / 27 (3.70%)	0 / 17 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	

Syncope			
subjects affected / exposed	2 / 27 (7.41%)	0 / 17 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			
subjects affected / exposed	0 / 27 (0.00%)	1 / 17 (5.88%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 27 (3.70%)	0 / 17 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancytopenia			
subjects affected / exposed	1 / 27 (3.70%)	0 / 17 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhagic anaemia			
subjects affected / exposed	1 / 27 (3.70%)	0 / 17 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Subileus			
subjects affected / exposed	1 / 27 (3.70%)	0 / 17 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	1 / 27 (3.70%)	2 / 17 (11.76%)	
occurrences causally related to treatment / all	1 / 1	2 / 2	
deaths causally related to treatment / all	1 / 1	0 / 0	
Vomiting			
subjects affected / exposed	0 / 27 (0.00%)	1 / 17 (5.88%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Renal and urinary disorders			
Nephrotic syndrome			
subjects affected / exposed	0 / 27 (0.00%)	1 / 17 (5.88%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			
subjects affected / exposed	1 / 27 (3.70%)	3 / 17 (17.65%)	
occurrences causally related to treatment / all	1 / 1	1 / 3	
deaths causally related to treatment / all	1 / 1	0 / 0	
Renal impairment			
subjects affected / exposed	0 / 27 (0.00%)	1 / 17 (5.88%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Joint effusion			
subjects affected / exposed	0 / 27 (0.00%)	1 / 17 (5.88%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Device related infection			
subjects affected / exposed	1 / 27 (3.70%)	0 / 17 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	1 / 27 (3.70%)	1 / 17 (5.88%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	1 / 27 (3.70%)	0 / 17 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Urinary tract infection			

subjects affected / exposed	1 / 27 (3.70%)	0 / 17 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			
subjects affected / exposed	1 / 27 (3.70%)	0 / 17 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	1 / 27 (3.70%)	0 / 17 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperkalaemia			
subjects affected / exposed	0 / 27 (0.00%)	2 / 17 (11.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoglycaemia			
subjects affected / exposed	1 / 27 (3.70%)	0 / 17 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolic acidosis			
subjects affected / exposed	0 / 27 (0.00%)	1 / 17 (5.88%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Sunitinib	Pazopanib	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	19 / 27 (70.37%)	9 / 17 (52.94%)	
Vascular disorders			
Blood pressure fluctuation			
subjects affected / exposed	1 / 27 (3.70%)	0 / 17 (0.00%)	
occurrences (all)	3	0	
Hypertension			

subjects affected / exposed occurrences (all)	5 / 27 (18.52%) 5	3 / 17 (17.65%) 3	
Pulmonary embolism subjects affected / exposed occurrences (all)	0 / 27 (0.00%) 0	1 / 17 (5.88%) 1	
Embolism subjects affected / exposed occurrences (all)	0 / 27 (0.00%) 0	1 / 17 (5.88%) 1	
Surgical and medical procedures Cancer surgery subjects affected / exposed occurrences (all)	1 / 27 (3.70%) 1	0 / 17 (0.00%) 0	
Toe operation subjects affected / exposed occurrences (all)	1 / 27 (3.70%) 1	0 / 17 (0.00%) 0	
General disorders and administration site conditions Abdominal pain subjects affected / exposed occurrences (all)	1 / 27 (3.70%) 1	1 / 17 (5.88%) 1	
Back pain subjects affected / exposed occurrences (all)	1 / 27 (3.70%) 1	0 / 17 (0.00%) 0	
Chills subjects affected / exposed occurrences (all)	2 / 27 (7.41%) 3	0 / 17 (0.00%) 0	
Oedema subjects affected / exposed occurrences (all)	2 / 27 (7.41%) 2	1 / 17 (5.88%) 1	
Oedema peripheral subjects affected / exposed occurrences (all)	1 / 27 (3.70%) 1	0 / 17 (0.00%) 0	
Fatigue subjects affected / exposed occurrences (all)	9 / 27 (33.33%) 10	5 / 17 (29.41%) 5	
Pyrexia			

subjects affected / exposed occurrences (all)	2 / 27 (7.41%) 2	0 / 17 (0.00%) 0	
Influenza like illness subjects affected / exposed occurrences (all)	0 / 27 (0.00%) 0	3 / 17 (17.65%) 3	
General physical health deterioration subjects affected / exposed occurrences (all)	5 / 27 (18.52%) 6	0 / 17 (0.00%) 0	
Pain in extremity subjects affected / exposed occurrences (all)	2 / 27 (7.41%) 2	2 / 17 (11.76%) 2	
Spinal pain subjects affected / exposed occurrences (all)	1 / 27 (3.70%) 2	0 / 17 (0.00%) 0	
Immune system disorders Allergic reaction to excipient subjects affected / exposed occurrences (all)	0 / 27 (0.00%) 0	1 / 17 (5.88%) 1	
Reproductive system and breast disorders Amenorrhoea subjects affected / exposed occurrences (all)	0 / 27 (0.00%) 0	1 / 17 (5.88%) 1	
Respiratory, thoracic and mediastinal disorders Dyspnoea subjects affected / exposed occurrences (all)	1 / 27 (3.70%) 1	0 / 17 (0.00%) 0	
Epistaxis subjects affected / exposed occurrences (all)	1 / 27 (3.70%) 2	0 / 17 (0.00%) 0	
Pleural effusion subjects affected / exposed occurrences (all)	2 / 27 (7.41%) 2	0 / 17 (0.00%) 0	
Investigations Blood bilirubin increased subjects affected / exposed occurrences (all)	0 / 27 (0.00%) 0	2 / 17 (11.76%) 4	

Blood creatinine increased subjects affected / exposed occurrences (all)	2 / 27 (7.41%) 3	0 / 17 (0.00%) 0	
Electrocardiogram QT prolonged subjects affected / exposed occurrences (all)	2 / 27 (7.41%) 2	0 / 17 (0.00%) 0	
Hyperkalaemia subjects affected / exposed occurrences (all)	1 / 27 (3.70%) 1	0 / 17 (0.00%) 0	
Hypokalaemia subjects affected / exposed occurrences (all)	2 / 27 (7.41%) 2	0 / 17 (0.00%) 0	
Cardiac disorders			
Arrhythmia subjects affected / exposed occurrences (all)	1 / 27 (3.70%) 1	0 / 17 (0.00%) 0	
Angina pectoris subjects affected / exposed occurrences (all)	1 / 27 (3.70%) 1	0 / 17 (0.00%) 0	
Sinus tachycardia subjects affected / exposed occurrences (all)	1 / 27 (3.70%) 1	0 / 17 (0.00%) 0	
Nervous system disorders			
Dysgeusia subjects affected / exposed occurrences (all)	6 / 27 (22.22%) 7	5 / 17 (29.41%) 5	
Aphasia subjects affected / exposed occurrences (all)	1 / 27 (3.70%) 1	0 / 17 (0.00%) 0	
Headache subjects affected / exposed occurrences (all)	1 / 27 (3.70%) 1	0 / 17 (0.00%) 0	
Neuralgia subjects affected / exposed occurrences (all)	1 / 27 (3.70%) 1	0 / 17 (0.00%) 0	
Paralysis			

subjects affected / exposed occurrences (all)	0 / 27 (0.00%) 0	1 / 17 (5.88%) 2	
Paraesthesia subjects affected / exposed occurrences (all)	2 / 27 (7.41%) 2	0 / 17 (0.00%) 0	
Polyneuropathy subjects affected / exposed occurrences (all)	1 / 27 (3.70%) 1	0 / 17 (0.00%) 0	
Speech disorder subjects affected / exposed occurrences (all)	1 / 27 (3.70%) 1	0 / 17 (0.00%) 0	
Syncope subjects affected / exposed occurrences (all)	1 / 27 (3.70%) 1	1 / 17 (5.88%) 1	
Blood and lymphatic system disorders			
Anaemia subjects affected / exposed occurrences (all)	3 / 27 (11.11%) 5	1 / 17 (5.88%) 2	
White blood cell count decreased subjects affected / exposed occurrences (all)	1 / 27 (3.70%) 1	0 / 17 (0.00%) 0	
Neutropenia subjects affected / exposed occurrences (all)	5 / 27 (18.52%) 6	0 / 17 (0.00%) 0	
Pancytopenia subjects affected / exposed occurrences (all)	1 / 27 (3.70%) 1	0 / 17 (0.00%) 0	
Thrombocytopenia subjects affected / exposed occurrences (all)	6 / 27 (22.22%) 14	0 / 17 (0.00%) 0	
Ear and labyrinth disorders			
Vertigo subjects affected / exposed occurrences (all)	1 / 27 (3.70%) 1	2 / 17 (11.76%) 2	
Eye disorders			

Retinal detachment subjects affected / exposed occurrences (all)	0 / 27 (0.00%) 0	1 / 17 (5.88%) 1	
Visual acuity reduced subjects affected / exposed occurrences (all)	1 / 27 (3.70%) 1	0 / 17 (0.00%) 0	
Gastrointestinal disorders			
Tongue discomfort subjects affected / exposed occurrences (all)	2 / 27 (7.41%) 3	0 / 17 (0.00%) 0	
Cheilitis subjects affected / exposed occurrences (all)	1 / 27 (3.70%) 1	0 / 17 (0.00%) 0	
Constipation subjects affected / exposed occurrences (all)	3 / 27 (11.11%) 3	0 / 17 (0.00%) 0	
Diarrhoea subjects affected / exposed occurrences (all)	3 / 27 (11.11%) 3	3 / 17 (17.65%) 4	
Dyspepsia subjects affected / exposed occurrences (all)	1 / 27 (3.70%) 1	0 / 17 (0.00%) 0	
Dysphagia subjects affected / exposed occurrences (all)	1 / 27 (3.70%) 1	0 / 17 (0.00%) 0	
Flatulence subjects affected / exposed occurrences (all)	3 / 27 (11.11%) 4	0 / 17 (0.00%) 0	
Gingival pain subjects affected / exposed occurrences (all)	1 / 27 (3.70%) 1	0 / 17 (0.00%) 0	
Haemorrhoidal haemorrhage subjects affected / exposed occurrences (all)	1 / 27 (3.70%) 1	0 / 17 (0.00%) 0	
Stomatitis			

subjects affected / exposed occurrences (all)	4 / 27 (14.81%) 4	2 / 17 (11.76%) 2	
Nausea subjects affected / exposed occurrences (all)	3 / 27 (11.11%) 3	2 / 17 (11.76%) 3	
Oral pain subjects affected / exposed occurrences (all)	1 / 27 (3.70%) 1	0 / 17 (0.00%) 0	
Faeces soft subjects affected / exposed occurrences (all)	1 / 27 (3.70%) 1	0 / 17 (0.00%) 0	
Pruritus genital subjects affected / exposed occurrences (all)	1 / 27 (3.70%) 1	0 / 17 (0.00%) 0	
Abdominal pain upper subjects affected / exposed occurrences (all)	3 / 27 (11.11%) 3	1 / 17 (5.88%) 1	
Oropharyngeal pain subjects affected / exposed occurrences (all)	1 / 27 (3.70%) 1	0 / 17 (0.00%) 0	
Glossodynia subjects affected / exposed occurrences (all)	2 / 27 (7.41%) 2	0 / 17 (0.00%) 0	
Vomiting subjects affected / exposed occurrences (all)	3 / 27 (11.11%) 3	3 / 17 (17.65%) 4	
Tongue coated subjects affected / exposed occurrences (all)	1 / 27 (3.70%) 1	0 / 17 (0.00%) 0	
Skin and subcutaneous tissue disorders			
Alopecia subjects affected / exposed occurrences (all)	1 / 27 (3.70%) 1	1 / 17 (5.88%) 1	
Dry skin subjects affected / exposed occurrences (all)	1 / 27 (3.70%) 1	1 / 17 (5.88%) 1	

Hyperhidrosis			
subjects affected / exposed	1 / 27 (3.70%)	0 / 17 (0.00%)	
occurrences (all)	1	0	
Ulcer			
subjects affected / exposed	1 / 27 (3.70%)	0 / 17 (0.00%)	
occurrences (all)	1	0	
Sputum abnormal			
subjects affected / exposed	1 / 27 (3.70%)	0 / 17 (0.00%)	
occurrences (all)	1	0	
Palmar-plantar erythrodysesthesia syndrome			
subjects affected / exposed	4 / 27 (14.81%)	0 / 17 (0.00%)	
occurrences (all)	7	0	
Erythema			
subjects affected / exposed	2 / 27 (7.41%)	0 / 17 (0.00%)	
occurrences (all)	2	0	
Pruritus			
subjects affected / exposed	1 / 27 (3.70%)	1 / 17 (5.88%)	
occurrences (all)	1	1	
Rash			
subjects affected / exposed	6 / 27 (22.22%)	1 / 17 (5.88%)	
occurrences (all)	6	1	
Skin discolouration			
subjects affected / exposed	5 / 27 (18.52%)	1 / 17 (5.88%)	
occurrences (all)	6	1	
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	2 / 27 (7.41%)	0 / 17 (0.00%)	
occurrences (all)	3	0	
Nocturia			
subjects affected / exposed	1 / 27 (3.70%)	0 / 17 (0.00%)	
occurrences (all)	1	0	
Pollakiuria			
subjects affected / exposed	1 / 27 (3.70%)	0 / 17 (0.00%)	
occurrences (all)	1	0	
Nephrolithiasis			

subjects affected / exposed occurrences (all)	1 / 27 (3.70%) 1	0 / 17 (0.00%) 0	
Chromaturia subjects affected / exposed occurrences (all)	1 / 27 (3.70%) 1	0 / 17 (0.00%) 0	
Endocrine disorders Hypothyroidism subjects affected / exposed occurrences (all)	0 / 27 (0.00%) 0	1 / 17 (5.88%) 1	
Hyperthyroidism subjects affected / exposed occurrences (all)	1 / 27 (3.70%) 1	1 / 17 (5.88%) 1	
Musculoskeletal and connective tissue disorders Pain in extremity subjects affected / exposed occurrences (all)	1 / 27 (3.70%) 1	0 / 17 (0.00%) 0	
Pubic pain subjects affected / exposed occurrences (all)	1 / 27 (3.70%) 2	0 / 17 (0.00%) 0	
Bone pain subjects affected / exposed occurrences (all)	1 / 27 (3.70%) 1	0 / 17 (0.00%) 0	
Walking disability subjects affected / exposed occurrences (all)	0 / 27 (0.00%) 0	1 / 17 (5.88%) 1	
Infections and infestations Bronchitis subjects affected / exposed occurrences (all)	0 / 27 (0.00%) 0	1 / 17 (5.88%) 1	
Oral herpes subjects affected / exposed occurrences (all)	1 / 27 (3.70%) 1	0 / 17 (0.00%) 0	
Gastroenteritis subjects affected / exposed occurrences (all)	1 / 27 (3.70%) 1	0 / 17 (0.00%) 0	
Laryngitis			

subjects affected / exposed occurrences (all)	1 / 27 (3.70%) 2	0 / 17 (0.00%) 0	
Sinusitis subjects affected / exposed occurrences (all)	1 / 27 (3.70%) 2	0 / 17 (0.00%) 0	
Blood thyroid stimulating hormone increased subjects affected / exposed occurrences (all)	1 / 27 (3.70%) 3	0 / 17 (0.00%) 0	
Metabolism and nutrition disorders			
Gout subjects affected / exposed occurrences (all)	0 / 27 (0.00%) 0	1 / 17 (5.88%) 1	
Decreased appetite subjects affected / exposed occurrences (all)	4 / 27 (14.81%) 4	3 / 17 (17.65%) 3	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported