Clinical trial results:
A prospective, open-label, multicenter, randomized phase II trial: Sequential therapy with BEvacizumab, RAd001 (everolimus) and AxiTinib in metastatic renal cell carcinoma (mRCC) (BERAT study).

Summary

EudraCT number	2011-005939-78
Trial protocol	DE
Global end of trial date	22 August 2016

Results information

Result version number	v1 (current)
This version publication date	02 August 2020
First version publication date	02 August 2020

Trial information

Trial identification

Sponsor protocol code	C-II-008

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-EWIV
Sponsor organisation address	Hanglüssgasse, 4/1-3, Wien, Austria, 1150
Public contact	Dr. Max Roessler, CESAR Cental European Society for Anticancer Drug Research-EWIV, 0043 1522 30 9316, max.roessler@cesar.or.at
Scientific contact	PD Dr. med. Viktor GRÜNWALD, Medizinische Hochschule Hannover, 0049 5115323140, Gruenwald.Viktor@mh-hannover.de

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	21 January 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	22 August 2016
Global end of trial reached?	Yes
Global end of trial date	22 August 2016
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

progression free survival (PFS) rate of 2nd line treatment at 6 months after randomisation

Protection of trial subjects:

All drugs used in the study have been approved and were used according to the technical information. Procedures that determine efficacy (CT scans, MRI) and safety (blood count, blood chemistry and coagulation) are performed as in routine operations and therefore do not represent an additional burden for those patients participating in this clinical trial. Blood samples taken outside the routine for the accompanying programs do not pose any additional risk to patients. In summary, it is not possible to predict whether there will be a direct benefit for the individual patients. However, the risk for patients in the study is not higher than for patients not treated in the study. Furthermore, there is a benefit for future patients due to the progress of knowledge. It can be concluded that the benefit of this research project outweighs the risks involved.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	07 November 2012
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Germany: 22
Worldwide total number of subjects	22
EEA total number of subjects	22

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)	13
From 65 to 84 years	9
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

10 study yites in Germany were activated for patient recruitment. Only 5 of the study sites actively recruited patients in the study. Patient recruitment took place from 07Nov12 (FPI) to 22Aug16 (LPLV).

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	First Line Treatment (TrL1)
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:

N.a.

Arms

Arm title	Bevacizumab / Interferon alpha

Arm description:

Bevacizumab is supplied as a 25 mg/ml concentrate for solution for infusion. The administrated dose of bevacizumab is 10 mg/kg of body weight given once every 2 weeks as an intravenous infusion. The necessary amount of bevacizumab should be withdrawn and diluted to the required administration volume with sodium chloride 9 mg/ml (0.9 %) solution for injection.
Patients will start therapy at increasing doses of interferon alpha (IFN), as described in the Roferon A® Package Insert or Summary of Product Characteristics. Initial dose is 3 mio units given thrice weekly s.c. The dose will be subsequently escalated to 6 and 9 mio units thrice weekly s.c. if the previous dose level has been tolerated.

Arm type	Experimental
Investigational medicinal product name	Bevacizumab
Investigational medicinal product code	
Other name	Avastin
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Bevacizumab is supplied as a 25 mg/ml concentrate for solution for infusion. The administrated dose of bevacizumab is 10 mg/kg of body weight given once every 2 weeks as an intravenous infusion. The necessary amount of bevacizumab should be withdrawn and diluted to the required administration volume with sodium chloride 9 mg/ml (0.9 %) solution for injection.

Investigational medicinal product name	Interferon alfa-2a
Investigational medicinal product code	
Other name	Roferon®-A
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Subcutaneous use

Dosage and administration details:

Patients will start therapy at increasing doses of interferon alpha (IFN), as described in the Roferon A® Package Insert or Summary of Product Characteristics. Initial dose is 3 mio units given thrice weekly s.c. The dose will be subsequently escalated to 6 and 9 mio units thrice weekly s.c. if the previous dose level has been tolerated.

Number of subjects in period 1	Bevacizumab / Interferon alpha
Started	22
Completed	22

Period 2	
Period 2 title	TrL2+3
Is this the baseline period?	Yes[1]
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms	
Are arms mutually exclusive?	Yes
Arm title	Arm A (Everolimus-Axitinib)

Arm description:

Patients receiving Everolimus followed by Axitinib.

Arm type	Experimental
Investigational medicinal product name	Everolimus
Investigational medicinal product code	
Other name	AFINITOR
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Everolimus is an oral rapalog that inhibits mTOR signaling in the context of the mTORC1 complex. In a double-blind, randomized, placebo-controlled Phase III trial, 10 mg everolimus administered once daily was compared with placebo in patients with metastatic RCC that had progressed on sunitinib, sorafenib, or both10. A significant difference in PFS was observed favoring everolimus (4.9 months vs. 1.9 months, hazard ratio 0.33, p 0.0001). Stomatitis, rash, and fatigue of mild-to-moderate severity were the most commonly observed adverse events that were more frequent with everolimus. Pneumonitis of any grade was reported in 14% of patients in the everolimus group.

Investigational medicinal product name	Axitinib
Investigational medicinal product code	
Other name	INLYTA®
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Axitinib is available as tablets in 2 different strengths: 5 mg, and 1 mg. Axitinib 5 mg will be taken orally twice daily on a continuous basis. Successive dose increase up to 10 mg BID may be offered on an individual base.

Arm title	Arm B (Axitinib-Everoliumus)

Arm description:

Patients receiving Axitinib followed by Everolimus.

Arm type	Experimental

Investigational medicinal product name	Axitinib
Investigational medicinal product code	
Other name	INLYTA®
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Axitinib is available as tablets in 2 different strengths: 5 mg, and 1 mg. Axitinib 5 mg will be taken orally twice daily on a continuous basis. Successive dose increase up to 10 mg BID may be offered on an individual base.

Investigational medicinal product name	Everolimus
Investigational medicinal product code	
Other name	AFINITOR
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Everolimus is an oral rapalog that inhibits mTOR signaling in the context of the mTORC1 complex. In a double-blind, randomized, placebo-controlled Phase III trial, 10 mg everolimus administered once daily was compared with placebo in patients with metastatic RCC that had progressed on sunitinib, sorafenib, or both10. A significant difference in PFS was observed favoring everolimus (4.9 months vs. 1.9 months, hazard ratio 0.33, p 0.0001). Stomatitis, rash, and fatigue of mild-to-moderate severity were the most commonly observed adverse events that were more frequent with everolimus. Pneumonitis of any grade was reported in 14% of patients in the everolimus group.

Notes:

[1] - Period 1 is not the baseline period. It is expected that period 1 will be the baseline period.

Justification: Baseline characterisitics have been assessed for Trl2+3 since in this phase patients where randomized.

Number of subjects in period 2[2][3]	Arm A (Everolimus-Axitinib)	Arm B (Axitinib-Everoliumus)
Started	5	5
Completed	5	5

Notes:

[2] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: Only 10 out of 22 patients enrolled in the study an treated in course of Trl1 where treated in course of Trl2+3

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

Justification: All 22 patients completed Trl1 in a way, that they were considered as part of the ITT population. However only 10 out of 22 patients where considered suitable for Trl2.

Baseline characteristics

Reporting groups	
Reporting group title	TrL2+3

Reporting group description: -

Reporting group values	TrL2+3	Total	
Number of subjects	10	10	
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	56.2		
standard deviation	± 10.69	-	
Gender categorical Units: Subjects			
Female	4	4	
Male	6	6	

Subject analysis sets	
Subject analysis set title	ArmA
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Patients which have been randomized in ArmA of the study

Subject analysis set title	ArmB
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Patients which have been randomized in ArmB of the study

Reporting group values	ArmA	ArmB	
Number of subjects	5	5	
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	54	58.4	
standard deviation	± 9.58	± 12.37	
Gender categorical Units: Subjects			
Female	2	2	
Male	3	3	

End points

End points reporting groups

Reporting group title	Bevacizumab / Interferon alpha
Reporting group description:	
Bevacizumab is supplied as a 25 mg/ml concentrate for solution for infusion. The administrated dose of bevacizumab is 10 mg/kg of body weight given once every 2 weeks as an intravenous infusion. The necessary amount of bevacizumab should be withdrawn and diluted to the required administration volume with sodium chloride 9 mg/ml (0.9 %) solution for injection. Patients will start therapy at increasing doses of interferon alpha (IFN), as described in the Roferon A® Package Insert or Summary of Product Characteristics. Initial dose is 3 mio units given thrice weekly s.c. The dose will be subsequently escalated to 6 and 9 mio units thrice weekly s.c. if the previous dose level has been tolerated.	
Reporting group title	Arm A (Everolimus-Axitinib)
Reporting group description:	
Patients receiving Everolimus followed by Axitinib.	
Reporting group title	Arm B (Axitinib-Everoliumus)
Reporting group description:	
Patients receiving Axitinib followed by Everolimus.	
Subject analysis set title	ArmA
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Patients which have been randomized in ArmA of the study	
Subject analysis set title	ArmB
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Patients which have been randomized in ArmB of the study	

Primary: Primary Endpoint

End point title	Primary Endpoint[1]
End point description:	
Primary objective of the study is: PFS rate of 2nd line treatment at 6 months after randomization in comparison of both groups .	
End point type	Primary
End point timeframe:	
PFS rate will be assessed at 6 months after randomization	

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: Since the study has been cancled. Therefore, the statistical analysis as outlined in the study protocol has not been performed. Instead a desricptiv statistic has been done.

End point values	Arm A (Everolimus-Axitinib)	Arm B (Axitinib-Everoliumus)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5	5		
Units: Days				
number (not applicable)	20	20		

Attachments (see zip file)	Kaplan Mayer/Kaplan Mayer.pdf

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All information on AEs and SAEs will be reported during the treatment phase up to 4 weeks after the end of the treatment phase. Any SAEs beyond 28 days after the last dose of study medication considered related to the study medication will be reported.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.0

Reporting groups

Reporting group title	TrL2+3 Arm A (Everolimus-Axitinib)

Reporting group description:

Patients receiving Everolimus followed by Axitinib.

Reporting group title	TrL2+3 Arm B (Axitinib-Everoliumus)

Reporting group description:

Patients receiving Axitinib followed by Everolimus.

Reporting group title	TrL1 Bevazicumab/Interferon

Reporting group description:

All patients received Bevacizumab/Interferon as 1st line treatment. This reporting group comprises only patients who did not go on to 2nd and 3rd line treatment.

Serious adverse events	TrL2+3 Arm A (Everolimus-Axitinib)	TrL2+3 Arm B (Axitinib-Everoliumus)	TrL1 Bevazicumab/Interferon
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 5 (60.00%)	3 / 5 (60.00%)	5 / 12 (41.67%)
number of deaths (all causes)	1	0	0
number of deaths resulting from adverse events	1	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Malignant neoplasm progression			
subjects affected / exposed	1 / 5 (20.00%)	0 / 5 (0.00%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	1 / 12 (8.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertensive crisis			

subjects affected / exposed	0 / 5 (0.00%)	1 / 5 (20.00%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombosis			
subjects affected / exposed	0 / 5 (0.00%)	1 / 5 (20.00%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Surgical and medical procedures			
Urethral stent insertion			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	1 / 12 (8.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
General physical health deterioration			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	1 / 12 (8.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia			
subjects affected / exposed	0 / 5 (0.00%)	1 / 5 (20.00%)	0 / 12 (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
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	1 / 5 (20.00%)	0 / 5 (0.00%)	0 / 12 (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			
Dyspnoea			
subjects affected / exposed	1 / 5 (20.00%)	1 / 5 (20.00%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemoptysis			

subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	1 / 12 (8.33%)
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			
Depression			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	1 / 12 (8.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Posterior reversible encephalopathy syndrome			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	1 / 12 (8.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	1 / 12 (8.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Anal fistula			
subjects affected / exposed	1 / 5 (20.00%)	0 / 5 (0.00%)	0 / 12 (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
Hepatobiliary disorders			
Cholangitis sclerosing			
subjects affected / exposed	0 / 5 (0.00%)	1 / 5 (20.00%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholelithiasis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	1 / 12 (8.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Back pain			

subjects affected / exposed	1 / 5 (20.00%)	0 / 5 (0.00%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Pneumonia			
subjects affected / exposed	1 / 5 (20.00%)	0 / 5 (0.00%)	1 / 12 (8.33%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Hypercalcaemia			
subjects affected / exposed	1 / 5 (20.00%)	0 / 5 (0.00%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperglycaemia			
subjects affected / exposed	1 / 5 (20.00%)	0 / 5 (0.00%)	0 / 12 (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

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

Non-serious adverse events	TrL2+3 Arm A (Everolimus-Axitinib)	TrL2+3 Arm B (Axitinib-Everoliumus)	TrL1 Bevazicumab/Interferon
Total subjects affected by non-serious adverse events			
subjects affected / exposed	5 / 5 (100.00%)	5 / 5 (100.00%)	12 / 12 (100.00%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Cancer pain			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Vascular disorders			
Hot flush			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Hypertension			
subjects affected / exposed	2 / 5 (40.00%)	3 / 5 (60.00%)	6 / 12 (50.00%)
occurrences (all)	12	9	8
Hypertensive crisis			

subjects affected / exposed	0 / 5 (0.00%)	1 / 5 (20.00%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Hypotension			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Thrombosis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	2 / 5 (40.00%)	1 / 5 (20.00%)	3 / 12 (25.00%)
occurrences (all)	2	1	3
Chills			
subjects affected / exposed	1 / 5 (20.00%)	3 / 5 (60.00%)	3 / 12 (25.00%)
occurrences (all)	1	3	3
Discomfort			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Face oedema			
subjects affected / exposed	0 / 5 (0.00%)	1 / 5 (20.00%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Fatigue			
subjects affected / exposed	5 / 5 (100.00%)	3 / 5 (60.00%)	9 / 12 (75.00%)
occurrences (all)	9	13	14
Feeling cold			
subjects affected / exposed	0 / 5 (0.00%)	1 / 5 (20.00%)	2 / 12 (16.67%)
occurrences (all)	0	2	2
Gait disturbance			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Influenza like illness			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Malaise			

subjects affected / exposed	0 / 5 (0.00%)	1 / 5 (20.00%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Mucosal dryness			
subjects affected / exposed	0 / 5 (0.00%)	1 / 5 (20.00%)	1 / 12 (8.33%)
occurrences (all)	0	1	1
Mucosal inflammation			
subjects affected / exposed	0 / 5 (0.00%)	1 / 5 (20.00%)	2 / 12 (16.67%)
occurrences (all)	0	1	2
Oedema			
subjects affected / exposed	1 / 5 (20.00%)	1 / 5 (20.00%)	0 / 12 (0.00%)
occurrences (all)	2	2	0
Pain			
subjects affected / exposed	2 / 5 (40.00%)	1 / 5 (20.00%)	2 / 12 (16.67%)
occurrences (all)	3	1	2
Peripheral swelling			
subjects affected / exposed	1 / 5 (20.00%)	0 / 5 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Pyrexia			
subjects affected / exposed	3 / 5 (60.00%)	3 / 5 (60.00%)	5 / 12 (41.67%)
occurrences (all)	8	3	7
Immune system disorders			
Seasonal allergy			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Periodontitis			
subjects affected / exposed	1 / 5 (20.00%)	0 / 5 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Sinusitis			
subjects affected / exposed	1 / 5 (20.00%)	0 / 5 (0.00%)	1 / 12 (8.33%)
occurrences (all)	1	0	2
Reproductive system and breast disorders			
Benign prostatic hyperplasia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Erectile dysfunction			

subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Pelvic pain			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	2 / 5 (40.00%)	3 / 5 (60.00%)	4 / 12 (33.33%)
occurrences (all)	3	7	4
Dysphonia			
subjects affected / exposed	4 / 5 (80.00%)	2 / 5 (40.00%)	3 / 12 (25.00%)
occurrences (all)	4	2	3
Dyspnoea			
subjects affected / exposed	2 / 5 (40.00%)	2 / 5 (40.00%)	3 / 12 (25.00%)
occurrences (all)	3	5	5
Dyspnoea exertional			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Epistaxis			
subjects affected / exposed	1 / 5 (20.00%)	1 / 5 (20.00%)	7 / 12 (58.33%)
occurrences (all)	1	1	12
Nasal dryness			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Nasal mucosal disorder			
subjects affected / exposed	1 / 5 (20.00%)	0 / 5 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Nasal septum perforation			
subjects affected / exposed	1 / 5 (20.00%)	0 / 5 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Oropharyngeal pain			
subjects affected / exposed	1 / 5 (20.00%)	0 / 5 (0.00%)	2 / 12 (16.67%)
occurrences (all)	1	0	3
Pleuritic pain			

subjects affected / exposed	1 / 5 (20.00%)	0 / 5 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Productive cough			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Rhinitis allergic			
subjects affected / exposed	0 / 5 (0.00%)	1 / 5 (20.00%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Sinus disorder			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Psychiatric disorders			
Depression			
subjects affected / exposed	0 / 5 (0.00%)	1 / 5 (20.00%)	1 / 12 (8.33%)
occurrences (all)	0	1	2
Disorientation			
subjects affected / exposed	1 / 5 (20.00%)	0 / 5 (0.00%)	1 / 12 (8.33%)
occurrences (all)	1	0	1
Enuresis			
subjects affected / exposed	1 / 5 (20.00%)	0 / 5 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Insomnia			
subjects affected / exposed	1 / 5 (20.00%)	1 / 5 (20.00%)	1 / 12 (8.33%)
occurrences (all)	1	1	1
Restlessness			
subjects affected / exposed	0 / 5 (0.00%)	1 / 5 (20.00%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Sleep disorder			
subjects affected / exposed	0 / 5 (0.00%)	1 / 5 (20.00%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Investigations			
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 5 (20.00%)	0 / 5 (0.00%)	0 / 12 (0.00%)
occurrences (all)	2	0	0
Blood creatine increased			

subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	4
Blood lactate dehydrogenase increased			
subjects affected / exposed	0 / 5 (0.00%)	1 / 5 (20.00%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Blood uric acid increased			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	2 / 12 (16.67%)
occurrences (all)	0	0	2
Breath sounds abnormal			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Protein urine present			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	2 / 12 (16.67%)
occurrences (all)	0	0	5
Transaminases increased			
subjects affected / exposed	1 / 5 (20.00%)	0 / 5 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Weight decreased			
subjects affected / exposed	3 / 5 (60.00%)	3 / 5 (60.00%)	2 / 12 (16.67%)
occurrences (all)	5	6	2
Diabetes mellitus			
subjects affected / exposed	0 / 5 (0.00%)	1 / 5 (20.00%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Hypercalcaemia			
subjects affected / exposed	1 / 5 (20.00%)	0 / 5 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Cardiac disorders			
Cardiac failure			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Tachycardia			
subjects affected / exposed	1 / 5 (20.00%)	1 / 5 (20.00%)	0 / 12 (0.00%)
occurrences (all)	1	1	0
Nervous system disorders			

Disturbance in attention			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Dizziness			
subjects affected / exposed	0 / 5 (0.00%)	1 / 5 (20.00%)	3 / 12 (25.00%)
occurrences (all)	0	1	3
Dysgeusia			
subjects affected / exposed	2 / 5 (40.00%)	1 / 5 (20.00%)	0 / 12 (0.00%)
occurrences (all)	2	1	0
Headache			
subjects affected / exposed	1 / 5 (20.00%)	2 / 5 (40.00%)	3 / 12 (25.00%)
occurrences (all)	1	3	4
Memory impairment			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Paraesthesia			
subjects affected / exposed	0 / 5 (0.00%)	2 / 5 (40.00%)	0 / 12 (0.00%)
occurrences (all)	0	2	0
Polyneuropathy			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	2 / 12 (16.67%)
occurrences (all)	0	0	2
Restless legs syndrome			
subjects affected / exposed	0 / 5 (0.00%)	1 / 5 (20.00%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Sensory disturbance			
subjects affected / exposed	0 / 5 (0.00%)	1 / 5 (20.00%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Somnolence			
subjects affected / exposed	1 / 5 (20.00%)	0 / 5 (0.00%)	1 / 12 (8.33%)
occurrences (all)	1	0	2
Vocal cord paralysis			
subjects affected / exposed	0 / 5 (0.00%)	1 / 5 (20.00%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Blood and lymphatic system disorders			
Anaemia			

subjects affected / exposed	1 / 5 (20.00%)	0 / 5 (0.00%)	0 / 12 (0.00%)
occurrences (all)	3	0	0
Leukocytosis			
subjects affected / exposed	0 / 5 (0.00%)	1 / 5 (20.00%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Neutropenia			
subjects affected / exposed	0 / 5 (0.00%)	1 / 5 (20.00%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Ear and labyrinth disorders			
Deafness			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Ear pain			
subjects affected / exposed	1 / 5 (20.00%)	0 / 5 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Eustachian tube disorder			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Vertigo			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Eye disorders			
Dry eye			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Eye inflammation			
subjects affected / exposed	1 / 5 (20.00%)	0 / 5 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Vision blurred			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Visual impairment			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Gastrointestinal disorders			

Abdominal distension			
subjects affected / exposed	0 / 5 (0.00%)	1 / 5 (20.00%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Abdominal pain			
subjects affected / exposed	0 / 5 (0.00%)	1 / 5 (20.00%)	2 / 12 (16.67%)
occurrences (all)	0	1	2
Abdominal pain upper			
subjects affected / exposed	0 / 5 (0.00%)	1 / 5 (20.00%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Anal inflammation			
subjects affected / exposed	0 / 5 (0.00%)	1 / 5 (20.00%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Cheilitis			
subjects affected / exposed	0 / 5 (0.00%)	1 / 5 (20.00%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Constipation			
subjects affected / exposed	1 / 5 (20.00%)	1 / 5 (20.00%)	0 / 12 (0.00%)
occurrences (all)	1	1	0
Diarrhoea			
subjects affected / exposed	4 / 5 (80.00%)	2 / 5 (40.00%)	3 / 12 (25.00%)
occurrences (all)	8	5	6
Dry mouth			
subjects affected / exposed	0 / 5 (0.00%)	2 / 5 (40.00%)	5 / 12 (41.67%)
occurrences (all)	0	2	5
Dysphagia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	2 / 12 (16.67%)
occurrences (all)	0	0	2
Flatulence			
subjects affected / exposed	1 / 5 (20.00%)	0 / 5 (0.00%)	0 / 12 (0.00%)
occurrences (all)	2	0	0
Gastritis			
subjects affected / exposed	0 / 5 (0.00%)	1 / 5 (20.00%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 5 (0.00%)	1 / 5 (20.00%)	0 / 12 (0.00%)
occurrences (all)	0	1	0

Gingival bleeding			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	2 / 12 (16.67%)
occurrences (all)	0	0	3
Lip swelling			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Nausea			
subjects affected / exposed	4 / 5 (80.00%)	2 / 5 (40.00%)	4 / 12 (33.33%)
occurrences (all)	11	3	4
Oral disorder			
subjects affected / exposed	1 / 5 (20.00%)	0 / 5 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Proctalgia			
subjects affected / exposed	0 / 5 (0.00%)	1 / 5 (20.00%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Stomatitis			
subjects affected / exposed	3 / 5 (60.00%)	3 / 5 (60.00%)	3 / 12 (25.00%)
occurrences (all)	4	8	4
Toothache			
subjects affected / exposed	1 / 5 (20.00%)	0 / 5 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Vomiting			
subjects affected / exposed	3 / 5 (60.00%)	2 / 5 (40.00%)	3 / 12 (25.00%)
occurrences (all)	5	6	3
Hepatobiliary disorders			
Hepatotoxicity			
subjects affected / exposed	0 / 5 (0.00%)	1 / 5 (20.00%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	1 / 5 (20.00%)	2 / 5 (40.00%)	1 / 12 (8.33%)
occurrences (all)	1	2	1
Dermatitis allergic			
subjects affected / exposed	0 / 5 (0.00%)	1 / 5 (20.00%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Dry skin			

subjects affected / exposed	1 / 5 (20.00%)	1 / 5 (20.00%)	1 / 12 (8.33%)
occurrences (all)	1	1	1
Erythema			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Hidradenitis			
subjects affected / exposed	0 / 5 (0.00%)	1 / 5 (20.00%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Hyperhidrosis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	2 / 12 (16.67%)
occurrences (all)	0	0	2
Hyperkeratosis			
subjects affected / exposed	0 / 5 (0.00%)	1 / 5 (20.00%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Lividity			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Nail disorder			
subjects affected / exposed	0 / 5 (0.00%)	1 / 5 (20.00%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Night sweats			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Onychoclasis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	2 / 5 (40.00%)	0 / 5 (0.00%)	1 / 12 (8.33%)
occurrences (all)	3	0	1
Pruritus			
subjects affected / exposed	0 / 5 (0.00%)	1 / 5 (20.00%)	2 / 12 (16.67%)
occurrences (all)	0	3	2
Psoriasis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	2 / 12 (16.67%)
occurrences (all)	0	0	2

Rash			
subjects affected / exposed	4 / 5 (80.00%)	2 / 5 (40.00%)	3 / 12 (25.00%)
occurrences (all)	6	2	3
Skin fissures			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Skin maceration			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	2
Swelling face			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	2
Xeroderma			
subjects affected / exposed	0 / 5 (0.00%)	1 / 5 (20.00%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	1 / 5 (20.00%)	0 / 5 (0.00%)	1 / 12 (8.33%)
occurrences (all)	1	0	1
Pollakiuria			
subjects affected / exposed	1 / 5 (20.00%)	0 / 5 (0.00%)	1 / 12 (8.33%)
occurrences (all)	1	0	1
Proteinuria			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	2 / 12 (16.67%)
occurrences (all)	0	0	2
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	2 / 5 (40.00%)	2 / 5 (40.00%)	1 / 12 (8.33%)
occurrences (all)	2	3	1
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 5 (20.00%)	2 / 5 (40.00%)	5 / 12 (41.67%)
occurrences (all)	1	5	9
Back pain			
subjects affected / exposed	0 / 5 (0.00%)	3 / 5 (60.00%)	1 / 12 (8.33%)
occurrences (all)	0	3	1

Bursitis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Flank pain			
subjects affected / exposed	2 / 5 (40.00%)	0 / 5 (0.00%)	1 / 12 (8.33%)
occurrences (all)	2	0	1
Foot deformity			
subjects affected / exposed	0 / 5 (0.00%)	1 / 5 (20.00%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Groin pain			
subjects affected / exposed	1 / 5 (20.00%)	0 / 5 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Joint swelling			
subjects affected / exposed	1 / 5 (20.00%)	0 / 5 (0.00%)	0 / 12 (0.00%)
occurrences (all)	2	0	0
Limb discomfort			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Muscle spasms			
subjects affected / exposed	0 / 5 (0.00%)	1 / 5 (20.00%)	1 / 12 (8.33%)
occurrences (all)	0	1	1
Muscular weakness			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Musculoskeletal chest pain			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	2 / 12 (16.67%)
occurrences (all)	0	0	2
Musculoskeletal discomfort			
subjects affected / exposed	0 / 5 (0.00%)	1 / 5 (20.00%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Musculoskeletal pain			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	2 / 12 (16.67%)
occurrences (all)	0	0	2
Myalgia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1

Osteoarthritis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	2 / 12 (16.67%)
occurrences (all)	0	0	4
Osteonecrosis of jaw			
subjects affected / exposed	1 / 5 (20.00%)	0 / 5 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Pain in extremity			
subjects affected / exposed	1 / 5 (20.00%)	1 / 5 (20.00%)	4 / 12 (33.33%)
occurrences (all)	2	1	5
Pain in jaw			
subjects affected / exposed	0 / 5 (0.00%)	1 / 5 (20.00%)	1 / 12 (8.33%)
occurrences (all)	0	1	1
Infections and infestations			
Bronchitis			
subjects affected / exposed	0 / 5 (0.00%)	1 / 5 (20.00%)	2 / 12 (16.67%)
occurrences (all)	0	1	2
Conjunctivitis			
subjects affected / exposed	1 / 5 (20.00%)	0 / 5 (0.00%)	0 / 12 (0.00%)
occurrences (all)	2	0	0
Folliculitis			
subjects affected / exposed	0 / 5 (0.00%)	1 / 5 (20.00%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Fungal skin infection			
subjects affected / exposed	1 / 5 (20.00%)	0 / 5 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Hordeolum			
subjects affected / exposed	0 / 5 (0.00%)	1 / 5 (20.00%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Oesophageal candidiasis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Otitis media			
subjects affected / exposed	0 / 5 (0.00%)	1 / 5 (20.00%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Pneumonia			

subjects affected / exposed	2 / 5 (40.00%)	0 / 5 (0.00%)	0 / 12 (0.00%)
occurrences (all)	2	0	0
Rhinitis			
subjects affected / exposed	0 / 5 (0.00%)	1 / 5 (20.00%)	3 / 12 (25.00%)
occurrences (all)	0	2	3
Root canal infection			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Upper respiratory tract infection			
subjects affected / exposed	0 / 5 (0.00%)	1 / 5 (20.00%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Urinary tract infection			
subjects affected / exposed	2 / 5 (40.00%)	0 / 5 (0.00%)	0 / 12 (0.00%)
occurrences (all)	3	0	0
Viral upper respiratory tract infection			
subjects affected / exposed	0 / 5 (0.00%)	2 / 5 (40.00%)	2 / 12 (16.67%)
occurrences (all)	0	3	4
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	2 / 5 (40.00%)	3 / 5 (60.00%)	4 / 12 (33.33%)
occurrences (all)	5	5	6
Hyperglycaemia			
subjects affected / exposed	2 / 5 (40.00%)	0 / 5 (0.00%)	0 / 12 (0.00%)
occurrences (all)	5	0	0
Hyperlipidaemia			
subjects affected / exposed	1 / 5 (20.00%)	0 / 5 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Hypocalcaemia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Hypoglycaemia			
subjects affected / exposed	0 / 5 (0.00%)	1 / 5 (20.00%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Hypokalaemia			
subjects affected / exposed	1 / 5 (20.00%)	1 / 5 (20.00%)	0 / 12 (0.00%)
occurrences (all)	1	1	0

Hyponatraemia subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	0 / 5 (0.00%) 0	1 / 12 (8.33%) 1

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
27 August 2013	According protocol version 1.0 the use of Tyrosinkinaseinhibitors Sunitinib, Pazopanib and Sorafenib where allowed as second line treatment in the study. In protocol version 2.0 this was changed to Axitinib alone, since this drug has been approved for the given indication and a superior efficacy has been shown. Furthermore, changes to the substudies have been made.
15 July 2015	Due to inadequate patient recruitment, the study was discontinued early.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported