Clinical trial results:
A Phase II Trial to Evaluate the Efficacy of AZD6094 (HMPL-504) in Patients with Papillary Renal Cell Carcinoma (PRCC)

Summary

EudraCT number	2014-001858-41
Trial protocol	GB ES
Global end of trial date	29 January 2017

Results information

Result version number	v1 (current)
This version publication date	08 April 2021
First version publication date	08 April 2021

Trial information

Trial identification

Sponsor protocol code	D5082C00002

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02127710
WHO universal trial number (UTN)	-
Other trial identifiers	Sarah Cannon Development Innovations: GU 111

Notes:

Sponsors

Sponsor organisation name	AstraZeneca
Sponsor organisation address	N/A, Södertälje, Sweden, S-151 85
Public contact	Senior Medical Director, Savolitinib, AstraZeneca, ClinicalTrialTransparency@astrazeneca.com
Scientific contact	Senior Medical Director, Savolitinib, AstraZeneca, ClinicalTrialTransparency@astrazeneca.com

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	22 July 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	29 January 2016
Global end of trial reached?	Yes
Global end of trial date	29 January 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the trial was to assess the anti-tumor activity of AZD6094 in patients with Papillary Renal Cell Carcinoma (PRCC), and in the subgroup of MET-positive patients as measured by Investigator assessment of overall response rate (ORR) according to Response Evaluation Criteria in Solid Tumours (RECIST) version 1.1. MET-driven PRCC was defined as any of the following: chromosome 7 copy gain, focal MET or HGF gene amplification, or MET kinase domain mutations.

Protection of trial subjects:

The primary mechanism for protection of the subjects in the trial was the Steering Committee comprised of multidisciplinary members selected by AstraZeneca and Sarah Cannon Development Innovations. The committee had nine members who were experts able to provide clinical and methodological expertise as it related to the development of AZD6094 in renal cancer. Any outcome of review by the Steering Committee that affected patient safety or study design was communicated in a timely manner to all participating sites by Sarah Cannon Development Innovations.

Background therapy:

None

Evidence for comparator:

This was a single arm study - there was no comparator.

Actual start date of recruitment	30 April 2014
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United States: 68
Country: Number of subjects enrolled	United Kingdom: 20
Country: Number of subjects enrolled	Canada: 16
Country: Number of subjects enrolled	Spain: 5
Worldwide total number of subjects	109
EEA total number of subjects	5

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)	59
From 65 to 84 years	49
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

One hundred thirty-one (131) subjects gave informed consent to be screened; 111 patients were enrolled; 20 patients were screen failures; 109 patients received at least one dose of AZD6094. Two patients were withdrawn prior to receiving any study drug. The study was conducted at 23 international sites in the US, Canada, UK, and Spain.

Pre-assignment

Screening details:

All patients were required to provide an archived or fresh tumour sample at enrolment to confirm eligibility, and for performance of the c-MET biomarker analysis. C-MET biomarker results determined the subgroup placement for data analyses as follows: c-MET positive (n=44), c-MET negative (n=46) and c-MET unknown (n=19).

Period 1

Period 1 title	Overall Study
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	c-MET positive

Arm description: -

Arm type	Experimental
Investigational medicinal product name	AZD6094
Investigational medicinal product code	
Other name	savolitinib
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

600 mg/day

Arm title	c-MET negative

Arm description: -

Arm type	Experimental
Investigational medicinal product name	AZD6094
Investigational medicinal product code	
Other name	savolitinib
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

600 mg/day

Arm title	c-MET Status Unknown

Arm description: -

Arm type	Experimental
Investigational medicinal product name	AZD6094
Investigational medicinal product code	
Other name	savolitinib
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

600 mg/day

Number of subjects in period 1	c-MET positive	c-MET negative	c-MET Status Unknown
Started	46	47	16
Completed	46	47	16

Period 2

Period 2 title	Full Study
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	No
Arm title	Safety Analysis Set

Arm description:

All participants who received at least one dose of AZD6094 are included in the Safety Analysis Set

Arm type	Experimental
Investigational medicinal product name	AZD6094
Investigational medicinal product code	
Other name	savolitinib
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

600 mg/day

Arm title	Efficacy Analysis Set

Arm description:

The efficacy analysis set consisted of 84 patients with central laboratory PRCC pathology confirmed and with measurable disease.

Arm type	Experimental
Investigational medicinal product name	AZD6094
Investigational medicinal product code	
Other name	savolitinib
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

600 mg/day

Number of subjects in period 2	Safety Analysis Set	Efficacy Analysis Set
Started	109	85
Completed	109	85

Period 3

Period 3 title	Pharmacokinetic Study Period
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Pharmacokinetic (PK) Analysis Set

Arm description:

The PK analysis set included all patients who received at least one dose of AZD6094 and had at least one AZD6094 plasma concentration measurement.

Arm type	Experimental
Investigational medicinal product name	AZD6094
Investigational medicinal product code	
Other name	savolitinib
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

600 mg/day

Number of subjects in period 3	Pharmacokinetic (PK) Analysis Set
Started	109
Completed	100
Not completed	9
Samples for PK analysis were not collected.	9

Baseline characteristics

Reporting groups	
Reporting group title	c-MET positive
Reporting group description: -	
Reporting group title	c-MET negative
Reporting group description: -	
Reporting group title	c-MET Status Unknown
Reporting group description: -	

Reporting group values	c-MET positive	c-MET negative	c-MET Status Unknown
Number of subjects	46	47	16
Age Categorical Units: Subjects			
<=18 years	0	0	0
Between 18 and 65 years	24	26	9
>=65 years	22	21	7
Age Continuous Units: years			
arithmetic mean	61.9	60.7	58.5
standard deviation	± 12.88	± 10.88	± 13.69
Gender, Male/Female Units: Subjects			
Female	13	11	7
Male	33	36	9
Race/Ethnicity, Customized Units: Subjects			
White	40	41	15
Black or African American	5	2	1
Asian	0	1	0
Other	1	3	0
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	6	6	2
Not Hispanic or Latino	40	41	14
ECOG Performance Status			
ECOG Performance Status: (0) = Fully active; (1) = Restricted in physically strenuous activity; (2) = Ambulatory and capable of self-care; (3) = Capable of limited self-care; (4) = Completely disabled			
Units: Subjects			
PS = 0	19	25	7
PS = 1	27	22	9
PRCC Confirmation from Central Laboratory Units: Subjects			
PRCC Confirmed	37	40	8
PRCC Not Confirmed	9	7	8
Stage Classification Units: Subjects			
Low	1	4	0

Intermediate	8	12	4
High	13	15	3
Missing	24	16	9
Renal Cell Classification Units: Subjects			
Type I papillary RCC	12	2	2
Type II papillary RCC	25	38	6
Missing or Unknown	9	7	8
MSKCC risk group			
Risk categories for patients were obtained from the Memorial Sloan Kettering Cancer Center (MSKCC) risk category prognostic model in advanced renal cell cancer, as follows: Favourable risk = 0 risk factors; Intermediate risk = 1 or 2 risk factors; Poor risk = 3 or more risk factors. Risk factors include: Karnofsky performance status < 80%; time from diagnosis to salvage treatment < 1 year; haemoglobin < LLN; corrected serum calcium > ULN; and serum LDH > 1.5 x ULN.			
Units: Subjects			
Favourable risk	3	10	2
Intermediate risk	28	14	7
Poor risk	3	5	2
Missing	12	18	5
Age Continuous | Units: years			
median	64	64	61
full range (min-max)	23 to 87	29 to 75	37 to 80
Weight Units: kilograms			
arithmetic mean	78.42	85.38	84.90
standard deviation	± 20.74	± 23.84	± 12.55
Weight Units: kilograms			
median	76.5	83.5	87.65
full range (min-max)	42 to 134	47 to 160.6	59.3 to 101.6

Reporting group values	Total		
Number of subjects	109		
Age Categorical Units: Subjects			
<=18 years	0		
Between 18 and 65 years	59		
>=65 years	50		
Age Continuous Units: years			
arithmetic mean			
standard deviation	-		
Gender, Male/Female Units: Subjects			
Female	31		
Male	78		
Race/Ethnicity, Customized Units: Subjects			
White	96		
Black or African American	8		
Asian	1		

Other	4		
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	14		
Not Hispanic or Latino	95		
ECOG Performance Status			
ECOG Performance Status: (0) = Fully active; (1) = Restricted in physically strenuous activity; (2) = Ambulatory and capable of self-care; (3) = Capable of limited self-care; (4) = Completely disabled			
Units: Subjects			
PS = 0	51		
PS = 1	58		
PRCC Confirmation from Central Laboratory Units: Subjects			
PRCC Confirmed	85		
PRCC Not Confirmed	24		
Stage Classification Units: Subjects			
Low	5		
Intermediate	24		
High	31		
Missing	49		
Renal Cell Classification Units: Subjects			
Type I papillary RCC	16		
Type II papillary RCC	69		
Missing or Unknown	24		
MSKCC risk group			
Risk categories for patients were obtained from the Memorial Sloan Kettering Cancer Center (MSKCC) risk category prognostic model in advanced renal cell cancer, as follows: Favourable risk = 0 risk factors; Intermediate risk = 1 or 2 risk factors; Poor risk = 3 or more risk factors. Risk factors include: Karnofsky performance status < 80%; time from diagnosis to salvage treatment < 1 year; haemoglobin < LLN; corrected serum calcium > ULN; and serum LDH > 1.5 x ULN.			
Units: Subjects			
Favourable risk	15		
Intermediate risk	49		
Poor risk	10		
Missing	35		
Age Continuous | Units: years median full range (min-max)	- -		
Weight Units: kilograms arithmetic mean standard deviation	- -		
Weight Units: kilograms median full range (min-max)	- -		

End points

End points reporting groups

Reporting group title	c-MET positive
Reporting group description: -	
Reporting group title	c-MET negative
Reporting group description: -	
Reporting group title	c-MET Status Unknown
Reporting group description: -	
Reporting group title	Safety Analysis Set
Reporting group description:	
All participants who received at least one dose of AZD6094 are included in the Safety Analysis Set	
Reporting group title	Efficacy Analysis Set
Reporting group description:	
The efficacy analysis set consisted of 84 patients with central laboratory PRCC pathology confirmed and with measurable disease.	
Reporting group title	Pharmacokinetic (PK) Analysis Set
Reporting group description:	
The PK analysis set included all patients who received at least one dose of AZD6094 and had at least one AZD6094 plasma concentration measurement.	

Primary: Objective Response Rate (RECIST Version 1.1) Stratified by c-MET Status in Efficacy Analysis Set (n=85)

End point title	Objective Response Rate (RECIST Version 1.1) Stratified by c-MET Status in Efficacy Analysis Set (n=85)[1]
End point description:	
Assess the anti-tumour activity of AZD6094 in patients with PRCC, and in the subgroup of MET-positive patients, as measured by Investigator-assessment of overall response rate (ORR) according to Response Evaluation Criteria in Solid Tumours (RECIST) Version 1.1.	
End point type	Primary
End point timeframe:	
Up to 12 months	

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: As per SAP (Appendix 12.1.9), ORR is defined as the percentage of patients with a confirmed programmatically calculated response of CR or PR. This is presented in this table.No statistical testing undertaken

End point values	c-MET positive	c-MET negative	Efficacy Analysis Set	c-MET Status Unknown
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	37	40	85	8
Units: Percentage				
number (not applicable)				
Complete Response	0	0	0	0
Partial Response	8.1	0	3.5	0

Statistical analyses

No statistical analyses for this end point

Primary: Objective Response Rate (RECIST Version 1.1) Stratified by c-MET Status in Safety Analysis (n=109)

End point title	Objective Response Rate (RECIST Version 1.1) Stratified by c-MET Status in Safety Analysis (n=109)[2]

End point description:

AAssess the anti-tumour activity of AZD6094 in patients with PRCC, and in the subgroup of MET-positive patients, as measured by Investigator-assessment of overall response rate (ORR) according to Response Evaluation Criteria in Solid Tumours (RECIST) Version 1.1.

End point type	Primary

End point timeframe:

Up to 12 months

Notes:

[2] - 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: As per CSP dated 4th August 2017, this objective is to characterise the PK of AZD6094 regardless c-MET status

End point values	c-MET positive	Safety Analysis Set	c-MET negative	c-MET Status Unknown
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	46	109	47	16
Units: Percentage				
number (not applicable)				
Complete Response	0	0	0	0
Partial Response	17.4	7.3	0	0

Statistical analyses

No statistical analyses for this end point

Secondary: Progression Free Survival (PFS) Stratified by c-MET Status in the Efficacy Analysis Set (n = 85)

End point title	Progression Free Survival (PFS) Stratified by c-MET Status in the Efficacy Analysis Set (n = 85)

End point description:

End point type	Secondary

End point timeframe:

Up to 12 months

End point values	c-MET positive	c-MET negative	Efficacy Analysis Set	c-MET Status Unknown
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	37	40	85	8
Units: weeks				
median (confidence interval 95%)	18.3 (12.3 to 35.4)	9.7 (6.1 to 12.4)	12.3 (6.7 to 17.6)	6.1 (5.1 to 999999.9)

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS) Stratified by c-MET Status in the Efficacy Analysis Set (n = 85)

End point title	Overall Survival (OS) Stratified by c-MET Status in the Efficacy Analysis Set (n = 85)

End point description:

End point type	Secondary

End point timeframe:

Up to 12 months

End point values	c-MET positive	c-MET negative	c-MET Status Unknown	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	37	40	8	
Units: weeks				
median (confidence interval 95%)	999999.9 (34.6 to 999999.9)	61.1 (29.4 to 999999.9)	51.5 (8.1 to 999999.9)	

Statistical analyses

No statistical analyses for this end point

Secondary: Progression Free Survival (PFS) Stratified by c-MET Status in the Safety Analysis Set (n = 109)

End point title	Progression Free Survival (PFS) Stratified by c-MET Status in the Safety Analysis Set (n = 109)

End point description:

End point type	Secondary

End point timeframe:

Up to 12 months

End point values	c-MET positive	c-MET negative	c-MET Status Unknown	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	46	47	16	
Units: weeks				
median (confidence interval 95%)	24.7 (17.7 to 35.4)	6.6 (6.1 to 11.9)	12.1 (6.1 to 41.9)	

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS) Stratified by c-MET Status in the Safety Analysis Set (n = 109)

End point title	Overall Survival (OS) Stratified by c-MET Status in the Safety Analysis Set (n = 109)

End point description:

End point type	Secondary

End point timeframe:

Up to 12 months

End point values	c-MET positive	c-MET negative	c-MET Status Unknown	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	46	47	16	
Units: weeks				
median (confidence interval 95%)	999999.9 (42.9 to 999999.9)	61.1 (40.6 to 106.7)	54.9 (18.4 to 999999.9)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Target Lesion Tumour Size at 12 Weeks in Efficacy Analysis Set (n=85)

End point title	Change from Baseline in Target Lesion Tumour Size at 12 Weeks in Efficacy Analysis Set (n=85)

End point description:

End point type	Secondary

End point timeframe:
12 Weeks (at 12 weeks timepoint)

End point values	c-MET positive	c-MET negative	c-MET Status Unknown	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	22	14	1	
Units: percentage				
arithmetic mean (standard deviation)	-6.3 (± 21.56)	3.4 (± 20.05)	7.1 (± 0)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Target Lesion Tumour Size at 12 Weeks in Safety Analysis Set (n=109)

End point title	Change from Baseline in Target Lesion Tumour Size at 12 Weeks in Safety Analysis Set (n=109)

End point description:

End point type	Secondary

End point timeframe:
12 Weeks (at 12 weeks timepoint)

End point values	c-MET positive	c-MET negative	c-MET Status Unknown	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	30	16	6	
Units: percentage				
arithmetic mean (standard deviation)	-10.9 (± 21.39)	4.3 (± 18.96)	5.1 (± 17.41)	

Statistical analyses

No statistical analyses for this end point

Secondary: Peak Plasma Concentration (Cmax) of AZD6094 Following Single Dose

End point title	Peak Plasma Concentration (Cmax) of AZD6094 Following Single Dose

End point description:

End point type	Secondary

End point timeframe:

24 Hours

End point values	Pharmacokinetic (PK) Analysis Set			
Subject group type	Reporting group			
Number of subjects analysed	53			
Units: ng/mL				
geometric mean (geometric coefficient of variation)				
AZD6094 peak plasma concentration	3038.8984 (± 44.4184)			

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Peak Plasma Concentration (tmax) of AZD6094 After Single Dose

End point title	Time to Peak Plasma Concentration (tmax) of AZD6094 After Single Dose

End point description:

End point type	Secondary

End point timeframe:

24 Hours

End point values	Pharmacokinetic (PK) Analysis Set			
Subject group type	Reporting group			
Number of subjects analysed	53			
Units: Hours				
median (full range (min-max))	2.0 (0.5 to 8.0)			

Statistical analyses

No statistical analyses for this end point

Secondary: Apparent Volume of Distribution of AZD6094 Following Single Dose

End point title	Apparent Volume of Distribution of AZD6094 Following Single Dose

End point description:

End point type	Secondary

End point timeframe:

24 Hours

End point values	Pharmacokinetic (PK) Analysis Set			
Subject group type	Reporting group			
Number of subjects analysed	19			
Units: Liters				
arithmetic mean (standard deviation)	137.4237 (± 36.5971)			

Statistical analyses

No statistical analyses for this end point

Secondary: Area Under Plasma Concentration Time Curve for AZD6094 After Single Dose

End point title	Area Under Plasma Concentration Time Curve for AZD6094 After Single Dose

End point description:

End point type	Secondary

End point timeframe:

24 Hours

End point values	Pharmacokinetic (PK) Analysis Set			
Subject group type	Reporting group			
Number of subjects analysed	19			
Units: h*ng/mL				
geometric mean (geometric coefficient of variation)	13144.7381 (± 36.4328)			

Statistical analyses

No statistical analyses for this end point

Secondary: Area Under Plasma Concentration Time Curve for AZD6094 After Single

Dose (time zero to last measurement)

End point title	Area Under Plasma Concentration Time Curve for AZD6094 After Single Dose (time zero to last measurement)

End point description:

End point type	Secondary

End point timeframe:

24 Hours

End point values	Pharmacokinetic (PK) Analysis Set			
Subject group type	Reporting group			
Number of subjects analysed	53			
Units: h*ng/mL				
geometric mean (geometric coefficient of variation)	13214.2441 (± 46.4616)			

Statistical analyses

No statistical analyses for this end point

Secondary: Apparent Total Clearance of AZD6094 from Plasma After Single Dose

End point title	Apparent Total Clearance of AZD6094 from Plasma After Single Dose

End point description:

End point type	Secondary

End point timeframe:

24 Hours

End point values	Pharmacokinetic (PK) Analysis Set			
Subject group type	Reporting group			
Number of subjects analysed	19			
Units: L/hour				
arithmetic mean (standard deviation)	48.4938 (± 17.3386)			

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Residence Time of AZD6094 After Single Dose

End point title	Mean Residence Time of AZD6094 After Single Dose

End point description:

End point type	Secondary

End point timeframe:

24 Hours

End point values	Pharmacokinetic (PK) Analysis Set			
Subject group type	Reporting group			
Number of subjects analysed	19			
Units: Hours				
arithmetic mean (standard deviation)	3.9837 (± 0.4813)			

Statistical analyses

No statistical analyses for this end point

Secondary: Elimination Half-Life of AZD6094 After Single Dose

End point title	Elimination Half-Life of AZD6094 After Single Dose

End point description:

End point type	Secondary

End point timeframe:

24 Hours

End point values	Pharmacokinetic (PK) Analysis Set			
Subject group type	Reporting group			
Number of subjects analysed	19			
Units: Hours				
arithmetic mean (standard deviation)	2.0499 (± 0.3820)			

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response

End point title	Duration of Response

End point description:

Duration of Response is the time from the first documentation of CR/PR until the date of progression, or death in the absence of progression. There were 8 responders: one of whom subsequently progressed or died and seven of whom were still classified as responders at the time of data cut-off and were therefore censored. It was not possible to determine a median or 75th percentile.

End point type	Secondary

End point timeframe:

Up to 12 months

End point values	Safety Analysis Set			
Subject group type	Reporting group			
Number of subjects analysed	8[3]			
Units: weeks				
median (inter-quartile range (Q1-Q3))	999999.9 (18.1 to 999999.9)			

Notes:

[3] - The median was not calculable because at data cut-off some participants were still responding.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: Up to 12 months	
Assessment type	Non-systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	18.1
Reporting groups	
Reporting group title	AZD6094 600 mg per day orally

Reporting group description: -

Serious adverse events	AZD6094 600 mg per day orally		
Total subjects affected by serious adverse events			
subjects affected / exposed	27 / 109 (24.77%)		
number of deaths (all causes)	59		
number of deaths resulting from adverse events	1		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Rectal cancer			
subjects affected / exposed	1 / 109 (0.92%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Pain			
subjects affected / exposed	1 / 109 (0.92%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Oedema			
subjects affected / exposed	1 / 109 (0.92%)		
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 / 109 (0.92%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pleural effusion				
subjects affected / exposed	1 / 109 (0.92%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumonitis				
subjects affected / exposed	1 / 109 (0.92%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Pulmonary embolism				
subjects affected / exposed	1 / 109 (0.92%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Psychiatric disorders				
Confused memory and fantasy	Additional description: Reporting PT: Confusional State			
subjects affected / exposed	1 / 109 (0.92%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Investigations				
Transaminases increased				
subjects affected / exposed	1 / 109 (0.92%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Cardiac disorders				
Pericarditis				
subjects affected / exposed	1 / 109 (0.92%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Myocardial infarction				
subjects affected / exposed	1 / 109 (0.92%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			

Nervous system disorders			
Hepatic encephalopathy			
subjects affected / exposed	1 / 109 (0.92%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	1 / 1		
Consciousness loss			
subjects affected / exposed	1 / 109 (0.92%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	3 / 109 (2.75%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Abdominal incarcerated hernia			
subjects affected / exposed	1 / 109 (0.92%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Abdominal pain			
subjects affected / exposed	1 / 109 (0.92%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Ascites			
subjects affected / exposed	2 / 109 (1.83%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Constipation			
subjects affected / exposed	2 / 109 (1.83%)		
occurrences causally related to treatment / all	1 / 4		
deaths causally related to treatment / all	0 / 0		
Nausea			

subjects affected / exposed	1 / 109 (0.92%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vomiting			
subjects affected / exposed	1 / 109 (0.92%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Small intestine carcinoma	Additional description: Reporting PT Term: Small Intestinal Obstruction		
subjects affected / exposed	1 / 109 (0.92%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	1 / 109 (0.92%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Drug-induced liver injury			
subjects affected / exposed	1 / 109 (0.92%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	4 / 109 (3.67%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Endocrine disorders			
Adrenal insufficiency			
subjects affected / exposed	1 / 109 (0.92%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Flank pain			

subjects affected / exposed	1 / 109 (0.92%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Cellulitis			
subjects affected / exposed	1 / 109 (0.92%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Lung Infection			
subjects affected / exposed	1 / 109 (0.92%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	1 / 109 (0.92%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Sepsis			
subjects affected / exposed	1 / 109 (0.92%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Urinary tract infection			
subjects affected / exposed	1 / 109 (0.92%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Wound infection			
subjects affected / exposed	1 / 109 (0.92%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	1 / 109 (0.92%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hyperkalemia			

subjects affected / exposed	1 / 109 (0.92%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hyponatraemia			
subjects affected / exposed	1 / 109 (0.92%)		
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	AZD6094 600 mg per day orally		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	107 / 109 (98.17%)		
Investigations			
Blood creatinine increased			
subjects affected / exposed	18 / 109 (16.51%)		
occurrences (all)	30		
Aspartate aminotransferase increased			
subjects affected / exposed	15 / 109 (13.76%)		
occurrences (all)	29		
Weight decreased			
subjects affected / exposed	14 / 109 (12.84%)		
occurrences (all)	18		
Alanine aminotransferase increased			
subjects affected / exposed	12 / 109 (11.01%)		
occurrences (all)	29		
Weight increased			
subjects affected / exposed	8 / 109 (7.34%)		
occurrences (all)	14		
Blood alklaine phosphatase increased			
subjects affected / exposed	7 / 109 (6.42%)		
occurrences (all)	8		
Nervous system disorders			

Dizziness			
subjects affected / exposed	11 / 109 (10.09%)		
occurrences (all)	11		
Dysgeusia			
subjects affected / exposed	9 / 109 (8.26%)		
occurrences (all)	10		
Headache			
subjects affected / exposed	8 / 109 (7.34%)		
occurrences (all)	9		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	17 / 109 (15.60%)		
occurrences (all)	31		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	49 / 109 (44.95%)		
occurrences (all)	63		
Peripheral oedema			
subjects affected / exposed	35 / 109 (32.11%)		
occurrences (all)	69		
Asthenia			
subjects affected / exposed	8 / 109 (7.34%)		
occurrences (all)	17		
Oedema			
subjects affected / exposed	8 / 109 (7.34%)		
occurrences (all)	9		
Chest pain			
subjects affected / exposed	7 / 109 (6.42%)		
occurrences (all)	7		
Mucosal inflammation			
subjects affected / exposed	6 / 109 (5.50%)		
occurrences (all)	6		
Pain			
subjects affected / exposed	5 / 109 (4.59%)		
occurrences (all)	8		
Chills			

subjects affected / exposed	5 / 109 (4.59%)		
occurrences (all)	7		
Pyrexia			
subjects affected / exposed	5 / 109 (4.59%)		
occurrences (all)	6		
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	56 / 109 (51.38%)		
occurrences (all)	81		
Vomiting			
subjects affected / exposed	34 / 109 (31.19%)		
occurrences (all)	51		
Constipation			
subjects affected / exposed	29 / 109 (26.61%)		
occurrences (all)	31		
Diarrhoea			
subjects affected / exposed	18 / 109 (16.51%)		
occurrences (all)	21		
Abdominal pain			
subjects affected / exposed	9 / 109 (8.26%)		
occurrences (all)	20		
Abdominal distension			
subjects affected / exposed	6 / 109 (5.50%)		
occurrences (all)	11		
Stomatitis			
subjects affected / exposed	6 / 109 (5.50%)		
occurrences (all)	7		
Ascites drainage			
subjects affected / exposed	5 / 109 (4.59%)		
occurrences (all)	6		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	16 / 109 (14.68%)		
occurrences (all)	18		
Dyspnoea			

subjects affected / exposed	16 / 109 (14.68%)		
occurrences (all)	27		
Dyspnoea exertional			
subjects affected / exposed	11 / 109 (10.09%)		
occurrences (all)	12		
Pleural effusion			
subjects affected / exposed	5 / 109 (4.59%)		
occurrences (all)	6		
Renal and urinary disorders			
Proteinuria			
subjects affected / exposed	11 / 109 (10.09%)		
occurrences (all)	21		
Psychiatric disorders			
Insomnia			
subjects affected / exposed	5 / 109 (4.59%)		
occurrences (all)	5		
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	16 / 109 (14.68%)		
occurrences (all)	20		
Arthalgia			
subjects affected / exposed	13 / 109 (11.93%)		
occurrences (all)	24		
Musculoskeletal chest pain			
subjects affected / exposed	9 / 109 (8.26%)		
occurrences (all)	10		
Pain in extremity			
subjects affected / exposed	11 / 109 (10.09%)		
occurrences (all)	21		
Flank pain			
subjects affected / exposed	9 / 109 (8.26%)		
occurrences (all)	14		
Musculoskeletal pain			
subjects affected / exposed	10 / 109 (9.17%)		
occurrences (all)	11		
Muscle spasm			

subjects affected / exposed	7 / 109 (6.42%)		
occurrences (all)	7		
Myalgia			
subjects affected / exposed	6 / 109 (5.50%)		
occurrences (all)	6		
Metabolism and nutrition disorders			
Hypoalbuminaemia			
subjects affected / exposed	13 / 109 (11.93%)		
occurrences (all)	20		
Decreased appetite			
subjects affected / exposed	25 / 109 (22.94%)		
occurrences (all)	37		
Hyperglycaemia			
subjects affected / exposed	8 / 109 (7.34%)		
occurrences (all)	14		
Hyponatraemia			
subjects affected / exposed	8 / 109 (7.34%)		
occurrences (all)	12		
Hyperkalemia			
subjects affected / exposed	7 / 109 (6.42%)		
occurrences (all)	16		
Hypomagneseama			
subjects affected / exposed	6 / 109 (5.50%)		
occurrences (all)	9		
Fluid balance positive			
subjects affected / exposed	5 / 109 (4.59%)		
occurrences (all)	8		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
03 March 2014	Amendment 1 revised the protocol as follows: 1) Exclude any patient receiving strong CYP1A2 inhibitor within 2 weeks prior to entry and instructions for investigators to advise patients to avoid concomitant use of strong CYP1A2 because CYP1A2 is active in the formation of metabolite M2; 2) Amended dose modification criteria to discontinue AZD6094 for patients who develop ≥ Grade 3 toxicity that does not resolve to ≤ Grade 1 within 2 weeks; 3) An echocardiogram or MUGA scan to assess LVEF will be conducted at Screening – Baseline and 12 weeks after study start; 4) Thyroid Stimulating Hormone (TSH), Free Thyroxine (Free T4) and Lactate Dehydrogenase (LDH) were added to the standard laboratory safety assessment panel; 5) An assessment of risk criteria in accordance with the Memorial Sloan Kettering Cancer Centre (MSKCC) risk category prognostic model in advanced renal cell cancer was added.
18 December 2014	Amendment 2 revised the protocol as follows: 1) The section regarding risk minimization activities was revised to add hepatic encephalopathy and to include information regarding a fatal event of hepatic encephalopathy; 2) Inclusion criteria regarding patients with known tumour thrombus or deep vein thrombosis (DVT) are eligible if stable on low molecular weight heparin (LMWH) for ≥ 2 weeks; 3) Revised exclusion criteria to allow patients with limited prior or current treatment with a c-MET inhibitor to enter the study if discussed with the Medical Monitor; 4) The section regarding restrictions during the study was revised to specify that acetaminophen (paracetamol) daily dose was limited to 3 grams/day or the maximum dose approved locally (if less than 3 grams/day) during the study; 5) The section regarding restrictions during the study was revised to specify that patients should abstain from eating large amounts of grapefruit or Seville oranges (and other products containing these fruits [e.g., juice or marmalade] during the study; 6) Advise Investigators to review the patient's concomitant medications, and evaluate the need for the patient to continue on hepatic metabolism modifying agents, such as statins; 7) The study plan was revised to include additional liver function monitoring; 8) To specify that patients should be in a fasted state at Cycle 1 Day 8 at 2-3 hours post-dose for the collection of a biopsy sample and blood for a PK sample.
05 June 2015	Amendment 3 revised the protocol as follows: 1) Information regarding safety, efficacy, and potential benefit in humans was updated to align with the Investigator's Brochure; 2) Include information on the potential for drug-drug interactions; 3) The primary and secondary objectives of the study were revised to include tumour assessment in the subgroup of MET-positive patients.; 4) The futility threshold for continuation of the study to Stage 2 was revised slightly; 5) The protocol was clarified to provide further detail on the non-binding futility analysis to be conducted after 20 evaluable patients were enrolled, marking the completion of Stage 1; 6) Formal hypothesis testing was added - if the study passes the futility analysis at the end of Stage 1, than the end-of-study analysis will be performed on the total data from the patients in both stages 1 and 2 combined; 7) At the end of the study the primary end-point (ORR) will be tested against the null hypothesis Ho; ORR ≤ 25% at the one-sided significance level of $\alpha = 0.025$ in two populations as co-primary objectives; the total population of confirmed PRCC patients and the subgroup of MET positive PRCC patients; 8) The sample size was expanded to a total of 75 evaluable patients provided the futility analysis of Stage 1 was satisfied.
18 April 2016	Amendment 4 revised the protocol as follows: 1) Extended follow-up and response assessments for patients without disease progression at the time of discontinuing study treatment was added; 2) The collection of urine for PK analysis was clarified.

27 May 2016	Amendment 5 revised the protocol as follows: New information on drug-drug interactions was included (metformin, digoxin, quinidine, loperamide, saquinavir and ritonavir). AZD6094 is a weak inhibitor of OATP1B1, OATP1B3 and BCRP in vitro, and the use of statins should be avoided as far as possible; AZD6094 is also an inhibitor of MATE1 and MATE2K, thus metformin should be used with caution in case of increased metformin exposure.
05 December 2016	Amendment 6 revised the protocol as follows: 1) New information and guidance regarding Stevens-Johnson syndrome was added; 2) Guidance for hepatotoxicity and dose modifications was updated and revised; 3) Investigator guidance for end of study access to the investigational drug was added and post database lock procedures for patients continuing to receive study drug.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

The secondary endpoint overall survival in both the Safety Analysis Set and the Efficacy Analysis could not be calculated as a finite number. Due to limitations of the EudraCT it was entered 999999.9 as system doesn’t recognise values like N/A.

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/28644771