Clinical trial results:
A Phase 2, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study of the Safety, Clinical Activity and Pharmacokinetics of Bosutinib (PF-05208763) Versus Placebo in Subjects with Autosomal Dominant Polycystic Kidney Disease (ADPKD)

Due to the EudraCT – Results system being out of service between 31 July 2015 and 12 January 2016, these results have been published in compliance with revised timelines.

Summary

EudraCT number	2010-023017-65
Trial protocol	SE ES CZ HU GB PL SK LT IT BG
Global end of trial date	29 August 2014

Results information

Result version number	v1 (current)
This version publication date	06 March 2016
First version publication date	06 March 2016

Trial information

Trial identification

Sponsor protocol code	B1871019

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01233869
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Pfizer, Inc.
Sponsor organisation address	235 E 42nd Street, New York, United States, 10017
Public contact	Pfizer Inc., Pfizer ClinicalTrials.gov Call Center,, 001 8007181021,
Scientific contact	Pfizer ClinicalTrials.gov Call Center, Pfizer, Inc., ClinicalTrials.gov_Inquiries@pfizer.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	17 June 2015
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	29 August 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the study was to demonstrate that bosutinib reduces the rate of kidney enlargement in subjects with Autosomal Dominant Polycystic Kidney Disease (ADPKD) entering the study with total kidney volume (TKV) >=750 cc and estimated glomerular filtration rate (eGFR) 60 >=mL/min/1.73m2.

Protection of trial subjects:

An independent external Data Monitoring Committee (eDMC) reviewed accumulating safety data on an ongoing basis. The eDMC may have, at any time, requested additional information from the sponsor. Based on these reviews, the eDMC had capacity to make recommendations to the sponsor that might impact the future conduct of the study. These may have included continuing the study as planned, amending safety-monitoring procedures, modifying the protocol or consent, or terminating the study. In addition, the eDMC was responsible for reviewing the safety and efficacy data for the interim analysis.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	16 December 2010
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Australia: 2
Country: Number of subjects enrolled	Canada: 5
Country: Number of subjects enrolled	Czech Republic: 21
Country: Number of subjects enrolled	Hungary: 8
Country: Number of subjects enrolled	Italy: 6
Country: Number of subjects enrolled	Korea, Republic of: 9
Country: Number of subjects enrolled	Lithuania: 1
Country: Number of subjects enrolled	Moldova, Republic of: 8
Country: Number of subjects enrolled	Poland: 44
Country: Number of subjects enrolled	Romania: 20
Country: Number of subjects enrolled	Slovakia: 7
Country: Number of subjects enrolled	Spain: 5
Country: Number of subjects enrolled	Sweden: 3
Country: Number of subjects enrolled	Switzerland: 2
Country: Number of subjects enrolled	United Kingdom: 2
Country: Number of subjects enrolled	United States: 26

Worldwide total number of subjects	169
EEA total number of subjects	117

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)	169
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

172 subjects were enrolled in this study, of which 169 received at least 1 dose of study treatment.

Period 1

Period 1 title	Initial Treatment Period (24 Months)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Investigator, Subject

Arms

Are arms mutually exclusive?	Yes
Arm title	Bosutinib 200 mg/day

Arm description:

Subjects received bosutinib 200 mg tablet orally once daily (QD) in the morning with food for 24 months in the Initial Treatment Period (ITP). After a 30-day washout period, subjects who entered the Extended Treatment Period (ETP) continued to receive bosutinib 200 mg orally QD for up to 46 months.

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

Dosage and administration details:

200 mg in the morning with food

Arm title	Bosutinib 400 mg/day

Arm description:

Subjects received bosutinib 400 mg tablet orally QD in the morning with food for 24 months in the ITP. All subjects were dose-reduced during the ITP based on a protocol amendment. Those who remained active in the study at the time of the amendment are represented in the bosutinib 400/200 mg/day group.

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

Dosage and administration details:

400 mg in the morning with food

Arm title	Bosutinib 400/200 mg/day

Arm description:

Subjects received bosutinib 400 mg and were dose-reduced to 200 mg tablet (based on protocol amendment) orally QD in the morning with food for 24 months in the ITP. After a 30-day washout period, subjects who entered the ETP continued to receive bosutinib 200 mg orally QD for up to 46 months.

Arm type	Experimental

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

Dosage and administration details:

400 mg (dose-reduced to 200 mg) in the morning with food

Arm title	Placebo

Arm description:

Subjects received placebo tablet orally QD in the morning with food for 24 months in the ITP. After a 30-day washout period, subjects who entered the ETP continued to receive placebo matched bosutinib QD for up to 46 months.

Arm type	Placebo
Investigational medicinal product name	placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

matched

Number of subjects in period 1	Bosutinib 200 mg/day	Bosutinib 400 mg/day	Bosutinib 400/200 mg/day
Started	58	31	24
Completed	34	3	22
Not completed	24	28	2
Adverse event, serious fatal	1	-	-
Adverse event, non-fatal	9	17	-
Not Related to Study Drug	14	11	2

Number of subjects in period 1	Placebo
Started	56
Completed	34
Not completed	22
Adverse event, serious fatal	-
Adverse event, non-fatal	3
Not Related to Study Drug	19

Period 2

Period 2 title	Washout Period 30 Days
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	Bosutinib 200 mg/day

Arm description:

Subjects received bosutinib 200 mg tablet orally once daily (QD) in the morning with food for 24 months in the Initial Treatment Period (ITP). After a 30-day washout period, subjects who entered the Extended Treatment Period (ETP) continued to receive bosutinib 200 mg orally QD for up to 46 months.

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

Dosage and administration details:

200 mg in the morning with food

Arm title	Bosutinib 400 mg/day

Arm description:

Subjects received bosutinib 400 mg tablet orally QD in the morning with food for 24 months in the ITP. All subjects were dose-reduced during the ITP based on a protocol amendment. Those who remained active in the study at the time of the amendment are represented in the bosutinib 400/200 mg/day group.

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

Dosage and administration details:

400 mg in the morning with food

Arm title	Bosutinib 400/200 mg/day

Arm description:

Subjects received bosutinib 400 mg and were dose-reduced to 200 mg tablet (based on protocol amendment) orally QD in the morning with food for 24 months in the ITP. After a 30-day washout period, subjects who entered the ETP continued to receive bosutinib 200 mg orally QD for up to 46 months.

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

Dosage and administration details:

400 mg (dose-reduced to 200 mg) in the morning with food

Arm title	Placebo

Arm description:

Subjects received placebo tablet orally QD in the morning with food for 24 months in the ITP. After a

30-day washout period, subjects who entered the ETP continued to receive placebo matched bosutinib QD for up to 46 months.

Arm type	Placebo
Investigational medicinal product name	placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

matched

Number of subjects in period 2	Bosutinib 200 mg/day	Bosutinib 400 mg/day	Bosutinib 400/200 mg/day
Started	34	3	22
Completed	34	3	22

Number of subjects in period 2	Placebo
Started	34
Completed	34

Period 3

Period 3 title	Extended Treatment Period (46 Months)
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	Bosutinib 200 mg/day

Arm description:

Subjects received bosutinib 200 mg tablet orally once daily (QD) in the morning with food for 24 months in the Initial Treatment Period (ITP). After a 30-day washout period, subjects who entered the Extended Treatment Period (ETP) continued to receive bosutinib 200 mg orally QD for up to 46 months.

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

Dosage and administration details:

200 mg in the morning with food

Arm title	Bosutinib 400 mg/day

Arm description:

Subjects received bosutinib 400 mg tablet orally QD in the morning with food for 24 months in the ITP. All subjects were dose-reduced during the ITP based on a protocol amendment. Those who remained active in the study at the time of the amendment are represented in the bosutinib 400/200 mg/day group.

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

Dosage and administration details:

400 mg in the morning with food

Arm title	Bosutinib 400/200 mg/day

Arm description:

Subjects received bosutinib 400 mg and were dose-reduced to 200 mg tablet (based on protocol amendment) orally QD in the morning with food for 24 months in the ITP. After a 30-day washout period, subjects who entered the ETP continued to receive bosutinib 200 mg orally QD for up to 46 months.

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

Dosage and administration details:

400 mg (dose-reduced to 200 mg) in the morning with food

Arm title	Placebo

Arm description:

Subjects received placebo tablet orally QD in the morning with food for 24 months in the ITP. After a 30-day washout period, Subjects who entered the ETP continued to receive placebo matched bosutinib QD for up to 46 months.

Arm type	Placebo
Investigational medicinal product name	placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

matched

Number of subjects in period 3	Bosutinib 200 mg/day	Bosutinib 400 mg/day	Bosutinib 400/200 mg/day
Started	34	3	22
Completed	20	0	17
Not completed	14	3	5
Consent withdrawn by subject	10	3	5
Adverse event, non-fatal	1	-	-
Unspecified	3	-	-

Lost to follow-up	-	-	-

Number of subjects in period 3	Placebo
Started	34
Completed	18
Not completed	16
Consent withdrawn by subject	11
Adverse event, non-fatal	1
Unspecified	3
Lost to follow-up	1

Baseline characteristics

Reporting groups	
Reporting group title	Bosutinib 200 mg/day
Reporting group description:	
Subjects received bosutinib 200 mg tablet orally once daily (QD) in the morning with food for 24 months in the Initial Treatment Period (ITP). After a 30-day washout period, subjects who entered the Extended Treatment Period (ETP) continued to receive bosutinib 200 mg orally QD for up to 46 months.	
Reporting group title	Bosutinib 400 mg/day
Reporting group description:	
Subjects received bosutinib 400 mg tablet orally QD in the morning with food for 24 months in the ITP. All subjects were dose-reduced during the ITP based on a protocol amendment. Those who remained active in the study at the time of the amendment are represented in the bosutinib 400/200 mg/day group.	
Reporting group title	Bosutinib 400/200 mg/day
Reporting group description:	
Subjects received bosutinib 400 mg and were dose-reduced to 200 mg tablet (based on protocol amendment) orally QD in the morning with food for 24 months in the ITP. After a 30-day washout period, subjects who entered the ETP continued to receive bosutinib 200 mg orally QD for up to 46 months.	
Reporting group title	Placebo
Reporting group description:	
Subjects received placebo tablet orally QD in the morning with food for 24 months in the ITP. After a 30-day washout period, subjects who entered the ETP continued to receive placebo matched bosutinib QD for up to 46 months.	

Reporting group values	Bosutinib 200 mg/day	Bosutinib 400 mg/day	Bosutinib 400/200 mg/day
Number of subjects	58	31	24
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	58	31	24
From 65-84 years	0	0	0
85 years and over	0	0	0
Age Continuous | Units: years			
arithmetic mean	37.9	41.3	36.4
standard deviation	± 8	± 4.9	± 7.8
Gender, Male/Female Units: participants			
Male	30	17	9
Female	28	14	15

Reporting group values	Placebo	Total	
Number of subjects	56	169	

Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	56	169	
From 65-84 years	0	0	
85 years and over	0	0	
Age Continuous | Units: years			
arithmetic mean	38.5		
standard deviation	± 7.4	-	
Gender, Male/Female Units: participants			
Male	21	77	
Female	35	92	

End points

End points reporting groups

Reporting group title	Bosutinib 200 mg/day

Reporting group description:

Subjects received bosutinib 200 mg tablet orally once daily (QD) in the morning with food for 24 months in the Initial Treatment Period (ITP). After a 30-day washout period, subjects who entered the Extended Treatment Period (ETP) continued to receive bosutinib 200 mg orally QD for up to 46 months.

Reporting group title	Bosutinib 400 mg/day

Reporting group description:

Subjects received bosutinib 400 mg tablet orally QD in the morning with food for 24 months in the ITP. All subjects were dose-reduced during the ITP based on a protocol amendment. Those who remained active in the study at the time of the amendment are represented in the bosutinib 400/200 mg/day group.

Reporting group title	Bosutinib 400/200 mg/day

Reporting group description:

Subjects received bosutinib 400 mg and were dose-reduced to 200 mg tablet (based on protocol amendment) orally QD in the morning with food for 24 months in the ITP. After a 30-day washout period, subjects who entered the ETP continued to receive bosutinib 200 mg orally QD for up to 46 months.

Reporting group title	Placebo

Reporting group description:

Subjects received placebo tablet orally QD in the morning with food for 24 months in the ITP. After a 30-day washout period, subjects who entered the ETP continued to receive placebo matched bosutinib QD for up to 46 months.

Reporting group title	Bosutinib 200 mg/day

Reporting group description:

Subjects received bosutinib 200 mg tablet orally once daily (QD) in the morning with food for 24 months in the Initial Treatment Period (ITP). After a 30-day washout period, subjects who entered the Extended Treatment Period (ETP) continued to receive bosutinib 200 mg orally QD for up to 46 months.

Reporting group title	Bosutinib 400 mg/day

Reporting group description:

Subjects received bosutinib 400 mg tablet orally QD in the morning with food for 24 months in the ITP. All subjects were dose-reduced during the ITP based on a protocol amendment. Those who remained active in the study at the time of the amendment are represented in the bosutinib 400/200 mg/day group.

Reporting group title	Bosutinib 400/200 mg/day

Reporting group description:

Subjects received bosutinib 400 mg and were dose-reduced to 200 mg tablet (based on protocol amendment) orally QD in the morning with food for 24 months in the ITP. After a 30-day washout period, subjects who entered the ETP continued to receive bosutinib 200 mg orally QD for up to 46 months.

Reporting group title	Placebo

Reporting group description:

Subjects received placebo tablet orally QD in the morning with food for 24 months in the ITP. After a 30-day washout period, subjects who entered the ETP continued to receive placebo matched bosutinib QD for up to 46 months.

Reporting group title	Bosutinib 200 mg/day

Reporting group description:

Subjects received bosutinib 200 mg tablet orally once daily (QD) in the morning with food for 24 months in the Initial Treatment Period (ITP). After a 30-day washout period, subjects who entered the Extended Treatment Period (ETP) continued to receive bosutinib 200 mg orally QD for up to 46 months.

Reporting group title	Bosutinib 400 mg/day

Reporting group description:

Subjects received bosutinib 400 mg tablet orally QD in the morning with food for 24 months in the ITP. All subjects were dose-reduced during the ITP based on a protocol amendment. Those who remained active in the study at the time of the amendment are represented in the bosutinib 400/200 mg/day group.

Reporting group title	Bosutinib 400/200 mg/day
Reporting group description:	
Subjects received bosutinib 400 mg and were dose-reduced to 200 mg tablet (based on protocol amendment) orally QD in the morning with food for 24 months in the ITP. After a 30-day washout period, subjects who entered the ETP continued to receive bosutinib 200 mg orally QD for up to 46 months.	
Reporting group title	Placebo
Reporting group description:	
Subjects received placebo tablet orally QD in the morning with food for 24 months in the ITP. After a 30-day washout period, Subjects who entered the ETP continued to receive placebo matched bosutinib QD for up to 46 months.	

Primary: Change From Baseline in Total Kidney Volume (TKV) at Month 25

End point title	Change From Baseline in Total Kidney Volume (TKV) at Month 25
End point description:	
TKV was measured by centrally evaluated Magnetic Resonance Imaging (MRI).	
End point type	Primary
End point timeframe:	
Baseline and Month 25 (end of Initial Treatment Period Visit [ITPV])	

End point values	Bosutinib 200 mg/day	Bosutinib 400 mg/day	Bosutinib 400/200 mg/day	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	27	6	21	33
Units: centimeter cube (cm^3)				
arithmetic mean (standard deviation)				
Baseline (n=27,6,21,33)	1686.38 (± 944.3)	1418.96 (± 629.34)	1487.48 (± 531.96)	1670.33 (± 640.69)
Change at Month 25 (n=23,3,20,30)	85.05 (± 231.09)	102.45 (± 257.3)	-6.18 (± 119.79)	175.36 (± 191.43)

Statistical analyses

Statistical analysis title	Annualized Rate of Kidney Enlargement
Statistical analysis description:	
Placebo versus Pooled Bosutinib	
Comparison groups	Bosutinib 200 mg/day v Bosutinib 400 mg/day v Bosutinib 400/200 mg/day v Placebo
Number of subjects included in analysis	87
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	3.86

Confidence interval	
level	95 %
sides	2-sided
lower limit	2.02
upper limit	5.74

Statistical analysis title	Annualized Rate of Kidney Enlargement
Statistical analysis description: Bosutinib 200 mg/day versus Bosutinib 400/200 mg/day	
Comparison groups	Bosutinib 200 mg/day v Bosutinib 400/200 mg/day
Number of subjects included in analysis	48
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.1234
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	1.83
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.5
upper limit	4.22

Statistical analysis title	Annualized Rate of Kidney Enlargement
Statistical analysis description: Placebo versus Bosutinib 200 mg/day	
Comparison groups	Bosutinib 200 mg/day v Placebo
Number of subjects included in analysis	60
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.005
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	3.06
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.93
upper limit	5.23

Statistical analysis title	Annualized Rate of Kidney Enlargement
Statistical analysis description: Placebo versus Bosutinib 400 mg/day	
Comparison groups	Bosutinib 400 mg/day v Placebo

Number of subjects included in analysis	39
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.1336
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	3.41
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.03
upper limit	8.05

Statistical analysis title	Annualized Rate of Kidney Enlargement
Statistical analysis description:	
Placebo versus Bosutinib 400/200 mg/day	
Comparison groups	Bosutinib 400/200 mg/day v Placebo
Number of subjects included in analysis	54
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	4.95
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.65
upper limit	7.3

Secondary: Change From Baseline in Estimated Glomerular Filtration Rate (eGFR) at Months 12, 24, 25 and Early Termination

End point title	Change From Baseline in Estimated Glomerular Filtration Rate (eGFR) at Months 12, 24, 25 and Early Termination
End point description:	
eGFR was centrally evaluated. Glomerular filtration rate (GFR) is an index of kidney function that describes the flow of filtered fluid through the kidney. The Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation was used to calculate eGFR. Month 25 is the end of the ITPV. '99999' means data is 'not applicable'.	
End point type	Secondary
End point timeframe:	
Baseline, Month 12, Month 24, Month 25 (ITPV), and early termination	

End point values	Bosutinib 200 mg/day	Bosutinib 400 mg/day	Bosutinib 400/200 mg/day	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	27	6	21	33
Units: mL/min/1.73m^2				
arithmetic mean (standard deviation)				
Change at Month 12 (n=26,4,21,31)	-6.38 (± 11.6)	-7.56 (± 11.27)	-11.52 (± 10.86)	1.3 (± 9.71)
Change at Month 24 (n=23,3,20,30)	-8.47 (± 15.02)	-21.59 (± 13.74)	-13.16 (± 13.41)	-7.95 (± 12.91)
Change at ITPV (n=23,3,20,30)	-5 (± 10.78)	-13.24 (± 12.45)	-9.92 (± 14.55)	-2.74 (± 18.01)
Change at Early Termination (n=6,3,1,4)	-11.91 (± 8.79)	0.78 (± 4.83)	-10.24 (± 99999)	-2.75 (± 21.35)

Statistical analyses

No statistical analyses for this end point

Secondary: Time to First Occurrence or Worsening of Hypertension

End point title	Time to First Occurrence or Worsening of Hypertension

End point description:

The time to first occurrence or worsening of hypertension was observed (defined as the need for increased dose of or need for additional anti-hypertensive medication). The numbers presented correspond to the very first occurrence or worsening of hypertension in that treatment group.

End point type	Secondary

End point timeframe:

Baseline up to Month 25 (end of ITPV)

End point values	Bosutinib 200 mg/day	Bosutinib 400 mg/day	Bosutinib 400/200 mg/day	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	42	9	24	43
Units: days	15	180	90	30

Statistical analyses

No statistical analyses for this end point

Secondary: Time to First Occurrence or Worsening of Back and/or Flank Pain

End point title	Time to First Occurrence or Worsening of Back and/or Flank Pain

End point description:

The time to first occurrence or worsening of back and/or flank pain was observed (defined as initial onset of polycystic kidney disease [PKD]-related chronic back and/or flank pain; initiation of pain medication treatment for PKD-related chronic back and/or flank pain; addition of a pain medicine for

treatment of PKD-related chronic back and/or flank pain; increase in dose of pain medication for treatment of PKD-related chronic back and/or flank pain). The numbers presented correspond to the very first occurrence or worsening of back and/or flank pain in that treatment group.

End point type	Secondary

End point timeframe:

Baseline up to Month 25 (end of ITPV)

End point values	Bosutinib 200 mg/day	Bosutinib 400 mg/day	Bosutinib 400/200 mg/day	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	42	9	24	43
Units: days	30	30	270	15

Statistical analyses

No statistical analyses for this end point

Secondary: Time to First Occurrence of Gross Hematuria

End point title	Time to First Occurrence of Gross Hematuria

End point description:

Gross hematuria is the presence of blood in the urine (defined as pink, red, or cola-colored urine due to the presence of red blood cells). The numbers presented correspond to the very first occurrence of gross hematuria in that treatment group.

End point type	Secondary

End point timeframe:

Baseline up to Month 25 (end of ITPV)

End point values	Bosutinib 200 mg/day	Bosutinib 400 mg/day	Bosutinib 400/200 mg/day	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	42	9	24	43
Units: days	330	180	180	45

Statistical analyses

No statistical analyses for this end point

Secondary: Time to First Occurrence of Proteinuria

End point title	Time to First Occurrence of Proteinuria

End point description:

Proteinuria is the presence of an excess of serum proteins in the urine, which may be an early sign of kidney disease The numbers presented correspond to the very first occurrence of proteinuria in that

treatment group.

End point type	Secondary

End point timeframe:

Baseline up to Month 25 (end of ITPV)

End point values	Bosutinib 200 mg/day	Bosutinib 400 mg/day	Bosutinib 400/200 mg/day	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	42	0[1]	24	43
Units: days	360		270	540

Notes:

[1] - No proteinuria was observed.

Statistical analyses

No statistical analyses for this end point

Secondary: Time to First Occurrence of End-Stage Renal Disease (ESRD) Requiring Dialysis >=56 Days

End point title	Time to First Occurrence of End-Stage Renal Disease (ESRD) Requiring Dialysis >=56 Days

End point description:

ESRD is when the kidneys permanently fail to work at a level needed for daily life.

End point type	Secondary

End point timeframe:

Baseline up to Month 25 (end of ITPV)

End point values	Bosutinib 200 mg/day	Bosutinib 400 mg/day	Bosutinib 400/200 mg/day	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	0[2]	0[3]	0[4]	0[5]
Units: days				

Notes:

[2] - No subjects developed ESRD during the treatment period.

[3] - No subjects developed ESRD during the treatment period.

[4] - No subjects developed ESRD during the treatment period.

[5] - No subjects developed ESRD during the treatment period.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With High Blood Urea Nitrogen (BUN) Levels

End point title	Number of Subjects With High Blood Urea Nitrogen (BUN) Levels

End point description:

A BUN test can reveal how well the kidneys are working by measuring the amount of urea nitrogen in the blood. A high BUN level (>1.3 times the upper limit of normal) may suggest that the kidneys are not working properly. Month 25 is the end of the ITPV.

End point type	Secondary

End point timeframe:

Day 15, Months 6, 12, 18, 24, and 25 (end of ITPV)

End point values	Bosutinib 200 mg/day	Bosutinib 400 mg/day	Bosutinib 400/200 mg/day	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	58	31	24	56
Units: subjects				
Day 15	0	0	2	0
Month 6	0	0	0	0
Month 12	0	0	0	0
Month 18	0	0	0	0
Month 24	0	0	1	0
End of ITPV	0	0	2	0

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With High Serum Creatinine (SCr) Levels

End point title	Number of Subjects With High Serum Creatinine (SCr) Levels

End point description:

A SCr test can reveal how well the kidneys are working by measuring the amount of urea nitrogen in the blood. A high SCr level (>1.3 times the upper limit of normal) may suggest that the kidneys are not working properly. Month 25 is the end of the ITPV.

End point type	Secondary

End point timeframe:

Day 15, Months 6, 12, 18, 24, and 25 (end of ITPV)

End point values	Bosutinib 200 mg/day	Bosutinib 400 mg/day	Bosutinib 400/200 mg/day	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	58	31	24	56
Units: subjects				
Day 15	0	1	0	0
Month 6	0	0	0	0
Month 12	0	0	0	1
Month 18	0	0	0	0
Month 24	0	1	1	1

End of ITPV	0	0	0	1

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum Observed Plasma Concentration (Cmax) of Bosutinib

End point title	Maximum Observed Plasma Concentration (Cmax) of

End point description:

End point type	Secondary

End point timeframe:

Day 1 (pre-dose and 1, 3, 5 and 24 hours post-dose), Day 15 (pre-dose and 1, 2, 3, 4, 6, 8 and 24 hours post-dose)

Notes:

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The PK parameter analysis population included all participants randomized and treated who had at least 1 of the PK parameters of primary interest; n=the number of participants analyzed at that time point in the respective arms.

End point values	Bosutinib 200 mg/day	Bosutinib 400 mg/day	Bosutinib 400/200 mg/day	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	58	31	24	
Units: nanograms per milliliter (ng/mL)				
geometric mean (geometric coefficient of variation)				
Day 1 (n=58,31,24)	32.61 (± 53)	74.87 (± 47)	84.57 (± 56)	
Day 15 (n=58,16,22)	68.72 (± 43)	127.9 (± 28)	155 (± 31)	

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Reach Maximum Observed Plasma Concentration (Tmax) of Bosutinib

End point title	Time to Reach Maximum Observed Plasma Concentration (Tmax) of Bosutinib[7]

End point description:

End point type	Secondary

End point timeframe:

Day 1 (pre-dose and 1, 3, 5 and 24 hours post-dose), Day 15 (pre-dose and 1, 2, 3, 4, 6, 8 and 24 hours post-dose)

Notes:

[7] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The PK parameter analysis population included all participants randomized and treated who had at least 1 of the PK parameters of primary interest; n=the number of participants analyzed at that time point in the respective arms.

End point values	Bosutinib 200 mg/day	Bosutinib 400 mg/day	Bosutinib 400/200 mg/day	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	58	31	24	
Units: hour				
median (full range (min-max))				
Day 1 (n=58,31,24)	3 (1 to 24)	3 (2.8 to 23.8)	4.86 (1 to 5.25)	
Day 15 (n=58,16,22)	3.95 (0 to 25.6)	3 (1 to 8)	5 (1 to 8.12)	

Statistical analyses

No statistical analyses for this end point

Secondary: Area Under the Concentration-Time Profile From Time 0 to the Dosing Interval (AUCtau) of Bosutinib

End point title	Area Under the Concentration-Time Profile From Time 0 to the Dosing Interval (AUCtau) of Bosutinib[8]

End point description:

Area under the concentration-time profile from time 0 to time tau, the dosing interval, where tau=24 hours.

End point type	Secondary

End point timeframe:

Day 1 (pre-dose and 1, 3, 5 and 24 hours post-dose), Day 15 (pre-dose and 1, 2, 3, 4, 6, 8 and 24 hours post-dose)

Notes:

[8] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The PK parameter analysis population included all participants randomized and treated who had at least 1 of the PK parameters of primary interest; n=the number of participants analyzed at that time point in the respective arms.

End point values	Bosutinib 200 mg/day	Bosutinib 400 mg/day	Bosutinib 400/200 mg/day	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	58	31	24	
Units: ng*hr/mL				
geometric mean (geometric coefficient of variation)				
Day 1 (n=58,30,24)	437 (± 48)	1040 (± 49)	1149 (± 50)	
Day 15 (n=58,16,22)	1059 (± 45)	2052 (± 36)	2384 (± 34)	

Statistical analyses

No statistical analyses for this end point

Secondary: Lowest Concentration Observed During the Dosing Interval (Cmin) of Bosutinib

End point title	Lowest Concentration Observed During the Dosing Interval (Cmin) of Bosutinib[9]

End point description:

End point type	Secondary

End point timeframe:

Day 15 (pre-dose and 1, 2, 3, 4, 6, 8 and 24 hours post-dose)

Notes:

[9] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The PK parameter analysis population included all participants randomized and treated who had at least 1 of the PK parameters of primary interest.

End point values	Bosutinib 200 mg/day	Bosutinib 400 mg/day	Bosutinib 400/200 mg/day	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	58	16	22	
Units: ng/mL				
geometric mean (geometric coefficient of variation)	25.15 (± 49)	19.6 (± 20880)	50.67 (± 50)	

Statistical analyses

No statistical analyses for this end point

Secondary: Apparent Oral Clearance (CL/F) of Bosutinib

End point title	Apparent Oral Clearance (CL/F) of Bosutinib[10]

End point description:

Clearance of a drug is a measure of the rate at which a drug is metabolized or eliminated by normal biological processes. Clearance obtained after oral dose (apparent oral clearance) is influenced by the fraction of the dose absorbed. Drug clearance is a quantitative measure of the rate at which a drug substance is removed from the blood.

End point type	Secondary

End point timeframe:

Day 15 (pre-dose and 1, 2, 3, 4, 6, 8 and 24 hours post-dose)

Notes:

[10] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The PK parameter analysis population included all participants randomized and treated who had at least 1 of the PK parameters of primary interest.

End point values	Bosutinib 200 mg/day	Bosutinib 400 mg/day	Bosutinib 400/200 mg/day	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	58	16	22	
Units: liters per hour (L/hr)				
geometric mean (geometric coefficient of variation)	188.8 (± 45)	195 (± 36)	167.8 (± 34)	

Statistical analyses

No statistical analyses for this end point

Secondary: Apparent Volume of Distribution (Vz/F) of Bosutinib

End point title	Apparent Volume of Distribution (Vz/F) of Bosutinib[11]

End point description:

Volume of distribution is defined as the theoretical volume in which the total amount of drug would need to be uniformly distributed to produce the desired plasma concentration of a drug. Apparent volume of distribution after oral dose (Vz/F) is influenced by the fraction absorbed.

End point type	Secondary

End point timeframe:

Day 1 (pre-dose and 1, 3, 5 and 24 hours post-dose), Day 15 (pre-dose and 1, 2, 3, 4, 6, 8 and 24 hours post-dose)

Notes:

[11] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The PK parameter analysis population included all participants randomized and treated who had at least 1 of the PK parameters of primary interest.

End point values	Bosutinib 200 mg/day	Bosutinib 400 mg/day	Bosutinib 400/200 mg/day	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0[12]	0[13]	0[14]	
Units: liters				
geometric mean (geometric coefficient of variation)	()	()	()	

Notes:

[12] - There was no sufficient data to well-characterize the terminal phase.

[13] - There was no sufficient data to well-characterize the terminal phase.

[14] - There was no sufficient data to well-characterize the terminal phase.

Statistical analyses

No statistical analyses for this end point

Secondary: Terminal Elimination Half-Life (t1/2) of Bosutinib

End point title	Terminal Elimination Half-Life (t1/2) of Bosutinib[15]

End point description:

t1/2 is the time measured for the plasma concentration to decrease by one half.

End point type	Secondary

End point timeframe:

Day 1 (pre-dose and 1, 3, 5 and 24 hours post-dose), Day 15 (pre-dose and 1, 2, 3, 4, 6, 8 and 24 hours post-dose)

Notes:

[15] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The PK parameter analysis population included all participants randomized and treated who had at least 1 of the PK parameters of primary interest.

End point values	Bosutinib 200 mg/day	Bosutinib 400 mg/day	Bosutinib 400/200 mg/day	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0[16]	0[17]	0[18]	
Units: hours				
arithmetic mean (standard deviation)	()	()	()	

Notes:

[16] - There was no sufficient data to well-characterize the terminal phase.

[17] - There was no sufficient data to well-characterize the terminal phase.

[18] - There was no sufficient data to well-characterize the terminal phase.

Statistical analyses

No statistical analyses for this end point

Secondary: Observed Accumulation Ratio (Rac) of Bosutinib

End point title	Observed Accumulation Ratio (Rac) of Bosutinib[19]

End point description:

Observed accumulation ratio (Rac) was calculated as AUC from time 0 to 24 hours (Day 15) divided by AUC from time 0 to 24 hours (Day 1).

End point type	Secondary

End point timeframe:

Day 15 (pre-dose and 1, 2, 3, 4, 6, 8 and 24 hours post-dose)

Notes:

[19] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The PK parameter analysis population included all participants randomized and treated who had at least 1 of the PK parameters of primary interest.

End point values	Bosutinib 200 mg/day	Bosutinib 400 mg/day	Bosutinib 400/200 mg/day	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	58	16	22	
Units: ratio				
geometric mean (geometric coefficient of variation)	2.452 (± 36)	2.28 (± 42)	2.075 (± 41)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Kidney Disease Quality of Life (KDQoL)-36 Scale Scores at Month 25

End point title	Change From Baseline in Kidney Disease Quality of Life (KDQoL)-36 Scale Scores at Month 25

End point description:

The KDQoL-36 is a 36-item questionnaire on kidney disease-specific measure of patient-reported quality of life with 5 subscales: physical and mental functioning (items 1-12); burden of kidney disease subscale (Burden, items 13-16); symptoms and problems (items 17-28); effects of kidney disease on daily life subscale (KDQoL, items 29-36). The raw scores are transformed linearly to a range of 0 to 100, with higher scores indicating better quality of life. M25=Month 25.

End point type	Secondary

End point timeframe:

Baseline and end of ITPV (Month 25)

End point values	Bosutinib 200 mg/day	Bosutinib 400 mg/day	Bosutinib 400/200 mg/day	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	42	9	24	43
Units: units on a scale				
arithmetic mean (standard deviation)				
Burden: Baseline (n=42,9,24,43)	84.23 (± 18.48)	84.72 (± 20.99)	79.43 (± 24.97)	74.86 (± 30.21)
Burden: Change at M25 (n=32,3,22,34)	-2.54 (± 15.7)	-2.08 (± 9.55)	0.57 (± 15.9)	1.84 (± 19.13)
KDQoL: Baseline (n=42,9,24,43)	93.3 (± 8.58)	92.01 (± 11.06)	91.54 (± 11.53)	90.41 (± 14.1)
KDQoL: Change at M25; n=32,3,22,34	1.07 (± 5.48)	3.13 (± 5.41)	-0.57 (± 9.72)	3.22 (± 9.5)
Mental: Baseline (n=42,9,24,43)	54.31 (± 6.39)	51.11 (± 12.87)	50.19 (± 9.28)	51.33 (± 8.58)
Mental: Change at M25 (n=32,3,22,34)	-1.5 (± 5.87)	6.55 (± 6.3)	1.34 (± 7.35)	0.12 (± 10.25)
Physical: Baseline (n=42,9,24,43)	50.52 (± 6.93)	51.78 (± 6.4)	49.64 (± 8.35)	47.17 (± 10.93)
Physical: Change at M25 (n=32,3,22,34)	-0.28 (± 5.81)	-7.59 (± 7.63)	-2.33 (± 8.16)	2.32 (± 8.34)
Symptoms/Problems: Baseline (n=42,9,24,43)	93.13 (± 6.96)	93.69 (± 7.35)	90.72 (± 9.31)	90.86 (± 9.29)
Symptoms/Problems: Change at M25 (n=32,3,22,34)	-2.42 (± 7.21)	-8.33 (± 9.19)	-3.75 (± 8.04)	0.27 (± 9.31)

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Number of Subjects With Treatment-Emergent Adverse Events (AEs) and Serious Adverse Events (SAEs)

End point title	Number of Subjects With Treatment-Emergent Adverse Events (AEs) and Serious Adverse Events (SAEs)

End point description:

An AE was any untoward medical occurrence in a subject who received study drug. An SAE was an AE resulting in any of the following outcomes or deemed significant for any other reason: death; initial or prolonged inpatient hospitalization; life-threatening experience (immediate risk of dying); persistent or significant disability/incapacity; congenital anomaly. Treatment-emergent are events between first dose

of study drug and up to 30 days after last dose that were absent before treatment or that worsened relative to pre-treatment state. AEs included both SAEs and non-SAEs.

End point type	Other pre-specified

End point timeframe:

Baseline up to 30 days after last study drug administration

End point values	Bosutinib 200 mg/day	Bosutinib 400 mg/day	Bosutinib 400/200 mg/day	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	58	31	24	56
Units: subjects				
AEs (serious and non-serious)	56	30	23	51
SAEs	12	4	6	5

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Number of Subjects With Laboratory Abnormalities Meeting the Criteria for Potential Clinical Concern

End point title	Number of Subjects With Laboratory Abnormalities Meeting the Criteria for Potential Clinical Concern

End point description:

The following laboratory parameters were analyzed: hematology (hemoglobin, hematocrit, red blood cell [RBC] count, RBC morphology, platelet count, white blood cell [WBC] count, total neutrophils, eosinophils, monocytes, basophils, lymphocytes); blood chemistry (blood urea nitrogen [BUN], creatinine, glucose, calcium, sodium, potassium, chloride, total bicarbonate, aspartate aminotransferase [AST], alanine aminotransferase [ALT], total bilirubin, alkaline phosphatase, uric acid, albumin, and total protein; urinalysis (pH, glucose, protein, blood, ketones, nitrites, leukocyte esterase, microscopy [if urine dipstick was positive for blood, protein, nitrites or leukocyte esterase]); others (coagulation panel, circulating immune complex, and complement activation).

End point type	Other pre-specified

End point timeframe:

Baseline up to 30 days after last study drug administration

End point values	Bosutinib 200 mg/day	Bosutinib 400 mg/day	Bosutinib 400/200 mg/day	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	58	31	24	56
Units: subjects	53	20	23	43

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Number of Subjects With Potentially Clinically Significant Vital Signs Findings

End point title	Number of Subjects With Potentially Clinically Significant Vital Signs Findings

End point description:

Vital signs assessment included pulse rate and blood pressure. Criteria for vital sign values meeting potential clinical concern included: supine/sitting pulse rate <40 or >120 beats per minute (bpm), standing pulse rate <40 or >140 bpm; systolic blood pressure (SBP) of >=30 millimeters of mercury (mm Hg) change from baseline in same posture or SBP <90 mm Hg, diastolic blood pressure (DBP) >=20 mmHg change from baseline in same posture or DBP <50 mm Hg. In the results table, SBP and DBP data are measured in 'mm Hg'; pulse rate is 'HR' and measured in 'bpm'.

End point type	Other pre-specified

End point timeframe:

Baseline up to 30 days after last study drug administration

End point values	Bosutinib 200 mg/day	Bosutinib 400 mg/day	Bosutinib 400/200 mg/day	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	58	31	24	56
Units: subjects				
Supine SBP <90 (n=2,2,1,4)	0	0	0	0
Sitting SBP <90 (n=58,29,24,54)	0	0	1	0
Supine DBP <50 (n=2,2,1,4)	0	0	0	0
Sitting DBP <50 (n=58,29,24,54)	0	1	1	0
Supine HR <40 or >120 (n=2,2,1,4)	0	0	0	0
Sitting HR <40 or >120 (n=58,29,24,54)	1	0	0	0
Supine SBP Decrease (n=2,2,1,4)	0	0	1	0
Sitting SBP Decrease (n=58,29,24,54)	2	1	2	2
Supine DBP Decrease (n=2,2,1,4)	0	0	1	0
Sitting DBP Decrease (n=58,29,24,54)	12	3	3	5
Supine SBP Increase (n=2,2,1,4)	0	0	0	0
Sitting SBP Increase (n=58,29,24,54)	3	1	3	3
Supine DBP Increase (n=2,2,1,4)	0	0	0	0
Sitting DBP Increase (n=58,29,24,54)	5	3	5	5

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Number of Subjects With Potentially Clinically Significant Electrocardiogram (ECG) Findings

End point title	Number of Subjects With Potentially Clinically Significant Electrocardiogram (ECG) Findings

End point description:

ECGs were centrally evaluated. ECG parameters included PR interval, QRS interval, and corrected QT

interval using Fridericia's formula (QTcF). Criteria for ECG changes meeting potential clinical concern included: PR interval greater than or equal to (≥)300 milliseconds (msec) or ≥25% increase when baseline is greater than (>)200 msec and ≥50% increase when baseline is less than or equal to (≤)200 msec; QRS interval ≥200 msec or ≥25%/50% increase from baseline; and QTcF ≥450 msec or ≥30 msec increase.

End point type	Other pre-specified

End point timeframe:

Baseline up to 30 days after last study drug administration

End point values	Bosutinib 200 mg/day	Bosutinib 400 mg/day	Bosutinib 400/200 mg/day	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	58	31	24	56
Units: subjects				
PR >=300 msec (n=58,31,24,56)	0	0	0	0
QRS >=200 msec (n=58,31,24,56)	0	0	0	0
QTcF 450-<480 msec (n=58,31,24,56)	3	2	0	6
QTcF 480-<500 msec (n=58,31,24,56)	0	0	0	0
QTcF >=500 msec (n=58,31,24,56)	0	0	0	0
PR >=25/50% Increase (n=57,28,23,52)	0	0	0	0
QRS >=25/50% Increase (n=57,28,23,52)	0	0	0	0
QTcF 30/60 msec Increase (n=57,28,23,52)	4	1	1	5
QTcF >=60 msec Increase (n=57,28,23,52)	0	0	0	0

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Baseline up to 30 days after last study drug administration

Adverse event reporting additional description:

The same event may appear as both an AE and a SAE. However, what is presented are distinct events. An event may be categorized as serious in one subject and as non-serious in another subject, or one subject may have experienced both a serious and non-serious event during the study.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.0

Reporting groups

Reporting group title	Bosutinib 200 mg/day

Reporting group description:

Subjects received bosutinib 200 mg tablet orally once daily (QD) in the morning with food for 24 months in the Initial Treatment Period (ITP). After a 30-day washout period, subjects who entered the Extended Treatment Period (ETP) continued to receive bosutinib 200 mg orally QD for up to 46 months.

Reporting group title	Bosutinib 400/200 mg/day

Reporting group description:

Subjects received bosutinib 400 mg and were dose-reduced to 200 mg tablet (based on protocol amendment) orally QD in the morning with food for 24 months in the ITP. After a 30-day washout period, subjects who entered the ETP continued to receive bosutinib 200 mg orally QD for up to 46 months.

Reporting group title	Placebo

Reporting group description:

Subjects received placebo tablet orally QD in the morning with food for 24 months in the ITP. After a 30-day washout period, subjects who entered the ETP continued to receive placebo matched bosutinib QD for up to 46 months.

Reporting group title	Bosutinib 400 mg/day

Reporting group description:

Subjects received bosutinib 400 mg tablet orally QD in the morning with food for 24 months in the ITP. All subjects were dose-reduced during the ITP based on a protocol amendment. Those who remained active in the study at the time of the amendment are represented in the bosutinib 400/200 mg/day group.

Serious adverse events	Bosutinib 200 mg/day	Bosutinib 400/200 mg/day	Placebo
Total subjects affected by serious adverse events			
subjects affected / exposed	12 / 58 (20.69%)	6 / 24 (25.00%)	5 / 56 (8.93%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	2 / 58 (3.45%)	0 / 24 (0.00%)	0 / 56 (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

Amylase increased			
subjects affected / exposed	0 / 58 (0.00%)	0 / 24 (0.00%)	0 / 56 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 58 (1.72%)	0 / 24 (0.00%)	0 / 56 (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
Lipase increased			
subjects affected / exposed	0 / 58 (0.00%)	0 / 24 (0.00%)	0 / 56 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Ventricular extrasystoles			
subjects affected / exposed	1 / 58 (1.72%)	0 / 24 (0.00%)	0 / 56 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Intracranial aneurysm			
subjects affected / exposed	0 / 58 (0.00%)	1 / 24 (4.17%)	0 / 56 (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
Syncope			
subjects affected / exposed	1 / 58 (1.72%)	0 / 24 (0.00%)	0 / 56 (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
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 58 (0.00%)	1 / 24 (4.17%)	0 / 56 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain			

subjects affected / exposed	1 / 58 (1.72%)	0 / 24 (0.00%)	0 / 56 (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
Peptic ulcer			
subjects affected / exposed	1 / 58 (1.72%)	0 / 24 (0.00%)	0 / 56 (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
Subileus			
subjects affected / exposed	1 / 58 (1.72%)	0 / 24 (0.00%)	0 / 56 (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
Reproductive system and breast disorders			
Cervix disorder			
subjects affected / exposed	0 / 58 (0.00%)	1 / 24 (4.17%)	0 / 56 (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
Hepatobiliary disorders			
Hepatitis acute			
subjects affected / exposed	0 / 58 (0.00%)	0 / 24 (0.00%)	0 / 56 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Insomnia			
subjects affected / exposed	1 / 58 (1.72%)	0 / 24 (0.00%)	0 / 56 (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
Psychosomatic disease			
subjects affected / exposed	1 / 58 (1.72%)	0 / 24 (0.00%)	0 / 56 (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
Renal and urinary disorders			
Calculus ureteric			

subjects affected / exposed	0 / 58 (0.00%)	1 / 24 (4.17%)	0 / 56 (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
Haematuria			
subjects affected / exposed	0 / 58 (0.00%)	0 / 24 (0.00%)	1 / 56 (1.79%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal cyst haemorrhage			
subjects affected / exposed	1 / 58 (1.72%)	1 / 24 (4.17%)	0 / 56 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal cyst ruptured			
subjects affected / exposed	0 / 58 (0.00%)	0 / 24 (0.00%)	1 / 56 (1.79%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal failure acute			
subjects affected / exposed	0 / 58 (0.00%)	0 / 24 (0.00%)	0 / 56 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal haemorrhage			
subjects affected / exposed	1 / 58 (1.72%)	0 / 24 (0.00%)	0 / 56 (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
Musculoskeletal and connective tissue disorders			
Osteonecrosis			
subjects affected / exposed	0 / 58 (0.00%)	0 / 24 (0.00%)	1 / 56 (1.79%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sacroiliitis			
subjects affected / exposed	1 / 58 (1.72%)	0 / 24 (0.00%)	0 / 56 (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
Spondylitis			

subjects affected / exposed	1 / 58 (1.72%)	0 / 24 (0.00%)	0 / 56 (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			
Appendicitis			
subjects affected / exposed	1 / 58 (1.72%)	0 / 24 (0.00%)	0 / 56 (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
Gastroenteritis			
subjects affected / exposed	0 / 58 (0.00%)	0 / 24 (0.00%)	0 / 56 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatitis C			
subjects affected / exposed	1 / 58 (1.72%)	0 / 24 (0.00%)	1 / 56 (1.79%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	0 / 58 (0.00%)	0 / 24 (0.00%)	0 / 56 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyelonephritis acute			
subjects affected / exposed	0 / 58 (0.00%)	1 / 24 (4.17%)	0 / 56 (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
Renal cyst infection			
subjects affected / exposed	0 / 58 (0.00%)	0 / 24 (0.00%)	1 / 56 (1.79%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	2 / 58 (3.45%)	1 / 24 (4.17%)	0 / 56 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			

subjects affected / exposed	1 / 58 (1.72%)	0 / 24 (0.00%)	0 / 56 (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

Serious adverse events	Bosutinib 400 mg/day		
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 31 (12.90%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 31 (3.23%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Amylase increased			
subjects affected / exposed	1 / 31 (3.23%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 31 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Lipase increased			
subjects affected / exposed	1 / 31 (3.23%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Ventricular extrasystoles			
subjects affected / exposed	0 / 31 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Intracranial aneurysm			

subjects affected / exposed	0 / 31 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Syncope			
subjects affected / exposed	0 / 31 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 31 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 31 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Peptic ulcer			
subjects affected / exposed	0 / 31 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Subileus			
subjects affected / exposed	0 / 31 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Reproductive system and breast disorders			
Cervix disorder			
subjects affected / exposed	0 / 31 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Hepatitis acute			

subjects affected / exposed	1 / 31 (3.23%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Insomnia			
subjects affected / exposed	0 / 31 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Psychosomatic disease			
subjects affected / exposed	0 / 31 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Calculus ureteric			
subjects affected / exposed	0 / 31 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Haematuria			
subjects affected / exposed	0 / 31 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Renal cyst haemorrhage			
subjects affected / exposed	1 / 31 (3.23%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal cyst ruptured			
subjects affected / exposed	1 / 31 (3.23%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal failure acute			
subjects affected / exposed	1 / 31 (3.23%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Renal haemorrhage			

subjects affected / exposed	0 / 31 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Osteonecrosis			
subjects affected / exposed	0 / 31 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Sacroiliitis			
subjects affected / exposed	0 / 31 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Spondylitis			
subjects affected / exposed	0 / 31 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Appendicitis			
subjects affected / exposed	0 / 31 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastroenteritis			
subjects affected / exposed	1 / 31 (3.23%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatitis C			
subjects affected / exposed	0 / 31 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	1 / 31 (3.23%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Pyelonephritis acute				
subjects affected / exposed	0 / 31 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Renal cyst infection				
subjects affected / exposed	0 / 31 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Sepsis				
subjects affected / exposed	0 / 31 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Urinary tract infection				
subjects affected / exposed	0 / 31 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			

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

Non-serious adverse events	Bosutinib 200 mg/day	Bosutinib 400/200 mg/day	Placebo
Total subjects affected by non-serious adverse events			
subjects affected / exposed	56 / 58 (96.55%)	23 / 24 (95.83%)	51 / 56 (91.07%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Uterine leiomyoma			
subjects affected / exposed	0 / 58 (0.00%)	1 / 24 (4.17%)	0 / 56 (0.00%)
occurrences (all)	0	1	0
Vascular disorders			
Hypertension			
subjects affected / exposed	8 / 58 (13.79%)	5 / 24 (20.83%)	9 / 56 (16.07%)
occurrences (all)	14	9	17
Hypotension			
subjects affected / exposed	1 / 58 (1.72%)	3 / 24 (12.50%)	0 / 56 (0.00%)
occurrences (all)	1	3	0
General disorders and administration site conditions			

Asthenia			
subjects affected / exposed	1 / 58 (1.72%)	3 / 24 (12.50%)	1 / 56 (1.79%)
occurrences (all)	1	3	1
Chest pain			
subjects affected / exposed	1 / 58 (1.72%)	0 / 24 (0.00%)	0 / 56 (0.00%)
occurrences (all)	1	0	0
Fatigue			
subjects affected / exposed	4 / 58 (6.90%)	2 / 24 (8.33%)	6 / 56 (10.71%)
occurrences (all)	4	2	8
Influenza-like illness			
subjects affected / exposed	2 / 58 (3.45%)	3 / 24 (12.50%)	6 / 56 (10.71%)
occurrences (all)	3	4	10
Oedema peripheral			
subjects affected / exposed	2 / 58 (3.45%)	1 / 24 (4.17%)	3 / 56 (5.36%)
occurrences (all)	2	1	4
Pain			
subjects affected / exposed	1 / 58 (1.72%)	0 / 24 (0.00%)	3 / 56 (5.36%)
occurrences (all)	1	0	3
Pyrexia			
subjects affected / exposed	2 / 58 (3.45%)	2 / 24 (8.33%)	1 / 56 (1.79%)
occurrences (all)	2	2	1
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	2 / 58 (3.45%)	0 / 24 (0.00%)	3 / 56 (5.36%)
occurrences (all)	2	0	3
Reproductive system and breast disorders			
Amenorrhoea			
subjects affected / exposed	0 / 58 (0.00%)	1 / 24 (4.17%)	0 / 56 (0.00%)
occurrences (all)	0	1	0
Cervical dysplasia			
subjects affected / exposed	0 / 58 (0.00%)	1 / 24 (4.17%)	0 / 56 (0.00%)
occurrences (all)	0	1	0
Menorrhagia			
subjects affected / exposed	1 / 58 (1.72%)	1 / 24 (4.17%)	1 / 56 (1.79%)
occurrences (all)	1	1	1
Metrorrhagia			

subjects affected / exposed	1 / 58 (1.72%)	1 / 24 (4.17%)	0 / 56 (0.00%)
occurrences (all)	1	2	0
Ovarian cyst			
subjects affected / exposed	0 / 58 (0.00%)	0 / 24 (0.00%)	1 / 56 (1.79%)
occurrences (all)	0	0	1
Vaginal inflammation			
subjects affected / exposed	0 / 58 (0.00%)	1 / 24 (4.17%)	1 / 56 (1.79%)
occurrences (all)	0	1	1
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	2 / 58 (3.45%)	3 / 24 (12.50%)	4 / 56 (7.14%)
occurrences (all)	4	3	5
Oropharyngeal pain			
subjects affected / exposed	5 / 58 (8.62%)	1 / 24 (4.17%)	2 / 56 (3.57%)
occurrences (all)	5	1	4
Psychiatric disorders			
Insomnia			
subjects affected / exposed	3 / 58 (5.17%)	0 / 24 (0.00%)	1 / 56 (1.79%)
occurrences (all)	4	0	1
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	18 / 58 (31.03%)	12 / 24 (50.00%)	4 / 56 (7.14%)
occurrences (all)	42	21	4
Amylase increased			
subjects affected / exposed	2 / 58 (3.45%)	3 / 24 (12.50%)	1 / 56 (1.79%)
occurrences (all)	5	5	1
Aspartate aminotransferase increased			
subjects affected / exposed	17 / 58 (29.31%)	6 / 24 (25.00%)	3 / 56 (5.36%)
occurrences (all)	26	8	3
Blood creatine phosphokinase increased			
subjects affected / exposed	11 / 58 (18.97%)	6 / 24 (25.00%)	5 / 56 (8.93%)
occurrences (all)	19	14	9
Blood creatinine increased			
subjects affected / exposed	2 / 58 (3.45%)	2 / 24 (8.33%)	2 / 56 (3.57%)
occurrences (all)	2	4	2

Blood lactate dehydrogenase increased			
subjects affected / exposed	0 / 58 (0.00%)	0 / 24 (0.00%)	0 / 56 (0.00%)
occurrences (all)	0	0	0
Blood phosphorus decreased			
subjects affected / exposed	0 / 58 (0.00%)	0 / 24 (0.00%)	0 / 56 (0.00%)
occurrences (all)	0	0	0
Gamma-glutamyltransferase increased			
subjects affected / exposed	4 / 58 (6.90%)	0 / 24 (0.00%)	0 / 56 (0.00%)
occurrences (all)	7	0	0
Haemoglobin decreased			
subjects affected / exposed	0 / 58 (0.00%)	2 / 24 (8.33%)	0 / 56 (0.00%)
occurrences (all)	0	2	0
Lipase increased			
subjects affected / exposed	5 / 58 (8.62%)	6 / 24 (25.00%)	3 / 56 (5.36%)
occurrences (all)	12	6	6
Weight increased			
subjects affected / exposed	0 / 58 (0.00%)	3 / 24 (12.50%)	0 / 56 (0.00%)
occurrences (all)	0	3	0
Injury, poisoning and procedural complications			
Excoriation			
subjects affected / exposed	3 / 58 (5.17%)	1 / 24 (4.17%)	0 / 56 (0.00%)
occurrences (all)	3	1	0
Cardiac disorders			
Pericardial effusion			
subjects affected / exposed	2 / 58 (3.45%)	2 / 24 (8.33%)	0 / 56 (0.00%)
occurrences (all)	2	2	0
Nervous system disorders			
Dizziness			
subjects affected / exposed	7 / 58 (12.07%)	4 / 24 (16.67%)	3 / 56 (5.36%)
occurrences (all)	7	5	3
Dysgeusia			
subjects affected / exposed	0 / 58 (0.00%)	0 / 24 (0.00%)	0 / 56 (0.00%)
occurrences (all)	0	0	0
Headache			

subjects affected / exposed	9 / 58 (15.52%)	2 / 24 (8.33%)	12 / 56 (21.43%)
occurrences (all)	12	6	48
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	7 / 58 (12.07%)	5 / 24 (20.83%)	2 / 56 (3.57%)
occurrences (all)	11	11	2
Eosinophilia			
subjects affected / exposed	3 / 58 (5.17%)	1 / 24 (4.17%)	0 / 56 (0.00%)
occurrences (all)	3	1	0
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	3 / 58 (5.17%)	2 / 24 (8.33%)	3 / 56 (5.36%)
occurrences (all)	3	2	3
Abdominal pain			
subjects affected / exposed	4 / 58 (6.90%)	2 / 24 (8.33%)	7 / 56 (12.50%)
occurrences (all)	8	2	15
Abdominal pain upper			
subjects affected / exposed	5 / 58 (8.62%)	8 / 24 (33.33%)	5 / 56 (8.93%)
occurrences (all)	6	11	11
Constipation			
subjects affected / exposed	2 / 58 (3.45%)	1 / 24 (4.17%)	1 / 56 (1.79%)
occurrences (all)	2	1	1
Diarrhoea			
subjects affected / exposed	26 / 58 (44.83%)	18 / 24 (75.00%)	11 / 56 (19.64%)
occurrences (all)	42	44	18
Dyspepsia			
subjects affected / exposed	6 / 58 (10.34%)	3 / 24 (12.50%)	3 / 56 (5.36%)
occurrences (all)	7	4	4
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 58 (0.00%)	0 / 24 (0.00%)	3 / 56 (5.36%)
occurrences (all)	0	0	4
Nausea			
subjects affected / exposed	21 / 58 (36.21%)	13 / 24 (54.17%)	9 / 56 (16.07%)
occurrences (all)	30	22	15
Vomiting			

subjects affected / exposed	6 / 58 (10.34%)	9 / 24 (37.50%)	4 / 56 (7.14%)
occurrences (all)	6	17	4
Hepatobiliary disorders			
Hepatocellular injury			
subjects affected / exposed	3 / 58 (5.17%)	0 / 24 (0.00%)	0 / 56 (0.00%)
occurrences (all)	6	0	0
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	4 / 58 (6.90%)	0 / 24 (0.00%)	1 / 56 (1.79%)
occurrences (all)	4	0	1
Alopecia			
subjects affected / exposed	2 / 58 (3.45%)	3 / 24 (12.50%)	3 / 56 (5.36%)
occurrences (all)	2	4	4
Dermatitis allergic			
subjects affected / exposed	2 / 58 (3.45%)	2 / 24 (8.33%)	0 / 56 (0.00%)
occurrences (all)	2	2	0
Pruritis			
subjects affected / exposed	1 / 58 (1.72%)	1 / 24 (4.17%)	1 / 56 (1.79%)
occurrences (all)	1	1	1
Rash maculo-papular			
subjects affected / exposed	0 / 58 (0.00%)	0 / 24 (0.00%)	0 / 56 (0.00%)
occurrences (all)	0	0	0
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	4 / 58 (6.90%)	1 / 24 (4.17%)	4 / 56 (7.14%)
occurrences (all)	4	1	5
Proteinuria			
subjects affected / exposed	1 / 58 (1.72%)	2 / 24 (8.33%)	3 / 56 (5.36%)
occurrences (all)	2	2	3
Renal failure acute			
subjects affected / exposed	2 / 58 (3.45%)	2 / 24 (8.33%)	0 / 56 (0.00%)
occurrences (all)	3	5	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	5 / 58 (8.62%)	1 / 24 (4.17%)	5 / 56 (8.93%)
occurrences (all)	8	2	6

Back pain			
subjects affected / exposed	9 / 58 (15.52%)	1 / 24 (4.17%)	8 / 56 (14.29%)
occurrences (all)	13	1	9
Flank pain			
subjects affected / exposed	10 / 58 (17.24%)	0 / 24 (0.00%)	5 / 56 (8.93%)
occurrences (all)	21	0	7
Muscle spasms			
subjects affected / exposed	3 / 58 (5.17%)	0 / 24 (0.00%)	3 / 56 (5.36%)
occurrences (all)	4	0	3
Musculoskeletal pain			
subjects affected / exposed	3 / 58 (5.17%)	2 / 24 (8.33%)	2 / 56 (3.57%)
occurrences (all)	4	2	2
Myalgia			
subjects affected / exposed	0 / 58 (0.00%)	0 / 24 (0.00%)	3 / 56 (5.36%)
occurrences (all)	0	0	3
Pain in extremity			
subjects affected / exposed	1 / 58 (1.72%)	0 / 24 (0.00%)	3 / 56 (5.36%)
occurrences (all)	1	0	3
Infections and infestations			
Bronchitis			
subjects affected / exposed	3 / 58 (5.17%)	2 / 24 (8.33%)	3 / 56 (5.36%)
occurrences (all)	3	2	3
Cystitis			
subjects affected / exposed	0 / 58 (0.00%)	3 / 24 (12.50%)	1 / 56 (1.79%)
occurrences (all)	0	3	1
Gastroenteritis viral			
subjects affected / exposed	0 / 58 (0.00%)	1 / 24 (4.17%)	3 / 56 (5.36%)
occurrences (all)	0	2	6
Nasopharyngitis			
subjects affected / exposed	12 / 58 (20.69%)	8 / 24 (33.33%)	8 / 56 (14.29%)
occurrences (all)	29	13	14
Influenza			
subjects affected / exposed	2 / 58 (3.45%)	1 / 24 (4.17%)	3 / 56 (5.36%)
occurrences (all)	2	2	3
Pharyngitis			

subjects affected / exposed	0 / 58 (0.00%)	3 / 24 (12.50%)	4 / 56 (7.14%)
occurrences (all)	0	3	9
Rhinitis			
subjects affected / exposed	2 / 58 (3.45%)	2 / 24 (8.33%)	2 / 56 (3.57%)
occurrences (all)	2	3	3
Sinusitis			
subjects affected / exposed	1 / 58 (1.72%)	0 / 24 (0.00%)	3 / 56 (5.36%)
occurrences (all)	1	0	3
Upper respiratory tract infection			
subjects affected / exposed	6 / 58 (10.34%)	7 / 24 (29.17%)	7 / 56 (12.50%)
occurrences (all)	10	9	11
Urinary tract infection			
subjects affected / exposed	8 / 58 (13.79%)	2 / 24 (8.33%)	8 / 56 (14.29%)
occurrences (all)	14	7	12
Vaginal infection			
subjects affected / exposed	1 / 58 (1.72%)	0 / 24 (0.00%)	3 / 56 (5.36%)
occurrences (all)	1	0	3
Viral infection			
subjects affected / exposed	2 / 58 (3.45%)	1 / 24 (4.17%)	3 / 56 (5.36%)
occurrences (all)	2	2	3
Vulvovaginal mycotic infection			
subjects affected / exposed	1 / 58 (1.72%)	1 / 24 (4.17%)	1 / 56 (1.79%)
occurrences (all)	1	2	1
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	2 / 58 (3.45%)	4 / 24 (16.67%)	0 / 56 (0.00%)
occurrences (all)	3	4	0
Hypophosphataemia			
subjects affected / exposed	2 / 58 (3.45%)	2 / 24 (8.33%)	1 / 56 (1.79%)
occurrences (all)	2	5	1

Non-serious adverse events	Bosutinib 400 mg/day		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	30 / 31 (96.77%)		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			

Uterine leiomyoma subjects affected / exposed occurrences (all)	0 / 31 (0.00%) 0		
Vascular disorders Hypertension subjects affected / exposed occurrences (all) Hypotension subjects affected / exposed occurrences (all)	 3 / 31 (9.68%) 3 0 / 31 (0.00%) 0		
General disorders and administration site conditions Asthenia subjects affected / exposed occurrences (all) Chest pain subjects affected / exposed occurrences (all) Fatigue subjects affected / exposed occurrences (all) Influenza-like illness subjects affected / exposed occurrences (all) Oedema peripheral subjects affected / exposed occurrences (all) Pain subjects affected / exposed occurrences (all) Pyrexia subjects affected / exposed occurrences (all)	 1 / 31 (3.23%) 1 2 / 31 (6.45%) 2 8 / 31 (25.81%) 9 1 / 31 (3.23%) 1 1 / 31 (3.23%) 1 0 / 31 (0.00%) 0 3 / 31 (9.68%) 3		
Immune system disorders Hypersensitivity subjects affected / exposed occurrences (all)	 1 / 31 (3.23%) 1		

Reproductive system and breast disorders			
Amenorrhoea			
subjects affected / exposed	0 / 31 (0.00%)		
occurrences (all)	0		
Cervical dysplasia			
subjects affected / exposed	0 / 31 (0.00%)		
occurrences (all)	0		
Menorrhagia			
subjects affected / exposed	0 / 31 (0.00%)		
occurrences (all)	0		
Metrorrhagia			
subjects affected / exposed	0 / 31 (0.00%)		
occurrences (all)	0		
Ovarian cyst			
subjects affected / exposed	1 / 31 (3.23%)		
occurrences (all)	1		
Vaginal inflammation			
subjects affected / exposed	0 / 31 (0.00%)		
occurrences (all)	0		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	3 / 31 (9.68%)		
occurrences (all)	3		
Oropharyngeal pain			
subjects affected / exposed	2 / 31 (6.45%)		
occurrences (all)	2		
Psychiatric disorders			
Insomnia			
subjects affected / exposed	1 / 31 (3.23%)		
occurrences (all)	1		
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	16 / 31 (51.61%)		
occurrences (all)	35		
Amylase increased			

subjects affected / exposed	4 / 31 (12.90%)		
occurrences (all)	7		
Aspartate aminotransferase increased			
subjects affected / exposed	11 / 31 (35.48%)		
occurrences (all)	19		
Blood creatine phosphokinase increased			
subjects affected / exposed	3 / 31 (9.68%)		
occurrences (all)	5		
Blood creatinine increased			
subjects affected / exposed	1 / 31 (3.23%)		
occurrences (all)	1		
Blood lactate dehydrogenase increased			
subjects affected / exposed	2 / 31 (6.45%)		
occurrences (all)	4		
Blood phosphorus decreased			
subjects affected / exposed	2 / 31 (6.45%)		
occurrences (all)	2		
Gamma-glutamyltransferase increased			
subjects affected / exposed	0 / 31 (0.00%)		
occurrences (all)	0		
Haemoglobin decreased			
subjects affected / exposed	0 / 31 (0.00%)		
occurrences (all)	0		
Lipase increased			
subjects affected / exposed	6 / 31 (19.35%)		
occurrences (all)	15		
Weight increased			
subjects affected / exposed	2 / 31 (6.45%)		
occurrences (all)	3		
Injury, poisoning and procedural complications			
Excoriation			
subjects affected / exposed	0 / 31 (0.00%)		
occurrences (all)	0		
Cardiac disorders			

Pericardial effusion subjects affected / exposed occurrences (all)	1 / 31 (3.23%) 1		
Nervous system disorders Dizziness subjects affected / exposed occurrences (all) Dysgeusia subjects affected / exposed occurrences (all) Headache subjects affected / exposed occurrences (all)	 2 / 31 (6.45%) 2 2 / 31 (6.45%) 2 3 / 31 (9.68%) 4		
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all) Eosinophilia subjects affected / exposed occurrences (all)	 4 / 31 (12.90%) 5 0 / 31 (0.00%) 0		
Gastrointestinal disorders Abdominal distension subjects affected / exposed occurrences (all) Abdominal pain subjects affected / exposed occurrences (all) Abdominal pain upper subjects affected / exposed occurrences (all) Constipation subjects affected / exposed occurrences (all) Diarrhoea subjects affected / exposed occurrences (all) Dyspepsia	 2 / 31 (6.45%) 3 8 / 31 (25.81%) 15 7 / 31 (22.58%) 11 2 / 31 (6.45%) 2 26 / 31 (83.87%) 59		

subjects affected / exposed	2 / 31 (6.45%)		
occurrences (all)	21		
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 31 (0.00%)		
occurrences (all)	0		
Nausea			
subjects affected / exposed	15 / 31 (48.39%)		
occurrences (all)	26		
Vomiting			
subjects affected / exposed	11 / 31 (35.48%)		
occurrences (all)	15		
Hepatobiliary disorders			
Hepatocellular injury			
subjects affected / exposed	0 / 31 (0.00%)		
occurrences (all)	0		
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	0 / 31 (0.00%)		
occurrences (all)	0		
Alopecia			
subjects affected / exposed	1 / 31 (3.23%)		
occurrences (all)	1		
Dermatitis allergic			
subjects affected / exposed	0 / 31 (0.00%)		
occurrences (all)	0		
Pruritis			
subjects affected / exposed	2 / 31 (6.45%)		
occurrences (all)	2		
Rash maculo-papular			
subjects affected / exposed	2 / 31 (6.45%)		
occurrences (all)	2		
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	3 / 31 (9.68%)		
occurrences (all)	4		
Proteinuria			

subjects affected / exposed	0 / 31 (0.00%)		
occurrences (all)	0		
Renal failure acute			
subjects affected / exposed	1 / 31 (3.23%)		
occurrences (all)	2		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 31 (0.00%)		
occurrences (all)	0		
Back pain			
subjects affected / exposed	2 / 31 (6.45%)		
occurrences (all)	3		
Flank pain			
subjects affected / exposed	5 / 31 (16.13%)		
occurrences (all)	6		
Muscle spasms			
subjects affected / exposed	1 / 31 (3.23%)		
occurrences (all)	4		
Musculoskeletal pain			
subjects affected / exposed	1 / 31 (3.23%)		
occurrences (all)	1		
Myalgia			
subjects affected / exposed	0 / 31 (0.00%)		
occurrences (all)	0		
Pain in extremity			
subjects affected / exposed	0 / 31 (0.00%)		
occurrences (all)	0		
Infections and infestations			
Bronchitis			
subjects affected / exposed	2 / 31 (6.45%)		
occurrences (all)	2		
Cystitis			
subjects affected / exposed	0 / 31 (0.00%)		
occurrences (all)	0		
Gastroenteritis viral			

subjects affected / exposed	0 / 31 (0.00%)		
occurrences (all)	0		
Nasopharyngitis			
subjects affected / exposed	3 / 31 (9.68%)		
occurrences (all)	3		
Influenza			
subjects affected / exposed	0 / 31 (0.00%)		
occurrences (all)	0		
Pharyngitis			
subjects affected / exposed	0 / 31 (0.00%)		
occurrences (all)	0		
Rhinitis			
subjects affected / exposed	0 / 31 (0.00%)		
occurrences (all)	0		
Sinusitis			
subjects affected / exposed	0 / 31 (0.00%)		
occurrences (all)	0		
Upper respiratory tract infection			
subjects affected / exposed	4 / 31 (12.90%)		
occurrences (all)	5		
Urinary tract infection			
subjects affected / exposed	2 / 31 (6.45%)		
occurrences (all)	2		
Vaginal infection			
subjects affected / exposed	0 / 31 (0.00%)		
occurrences (all)	0		
Viral infection			
subjects affected / exposed	0 / 31 (0.00%)		
occurrences (all)	0		
Vulvovaginal mycotic infection			
subjects affected / exposed	0 / 31 (0.00%)		
occurrences (all)	0		
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	4 / 31 (12.90%)		
occurrences (all)	5		

Hypophosphataemia subjects affected / exposed occurrences (all)	0 / 31 (0.00%) 0		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
21 February 2012	Reduced sample size from 275 subjects to 190 subjects. Changed secondary objectives to investigation of eGFR over the study and removed demonstration that a reduction in rate of kidney enlargement is predictive of a reduction in decline in eGFR.
07 October 2013	Reduced dose for Cohort B from 400 mg/day to 200 mg/day and removed the matching placebo for subjects in the 200 mg/day cohort.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported