Clinical trial results:
A PHASE 2, RANDOMIZED, PARALLEL GROUP, DOSE-FINDING, MULTICENTER, MULTINATIONAL STUDY OF THE SAFETY, TOLERABILITY AND PILOT EFFICACY OF THREE BLINDED DOSES OF THE ORAL FACTOR Xa INHIBITOR BETRIXABAN COMPARED WITH OPEN- LABEL, DOSE-ADJUSTED WARFARIN IN PATIENTS WITH NON-VALVULAR ATRIAL FIBRILLATION

Summary

EudraCT number	2008-005977-37
Trial protocol	DE
Global end of trial date	05 November 2009

Results information

Result version number	v1 (current)
This version publication date	28 December 2017
First version publication date	28 December 2017

Trial information

Trial identification

Sponsor protocol code	08-015

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00742859
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Portola Pharmaceuticals, Inc.
Sponsor organisation address	270 East Grand Avenue, South San Francisco, United States, 94080
Public contact	Janice Castillo, Portola Pharmaceuticals, Inc., 001 650-246-7360,
Scientific contact	Janice Castillo, Portola Pharmaceuticals, Inc., 001 650-246-7360,

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	18 July 2012
Is this the analysis of the primary completion data?	Yes
Primary completion date	31 August 2009
Global end of trial reached?	Yes
Global end of trial date	05 November 2009
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of the trial is to assess the safety and tolerability of betrixaban at doses of 40 mg, 60 mg and 80 mg given orally once a day for at least 3 months compared to a dose-adjusted Vitamin K antagonist in patients with non-valvular AF.

Protection of trial subjects:

The conduct of this clinical study met local legal and regulatory requirements. The study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and the International Conference on Harmonization guideline E6: Good Clinical Practice. Before entering the study, the informed consent explained to all subjects and/or their legally authorized representative. Participating subjects and/or their legally authorized representative signed informed consent form and could withdraw from the study at any time. Only investigators qualified by training and experience were selected as appropriate experts to investigate the study drug.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	31 October 2008
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	Germany: 12
Country: Number of subjects enrolled	United States: 369
Country: Number of subjects enrolled	Canada: 127
Worldwide total number of subjects	508
EEA total number of subjects	12

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)	81
From 65 to 84 years	397
85 years and over	30

Subject disposition

Recruitment

Recruitment details:

Between 31 October 2008 and 05 November 2009, 508 patients were enrolled by 35 study centers in 3 countries (USA, Canada, Germany). Patients were randomized to 1 of 4 treatment groups (1:1:1:1 allocation). The study was open-label for warfarin, while the 3 daily doses of betrixaban (40, 60, or 80 mg) were double-blinded.

Pre-assignment

Screening details:

561 patients were screened for study participation. Of these patients, 508 were randomized, all of whom received at least 1 dose of study drug.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Investigator, Subject, Monitor, Data analyst, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Betrixaban 40 mg

Arm description:

Betrixaban 40 mg once daily for at least 3 months and no longer than approximately 11 months

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

Dosage and administration details:

Betrixaban 40 mg once daily for at least 3 months and no longer than approximately 11 months

Arm title	Betrixaban 60 mg

Arm description:

Betrixaban 60 mg once daily for at least 3 months and no longer than approximately 11 months

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

Dosage and administration details:

Betrixaban 60 mg once daily for at least 3 months and no longer than approximately 11 months

Arm title	Betrixaban 80 mg

Arm description:

Betrixaban 80 mg once daily for at least 3 months and no longer than approximately 11 months

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

Dosage and administration details:

Betrixaban 80 mg once daily for at least 3 months and no longer than approximately 11 months

Arm title	Warfarin

Arm description:

Dose-adjusted warfarin to maintain an INR of 2.0 to 3.0 with INR measured at maximum intervals of 4 weeks. Treatment duration was at least 3 months and no longer than approximately 11 months

Arm type	Active comparator
Investigational medicinal product name	Warfarin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Dose-adjusted warfarin to maintain an INR of 2.0 to 3.0 with INR measured at maximum intervals of 4 weeks. Treatment duration was at least 3 months and no longer than approximately 11 months

Number of subjects in period 1	Betrixaban 40 mg	Betrixaban 60 mg	Betrixaban 80 mg
Started	127	127	127
Completed	116	115	116
Not completed	11	12	11
Adverse event, serious fatal	1	-	-
Physician decision	1	2	-
Consent withdrawn by subject	4	2	4
Amendment 2 Pt off Study Drug for >4 weeks	-	1	1
Adverse event, non-fatal	5	6	3
Sponsor request visit schedule noncompliance	-	-	-
Sponsor request PT out of town	-	-	1
Site Error	-	-	1
Endpoint	-	1	1

Number of subjects in period 1	Warfarin
Started	127
Completed	119
Not completed	8
Adverse event, serious fatal	1

Physician decision	-
Consent withdrawn by subject	1
Amendment 2 Pt off Study Drug for >4 weeks	-
Adverse event, non-fatal	1
Sponsor request visit schedule noncompliance	1
Sponsor request PT out of town	1
Site Error	1
Endpoint	2

Baseline characteristics

Reporting groups	
Reporting group title	Betrixaban 40 mg
Reporting group description:	
Betrixaban 40 mg once daily for at least 3 months and no longer than approximately 11 months	

Reporting group title	Betrixaban 60 mg
Reporting group description:	
Betrixaban 60 mg once daily for at least 3 months and no longer than approximately 11 months	

Reporting group title	Betrixaban 80 mg
Reporting group description:	
Betrixaban 80 mg once daily for at least 3 months and no longer than approximately 11 months	

Reporting group title	Warfarin
Reporting group description:	
Dose-adjusted warfarin to maintain an INR of 2.0 to 3.0 with INR measured at maximum intervals of 4 weeks. Treatment duration was at least 3 months and no longer than approximately 11 months	

Reporting group values	Betrixaban 40 mg	Betrixaban 60 mg	Betrixaban 80 mg
Number of subjects	127	127	127
Age categorical			
All randomized patients who took at least 1 dose of study medication after randomization.			
Units: Subjects			
<=64 years	21	19	22
65<=age<85 years	97	96	100
age >=85 years	9	12	5
Age continuous			
Units: years			
arithmetic mean	73.3	73.8	72.0
standard deviation	± 8.5	± 8.35	± 7.65
Gender categorical			
All randomized patients who took at least 1 dose of study medication after randomization.			
Units: Subjects			
Female	79	81	89
Male	48	46	38

Reporting group values	Warfarin	Total	
Number of subjects	127	508	
Age categorical			
All randomized patients who took at least 1 dose of study medication after randomization.			
Units: Subjects			
<=64 years	19	81	
65<=age<85 years	104	397	

age >=85 years	4	30	

Age continuous			
Units: years			
arithmetic mean	72.7		
standard deviation	± 8.75	-	
Gender categorical			
All randomized patients who took at least 1 dose of study medication after randomization.			
Units: Subjects			
Female	89	338	
Male	38	170	

End points

End points reporting groups

Reporting group title	Betrixaban 40 mg

Reporting group description:

Betrixaban 40 mg once daily for at least 3 months and no longer than approximately 11 months

Reporting group title	Betrixaban 60 mg

Reporting group description:

Betrixaban 60 mg once daily for at least 3 months and no longer than approximately 11 months

Reporting group title	Betrixaban 80 mg

Reporting group description:

Betrixaban 80 mg once daily for at least 3 months and no longer than approximately 11 months

Reporting group title	Warfarin

Reporting group description:

Dose-adjusted warfarin to maintain an INR of 2.0 to 3.0 with INR measured at maximum intervals of 4 weeks. Treatment duration was at least 3 months and no longer than approximately 11 months

Primary: Exposure-adjusted incidence rate of major or clinically relevant non-major bleeding episode

End point title	Exposure-adjusted incidence rate of major or clinically relevant non-major bleeding episode

End point description:

The primary endpoint is the time to the first occurrence of major or clinically relevant non-major bleeding. This was presented as the exposure adjusted incidence rate which was calculated as number of subjects experiencing the event divided by total person years across all subjects, where if a patient experiencing the event, year was from first dose date to the first occurrence of the event, and to last study date if not. The confidence interval was calculated via the exact Poisson distribution.

End point type	Primary

End point timeframe:

A maximum of 1 year

End point values	Betrixaban 40 mg	Betrixaban 60 mg	Betrixaban 80 mg	Warfarin
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	127	127	127	127
Units: Number of Participants				
number (confidence interval 95%)	2.02 (0.05 to 11.3)	10.1 (3.28 to 23.6)	10.5 (3.41 to 24.5)	14.6 (5.85 to 30.0)

Statistical analyses

Statistical analysis title	Betrixaban 40 mg

Statistical analysis description:

Incidence rate indicating the number of patients reporting events per 100 patient years. 95% CI was calculated via exact method assuming Poisson distribution.

Comparison groups	Warfarin v Betrixaban 40 mg
Number of subjects included in analysis	254
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.035
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.14
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.017
upper limit	1.14

Statistical analysis title	Betrixaban 60 mg
Comparison groups	Warfarin v Betrixaban 60 mg
Number of subjects included in analysis	254
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.546
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.711
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.225
upper limit	2.24

Statistical analysis title	Betrixaban 80 mg
Comparison groups	Warfarin v Betrixaban 80 mg
Number of subjects included in analysis	254
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.712
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.755

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.239
upper limit	2.39

Secondary: Exposure-adjusted incidence rate of any bleeding (major, clinically relevant non-major, or minimal)

End point title	Exposure-adjusted incidence rate of any bleeding (major, clinically relevant non-major, or minimal)

End point description:

The time to the first occurrence of any bleeding event. This was presented as the exposure adjusted incidence rate which was calculated as number of subjects experiencing the event divided by total person years across all subjects, where if a patient experiencing the event, year was from first dose date to the first occurrence of the event, and to last study date if not. The confidence interval was calculated via the exact Poisson distribution.

End point type	Secondary

End point timeframe:

A maximum of 1 year

End point values	Betrixaban 40 mg	Betrixaban 60 mg	Betrixaban 80 mg	Warfarin
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	127	127	127	127
Units: number of patients per 100 patient years				
number (confidence interval 95%)	50.5 (31.7 to 76.5)	77.9 (53.3 to 110)	56.0 (35.9 to 83.4)	103 (73.6 to 140)

Statistical analyses

Statistical analysis title	Betrixaban 40 mg

Statistical analysis description:

Incidence rate indicating the number of patients reporting events per 100 patient years. 95% CI was calculated via exact method assuming Poisson distribution.

Comparison groups	Warfarin v Betrixaban 40 mg
Number of subjects included in analysis	254
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.011
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.508

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.301
upper limit	0.856

Statistical analysis title	Betrixaban 60 mg

Statistical analysis description:

Incidence rate indicating the number of patients reporting events per 100 patient years. 95% CI was calculated via exact method assuming Poisson distribution.

Comparison groups	Warfarin v Betrixaban 60 mg
Number of subjects included in analysis	254
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.308
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.767
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.481
upper limit	1.22

Statistical analysis title	Betrixaban 80 mg

Statistical analysis description:

Incidence rate indicating the number of patients reporting events per 100 patient years. 95% CI was calculated via exact method assuming Poisson distribution.

Comparison groups	Warfarin v Betrixaban 80 mg
Number of subjects included in analysis	254
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.022
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.551
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.332
upper limit	0.914

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From first dose date (including) till the end of study

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.0

Reporting groups

Reporting group title	Betrixaban 40 mg

Reporting group description:

Betrixaban 40 mg once daily for at least 3 months and no longer than approximately 11 months

Reporting group title	Betrixaban 60 mg

Reporting group description:

Betrixaban 60 mg once daily for at least 3 months and no longer than approximately 11 months

Reporting group title	Betrixaban 80 mg

Reporting group description:

Betrixaban 80 mg once daily for at least 3 months and no longer than approximately 11 months

Reporting group title	Warfarin

Reporting group description:

Dose-adjusted warfarin to maintain an INR of 2.0 to 3.0 with INR measured at maximum intervals of 4 weeks. Treatment duration was at least 3 months and no longer than approximately 11 months

Serious adverse events	Betrixaban 40 mg	Betrixaban 60 mg	Betrixaban 80 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	12 / 127 (9.45%)	12 / 127 (9.45%)	11 / 127 (8.66%)
number of deaths (all causes)	0	0	2
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Acute myeloid leukaemia			
subjects affected / exposed	0 / 127 (0.00%)	0 / 127 (0.00%)	0 / 127 (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
Breast cancer			
subjects affected / exposed	0 / 127 (0.00%)	0 / 127 (0.00%)	1 / 127 (0.79%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac neoplasm unspecified			

subjects affected / exposed	0 / 127 (0.00%)	1 / 127 (0.79%)	0 / 127 (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
Chronic lymphocytic leukaemia			
subjects affected / exposed	0 / 127 (0.00%)	0 / 127 (0.00%)	1 / 127 (0.79%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colon cancer recurrent			
subjects affected / exposed	0 / 127 (0.00%)	0 / 127 (0.00%)	1 / 127 (0.79%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung neoplasm malignant			
subjects affected / exposed	0 / 127 (0.00%)	0 / 127 (0.00%)	1 / 127 (0.79%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Renal cancer			
subjects affected / exposed	0 / 127 (0.00%)	1 / 127 (0.79%)	0 / 127 (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
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	0 / 127 (0.00%)	1 / 127 (0.79%)	0 / 127 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypotension			
subjects affected / exposed	0 / 127 (0.00%)	0 / 127 (0.00%)	1 / 127 (0.79%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	0 / 127 (0.00%)	0 / 127 (0.00%)	1 / 127 (0.79%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Non-cardiac chest pain			
subjects affected / exposed	0 / 127 (0.00%)	1 / 127 (0.79%)	0 / 127 (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
Reproductive system and breast disorders			
Prostatic obstruction			
subjects affected / exposed	0 / 127 (0.00%)	0 / 127 (0.00%)	1 / 127 (0.79%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 127 (0.79%)	1 / 127 (0.79%)	1 / 127 (0.79%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Asthma			
subjects affected / exposed	0 / 127 (0.00%)	0 / 127 (0.00%)	0 / 127 (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
Pleural effusion			
subjects affected / exposed	1 / 127 (0.79%)	0 / 127 (0.00%)	0 / 127 (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
Psychiatric disorders			
Hallucination			
subjects affected / exposed	0 / 127 (0.00%)	0 / 127 (0.00%)	1 / 127 (0.79%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
International normalised ratio increased			
subjects affected / exposed	0 / 127 (0.00%)	0 / 127 (0.00%)	0 / 127 (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
Injury, poisoning and procedural complications			

Fall			
subjects affected / exposed	0 / 127 (0.00%)	0 / 127 (0.00%)	0 / 127 (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			
Cardiac failure congestive			
subjects affected / exposed	0 / 127 (0.00%)	0 / 127 (0.00%)	1 / 127 (0.79%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial fibrillation			
subjects affected / exposed	1 / 127 (0.79%)	1 / 127 (0.79%)	1 / 127 (0.79%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ventricular tachycardia			
subjects affected / exposed	1 / 127 (0.79%)	0 / 127 (0.00%)	0 / 127 (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
Angina unstable			
subjects affected / exposed	0 / 127 (0.00%)	1 / 127 (0.79%)	0 / 127 (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
Coronary artery disease			
subjects affected / exposed	1 / 127 (0.79%)	0 / 127 (0.00%)	0 / 127 (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
Coronary artery stenosis			
subjects affected / exposed	0 / 127 (0.00%)	0 / 127 (0.00%)	0 / 127 (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
Sick sinus syndrome			
subjects affected / exposed	1 / 127 (0.79%)	0 / 127 (0.00%)	0 / 127 (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
Nervous system disorders			

Cerebrovascular accident			
subjects affected / exposed	0 / 127 (0.00%)	0 / 127 (0.00%)	1 / 127 (0.79%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Grand mal convulsion			
subjects affected / exposed	0 / 127 (0.00%)	1 / 127 (0.79%)	0 / 127 (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
Lumbar radiculopathy			
subjects affected / exposed	0 / 127 (0.00%)	1 / 127 (0.79%)	0 / 127 (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
Presyncope			
subjects affected / exposed	0 / 127 (0.00%)	0 / 127 (0.00%)	0 / 127 (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
Syncope			
subjects affected / exposed	1 / 127 (0.79%)	0 / 127 (0.00%)	0 / 127 (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	1 / 127 (0.79%)	0 / 127 (0.00%)	1 / 127 (0.79%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombocytopenia			
subjects affected / exposed	1 / 127 (0.79%)	0 / 127 (0.00%)	0 / 127 (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
Gastrointestinal disorders			
Abdominal hernia obstructive			
subjects affected / exposed	0 / 127 (0.00%)	0 / 127 (0.00%)	1 / 127 (0.79%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Abdominal pain upper			
subjects affected / exposed	0 / 127 (0.00%)	0 / 127 (0.00%)	0 / 127 (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
Nausea			
subjects affected / exposed	0 / 127 (0.00%)	0 / 127 (0.00%)	1 / 127 (0.79%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocrine disorders			
Inappropriate antidiuretic hormone secretion			
subjects affected / exposed	0 / 127 (0.00%)	1 / 127 (0.79%)	0 / 127 (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
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 127 (0.00%)	0 / 127 (0.00%)	1 / 127 (0.79%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ligament disorder			
subjects affected / exposed	1 / 127 (0.79%)	0 / 127 (0.00%)	0 / 127 (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
Muscular weakness			
subjects affected / exposed	1 / 127 (0.79%)	0 / 127 (0.00%)	0 / 127 (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			
Cellulitis			
subjects affected / exposed	1 / 127 (0.79%)	1 / 127 (0.79%)	0 / 127 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cystitis			

subjects affected / exposed	0 / 127 (0.00%)	1 / 127 (0.79%)	0 / 127 (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
Urinary tract infection			
subjects affected / exposed	1 / 127 (0.79%)	0 / 127 (0.00%)	0 / 127 (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
Bronchitis			
subjects affected / exposed	0 / 127 (0.00%)	0 / 127 (0.00%)	0 / 127 (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
Pneumonia			
subjects affected / exposed	0 / 127 (0.00%)	1 / 127 (0.79%)	0 / 127 (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
Pyelonephritis			
subjects affected / exposed	1 / 127 (0.79%)	0 / 127 (0.00%)	0 / 127 (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
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	0 / 127 (0.00%)	0 / 127 (0.00%)	0 / 127 (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
Diabetes mellitus inadequate control			
subjects affected / exposed	0 / 127 (0.00%)	1 / 127 (0.79%)	0 / 127 (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
Fluid overload			
subjects affected / exposed	1 / 127 (0.79%)	0 / 127 (0.00%)	0 / 127 (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
Gout			

subjects affected / exposed	0 / 127 (0.00%)	0 / 127 (0.00%)	0 / 127 (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
Hypoglycaemia			
subjects affected / exposed	0 / 127 (0.00%)	0 / 127 (0.00%)	1 / 127 (0.79%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Warfarin		
Total subjects affected by serious adverse events			
subjects affected / exposed	12 / 127 (9.45%)		
number of deaths (all causes)	1		
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Acute myeloid leukaemia			
subjects affected / exposed	1 / 127 (0.79%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Breast cancer			
subjects affected / exposed	0 / 127 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cardiac neoplasm unspecified			
subjects affected / exposed	0 / 127 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Chronic lymphocytic leukaemia			
subjects affected / exposed	0 / 127 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Colon cancer recurrent			
subjects affected / exposed	0 / 127 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Lung neoplasm malignant			
subjects affected / exposed	0 / 127 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Renal cancer			
subjects affected / exposed	0 / 127 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	0 / 127 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hypotension			
subjects affected / exposed	0 / 127 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	0 / 127 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Non-cardiac chest pain			
subjects affected / exposed	0 / 127 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Reproductive system and breast disorders			
Prostatic obstruction			
subjects affected / exposed	0 / 127 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			

subjects affected / exposed	0 / 127 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Asthma			
subjects affected / exposed	1 / 127 (0.79%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pleural effusion			
subjects affected / exposed	0 / 127 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Hallucination			
subjects affected / exposed	0 / 127 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Investigations			
International normalised ratio increased			
subjects affected / exposed	1 / 127 (0.79%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	1 / 127 (0.79%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Cardiac failure congestive			
subjects affected / exposed	3 / 127 (2.36%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 1		
Atrial fibrillation			

subjects affected / exposed	0 / 127 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Ventricular tachycardia			
subjects affected / exposed	1 / 127 (0.79%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Angina unstable			
subjects affected / exposed	0 / 127 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Coronary artery disease			
subjects affected / exposed	0 / 127 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Coronary artery stenosis			
subjects affected / exposed	1 / 127 (0.79%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Sick sinus syndrome			
subjects affected / exposed	0 / 127 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	0 / 127 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Grand mal convulsion			
subjects affected / exposed	0 / 127 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Lumbar radiculopathy			

subjects affected / exposed	0 / 127 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Presyncope			
subjects affected / exposed	1 / 127 (0.79%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Syncope			
subjects affected / exposed	0 / 127 (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 / 127 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Thrombocytopenia			
subjects affected / exposed	0 / 127 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Abdominal hernia obstructive			
subjects affected / exposed	0 / 127 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Abdominal pain upper			
subjects affected / exposed	1 / 127 (0.79%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nausea			
subjects affected / exposed	0 / 127 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Endocrine disorders			

Inappropriate antidiuretic hormone secretion				
subjects affected / exposed	0 / 127 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Musculoskeletal and connective tissue disorders				
Back pain				
subjects affected / exposed	0 / 127 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Ligament disorder				
subjects affected / exposed	0 / 127 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Muscular weakness				
subjects affected / exposed	0 / 127 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Infections and infestations				
Cellulitis				
subjects affected / exposed	0 / 127 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cystitis				
subjects affected / exposed	1 / 127 (0.79%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Urinary tract infection				
subjects affected / exposed	1 / 127 (0.79%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Bronchitis				

subjects affected / exposed	1 / 127 (0.79%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumonia				
subjects affected / exposed	0 / 127 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pyelonephritis				
subjects affected / exposed	0 / 127 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Metabolism and nutrition disorders				
Decreased appetite				
subjects affected / exposed	1 / 127 (0.79%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Diabetes mellitus inadequate control				
subjects affected / exposed	0 / 127 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Fluid overload				
subjects affected / exposed	0 / 127 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gout				
subjects affected / exposed	1 / 127 (0.79%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hypoglycaemia				
subjects affected / exposed	0 / 127 (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: 3 %

Non-serious adverse events	Betrixaban 40 mg	Betrixaban 60 mg	Betrixaban 80 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	61 / 127 (48.03%)	68 / 127 (53.54%)	53 / 127 (41.73%)
Investigations			
Liver function test abnormal			
subjects affected / exposed	1 / 127 (0.79%)	4 / 127 (3.15%)	0 / 127 (0.00%)
occurrences (all)	1	5	0
Vascular disorders			
Hypertension			
subjects affected / exposed	3 / 127 (2.36%)	3 / 127 (2.36%)	1 / 127 (0.79%)
occurrences (all)	3	3	1
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	1 / 127 (0.79%)	0 / 127 (0.00%)	1 / 127 (0.79%)
occurrences (all)	2	0	2
Nervous system disorders			
Dizziness			
subjects affected / exposed	12 / 127 (9.45%)	9 / 127 (7.09%)	6 / 127 (4.72%)
occurrences (all)	12	11	6
Headache			
subjects affected / exposed	5 / 127 (3.94%)	6 / 127 (4.72%)	9 / 127 (7.09%)
occurrences (all)	6	6	9
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	5 / 127 (3.94%)	1 / 127 (0.79%)	2 / 127 (1.57%)
occurrences (all)	5	1	2
Fatigue			
subjects affected / exposed	7 / 127 (5.51%)	5 / 127 (3.94%)	4 / 127 (3.15%)
occurrences (all)	7	6	4
Oedema peripheral			
subjects affected / exposed	8 / 127 (6.30%)	10 / 127 (7.87%)	6 / 127 (4.72%)
occurrences (all)	8	11	7
Gastrointestinal disorders			
Abdominal pain			

subjects affected / exposed	2 / 127 (1.57%)	5 / 127 (3.94%)	2 / 127 (1.57%)
occurrences (all)	2	5	2
Constipation			
subjects affected / exposed	9 / 127 (7.09%)	8 / 127 (6.30%)	3 / 127 (2.36%)
occurrences (all)	10	8	3
Diarrhoea			
subjects affected / exposed	4 / 127 (3.15%)	10 / 127 (7.87%)	9 / 127 (7.09%)
occurrences (all)	4	11	11
Dyspepsia			
subjects affected / exposed	7 / 127 (5.51%)	0 / 127 (0.00%)	4 / 127 (3.15%)
occurrences (all)	7	0	4
Nausea			
subjects affected / exposed	2 / 127 (1.57%)	5 / 127 (3.94%)	14 / 127 (11.02%)
occurrences (all)	2	5	15
Vomiting			
subjects affected / exposed	1 / 127 (0.79%)	2 / 127 (1.57%)	6 / 127 (4.72%)
occurrences (all)	1	2	6
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	3 / 127 (2.36%)	8 / 127 (6.30%)	3 / 127 (2.36%)
occurrences (all)	3	8	3
Dyspnoea			
subjects affected / exposed	4 / 127 (3.15%)	3 / 127 (2.36%)	5 / 127 (3.94%)
occurrences (all)	4	3	5
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	4 / 127 (3.15%)	3 / 127 (2.36%)	3 / 127 (2.36%)
occurrences (all)	4	3	3
Psychiatric disorders			
Insomnia			
subjects affected / exposed	2 / 127 (1.57%)	4 / 127 (3.15%)	5 / 127 (3.94%)
occurrences (all)	3	4	5
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	3 / 127 (2.36%)	6 / 127 (4.72%)	3 / 127 (2.36%)
occurrences (all)	5	6	3

Back pain			
subjects affected / exposed	5 / 127 (3.94%)	6 / 127 (4.72%)	6 / 127 (4.72%)
occurrences (all)	5	6	6
Infections and infestations			
Bronchitis			
subjects affected / exposed	1 / 127 (0.79%)	2 / 127 (1.57%)	4 / 127 (3.15%)
occurrences (all)	1	2	4
Influenza			
subjects affected / exposed	2 / 127 (1.57%)	1 / 127 (0.79%)	4 / 127 (3.15%)
occurrences (all)	2	1	4
Nasopharyngitis			
subjects affected / exposed	5 / 127 (3.94%)	5 / 127 (3.94%)	3 / 127 (2.36%)
occurrences (all)	6	5	4
Upper respiratory tract infection			
subjects affected / exposed	5 / 127 (3.94%)	1 / 127 (0.79%)	4 / 127 (3.15%)
occurrences (all)	7	1	4
Urinary tract infection			
subjects affected / exposed	3 / 127 (2.36%)	1 / 127 (0.79%)	2 / 127 (1.57%)
occurrences (all)	3	1	3

Non-serious adverse events	Warfarin		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	50 / 127 (39.37%)		
Investigations			
Liver function test abnormal			
subjects affected / exposed	3 / 127 (2.36%)		
occurrences (all)	3		
Vascular disorders			
Hypertension			
subjects affected / exposed	4 / 127 (3.15%)		
occurrences (all)	4		
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	4 / 127 (3.15%)		
occurrences (all)	4		
Nervous system disorders			
Dizziness			

subjects affected / exposed	3 / 127 (2.36%)		
occurrences (all)	3		
Headache			
subjects affected / exposed	3 / 127 (2.36%)		
occurrences (all)	3		
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	3 / 127 (2.36%)		
occurrences (all)	3		
Fatigue			
subjects affected / exposed	4 / 127 (3.15%)		
occurrences (all)	4		
Oedema peripheral			
subjects affected / exposed	11 / 127 (8.66%)		
occurrences (all)	12		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 127 (0.79%)		
occurrences (all)	1		
Constipation			
subjects affected / exposed	3 / 127 (2.36%)		
occurrences (all)	3		
Diarrhoea			
subjects affected / exposed	1 / 127 (0.79%)		
occurrences (all)	1		
Dyspepsia			
subjects affected / exposed	1 / 127 (0.79%)		
occurrences (all)	1		
Nausea			
subjects affected / exposed	2 / 127 (1.57%)		
occurrences (all)	2		
Vomiting			
subjects affected / exposed	1 / 127 (0.79%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			

Cough subjects affected / exposed occurrences (all)	3 / 127 (2.36%) 3		
Dyspnoea subjects affected / exposed occurrences (all)	2 / 127 (1.57%) 2		
Skin and subcutaneous tissue disorders Rash subjects affected / exposed occurrences (all)	1 / 127 (0.79%) 1		
Psychiatric disorders Insomnia subjects affected / exposed occurrences (all)	0 / 127 (0.00%) 0		
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all)	4 / 127 (3.15%) 4		
Back pain subjects affected / exposed occurrences (all)	2 / 127 (1.57%) 2		
Infections and infestations Bronchitis subjects affected / exposed occurrences (all)	0 / 127 (0.00%) 0		
Influenza subjects affected / exposed occurrences (all)	1 / 127 (0.79%) 1		
Nasopharyngitis subjects affected / exposed occurrences (all)	10 / 127 (7.87%) 11		
Upper respiratory tract infection subjects affected / exposed occurrences (all)	3 / 127 (2.36%) 3		
Urinary tract infection			

subjects affected / exposed occurrences (all)	4 / 127 (3.15%) 5		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
30 October 2008	•Investigational site was added & PI was added to Steering Committee •Drug packaging change from blister pack to bottle capsules •Modification of Inclusion and Exclusion Criteria •Modification of lab samples collected •Additional clarifications, deletions and administrative corrections were made throughout the document and Appendices to improve clarity and consistency.
06 May 2009	•Modification of Inclusion and Exclusion Criteria •Allowed flexibility with drug dosing time •Modification of lab samples collected •Endpoint Definitions were added •Additional clarifications, deletions and administrative corrections were made throughout the document and Appendices to improve clarity and consistency.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported