ClinicalTrials.gov Protocol and Results Registration System (PRS) Receipt
Release Date: 03/20/2012

ClinicalTrials.gov ID: NCT00684307

Study Identification

Unique Protocol ID:	D1250C00008
Brief Title:	Prevention of Stroke and Systemic Embolic Events in Patients With Atrial Fibrillation
Official Title:	A Controlled, Randomized, Parallel, Multicentre Study to Assess Safety and Tolerability of the Oral Direct Thrombin Inhibitor AZD0837, Given as an Extended-release Formulation, in the Prevention of Stroke and Systemic Embolic Events in Patients With Atrial Fibrillation
Secondary IDs:	

Study Status

Record Verification:	March 2012
Overall Status:	Completed
Study Start:	February 2007
Primary Completion:	June 2008 [Actual]
Study Completion:	June 2008 [Actual]

Sponsor/Collaborators

Sponsor:	AstraZeneca
Responsible Party:	Sponsor
Collaborators:	

Oversight

FDA Regulated?:	Yes

Applicable Trial?:	Section 801 Clinical Trial? Yes Delayed Posting? No
IND/IDE Protocol?:	No
Review Board:	Approval Status: Approved Approval Number: 6640/6400, approved 2006-11-30 Board Name: National Ethic Committee Board Affiliation: The Federal Board of Drug Quality Control Phone: 7-49-5625-4386 Email:
Data Monitoring?:	Yes
Plan to Share Data?:	
Oversight Authorities:	Austria: Agency for Health and Food Safety Denmark: Danish Medicines Agency Hungary: National Institute of Pharmacy Ireland: Irish Medicines Board Norway: Norwegian Medicines Agency Poland: Office for Registration of Medicinal Products, Medical Devices and Biocidal Products Russia: Ministry of Health of the Russian Federation Sweden: Medical Products Agency United Kingdom: Medicines and Healthcare Products Regulatory Agency

Study Description

Brief Summary:	The main purpose of this study is to provide dose-guiding information by assessing the safety and tolerability of 4 different dosing regimens of an extended-release (ER) formulation of AZD0837 compared with well-controlled, dose-adjusted Vitamin-K antagonists (VKA) (aiming for an international normalized ratio (INR) 2.0 to 3.0) in patients with non-valvular atrial fibrillation (AF) with one or more additional risk factors for stroke.
Detailed Description:	

Conditions

Conditions:	Nonvalvular Atrial Fibrillation
Keywords:	Anticoagulant Treatment Risk Factors For Stroke

Study Design

Study Type:	Interventional

Primary Purpose:	Prevention
Study Phase:	Phase 2
Intervention Model:	Parallel Assignment
Number of Arms:	5
Masking:	Double Blind (Subject, Caregiver, Investigator)
Allocation:	Randomized
Endpoint Classification:	Safety Study
Enrollment:	1084 [Actual]

Arms and Interventions

Arms	Assigned Interventions
Experimental: 1 AZD0837 450 mg	Drug: AZD0837 ER tablet, PO, once daily for a period of 3-9 months. Other Names: • AZD0837
Experimental: 2 AZD0837 200 mg	Drug: AZD0837 ER tablet, PO, twice daily for a period of 3-9 months
Experimental: 3 AZD0837 300 mg	Drug: AZD0837 ER tablet, PO, once daily for a period of 3-9 months. Other Names: • AZD0837
Experimental: 4 AZD0837 150 mg	Drug: AZD0837 ER tablet, PO, once daily for a period of 3-9 months. Other Names: • AZD0837
Active Comparator: 5 Vitamin-K antagonist at INR 2-3	Drug: Vitamin-K antagonist at INR 2-3 Tablet, PO for a period of 3-9 months. Other Names: • Warfarin

Outcome Measures

[See Results Section.]

Eligibility

Minimum Age: 18 Years

Maximum Age:

Gender: Both

Accepts Healthy Volunteers?: No

Criteria: Inclusion Criteria:

- Nonvalvular AF (NVAF) verified by at least two ECGs in the last year separated by at least one week.
- Previous cerebral ischemic attack (stroke or TIA, >30 days prior to randomization)
- Previous systemic embolism.
- Symptomatic congestive heart failure (CHF)
- Impaired left ventricular systolic function
- Diabetes mellitus
- Hypertension requiring anti-hypertensive treatment.

Exclusion Criteria:

- AF secondary to reversible disorders, eg hyperthyroidism, drugs and pulmonary embolism
- Known contraindication to VKA treatment
- Presence of a valvular heart disease, mechanical heart valves, active endocarditis, left ventricular aneurysm or thrombus, atrial myxoma or any condition other than AF requiring chronic anticoagulation treatment
- Conditions associated with increased risk of major bleeding for example: history of intracranial bleeding, history of bleeding gastrointestinal disorder or major surgical procedure or trauma two weeks prior to randomization

Contacts/Locations

Study Officials: Gregory Y Lip, Prof
Study Principal Investigator
University Department of Medicine, City Hospital, Birmingham, B18 7QH, England, UK

Locations:

References

Citations:

Links:

Study Data/Documents:

Study Results

Participant Flow

Recruitment Details	The study population included male and female participants >18 years of age with chronic non-valvular Atrial Fibrillation. The participants were recruited during the time period from 20 February 2007 to 5 June 2008 at medical clinics in Europe.
Pre-Assignment Details	Participants were enrolled in the study up to two weeks before randomisation and treatment assignment. Participants that were already treated with Vitamin K Antagonists (VKA) at the time of enrollment had their dose adjusted to achive INR <2.0 at the time of randomisation. If this was not achieved the participant was discontinued from the study.

Reporting Groups

	Description
150 mg od	AZD0837 150 mg od
300 mg od	AZD0837 300 mg od
450 mg od	AZD0837 450 mg od
200 mg bd	AZD0837 200 mg bd
VKA INR 2-3	

Overall Study

	150 mg od	300 mg od	450 mg od	200 mg bd	VKA INR 2-3
Started	164 [1]	151	156	160	318
On Treatment Period Started	164	151	156	160	318
On Treatment Period Completed	140 [2]	129	128	128	293
Completed	140	129	128	128	293
Not Completed	24	22	28	32	25
Adverse Event	11	6	15	16	8
Development of increasing Liver Function	0	2	0	1	0
Fullfillment of exclusion criteria	1	0	0	3	1
Incorrect enrolment or randomization	4	0	0	0	0
Interupted IP for more than 7 days	0	4	1	3	3

	150 mg od	300 mg od	450 mg od	200 mg bd	VKA INR 2-3
Severe non compliance to protocol	1	0	0	1	2
Participant not willing to continue	7	10	11	5	8
Criteria from the CSR	0	0	1	3	3

[1] Patients who received treatment
[2] Patients who completed treatment

Baseline Characteristics

Reporting Groups

	Description
150 mg od	AZD0837 150 mg od
300 mg od	AZD0837 300 mg od
450 mg od	AZD0837 450 mg od
200 mg bd	AZD0837 200 mg bd
VKA INR 2-3	

Baseline Measures

	150 mg od	300 mg od	450 mg od	200 mg bd	VKA INR 2-3	Total
Number of Participants	164	151	156	160	318	949
Age, Continuous [units: Years] Mean (Standard Deviation)	9.0 (69.9)	9.0 (69.8)	9.4 (69.3)	9.4 (67.8)	9.1 (68.3)	9.18 (69.02)
Gender, Male/Female [units: Participants]						
Female	47	47	49	53	103	299
Male	117	104	107	107	215	650

Outcome Measures

1. Primary Outcome Measure:

Measure Title	Bleeding Events

Measure Description	Number of patients with a bleeding event while on study drug. Patients with multiple events are counted once
Time Frame	36 weeks according to protocol. For patients who discontinued treatment the time frame was <36 weeks. Mean number of weeks was 21 weeks (baseline to end of treatment visit)
Safety Issue?	Yes

Analysis Population Description
[Not Specified]

Reporting Groups

	Description
150 mg od	AZD0837 150 mg od
300 mg od	AZD0837 300 mg od
450 mg od	AZD0837 450 mg od
200 mg bd	AZD0837 200 mg bd
VKA INR 2-3	

Measured Values

	150 mg od	300 mg od	450 mg od	200 mg bd	VKA INR 2-3
Number of Participants Analyzed	164	151	156	160	318
Bleeding Events [units: Participants]	18	8	22	17	46

2. Primary Outcome Measure:

Measure Title	Creatinine
Measure Description	Change in Creatinine values from baseline to week 12 visit for patients while on study drug (week 12 visit-baseline)
Time Frame	12 weeks according to protocol.(baseline to week 12 visit)
Safety Issue?	Yes

Analysis Population Description
[Not Specified]

Reporting Groups

	Description
150 mg od	AZD0837 150 mg od
300 mg od	AZD0837 300 mg od
450 mg od	AZD0837 450 mg od
200 mg bd	AZD0837 200 mg bd
VKA INR 2-3	

Measured Values

	150 mg od	300 mg od	450 mg od	200 mg bd	VKA INR 2-3
Number of Participants Analyzed	141	132	133	134	298
Creatinine [units: umol/L] Mean (Standard Deviation)	5.95 (11.18)	4.81 (12.74)	7.56 (14.95)	9.22 (11.24)	0.43 (11.79)

3. Primary Outcome Measure:

Measure Title	Alanine Aminotransferase (ALAT)
Measure Description	Number of patients while on study drug with ALAT>=3 times upper limit of normal.l
Time Frame	36 weeks according to protocol. For patients who discontinued treatment the time frame was <36 weeks. Mean number of weeks was 21 weeks (baseline to end of treatment visit)
Safety Issue?	Yes

Analysis Population Description

[Not Specified]

Reporting Groups

	Description
150 mg od	AZD0837 150 mg od
300 mg od	AZD0837 300 mg od
450 mg od	AZD0837 450 mg od
200 mg bd	AZD0837 200 mg bd
VKA INR 2-3	

Measured Values

	150 mg od	300 mg od	450 mg od	200 mg bd	VKA INR 2-3
Number of Participants Analyzed	156	147	150	152	315
Alanine Aminotransferase (ALAT) [units: Participants]	6	1	5	2	5

4. Primary Outcome Measure:

Measure Title	Bilirubin
Measure Description	Number of patients while on study drug with Bilirubin>=2 times upper limit of normal
Time Frame	36 weeks according to protocol. For patients who discontinued treatment the time frame was <36 weeks. Mean number of weeks was 21 weeks (baseline to end of treatment visit)
Safety Issue?	Yes

Analysis Population Description

[Not Specified]

Reporting Groups

	Description
150 mg od	AZD0837 150 mg od
300 mg od	AZD0837 300 mg od
450 mg od	AZD0837 450 mg od
200 mg bd	AZD0837 200 mg bd
VKA INR 2-3	

Measured Values

	150 mg od	300 mg od	450 mg od	200 mg bd	VKA INR 2-3
Number of Participants Analyzed	156	147	150	152	315
Bilirubin [units: Participants]	1	0	0	3	2

5. Secondary Outcome Measure:

Measure Title	D-Dimer
Measure Description	Change in D-Dimer values from enrolment to week 12 visit for VKA naïve patients while on study drug (week 12 visit-enrolment)
Time Frame	14 weeks according to protocol.(enrolment to week 12 visit)
Safety Issue?	Yes

Analysis Population Description
[Not Specified]

Reporting Groups

	Description
150 mg od	AZD0837 150 mg od
300 mg od	AZD0837 300 mg od
450 mg od	AZD0837 450 mg od
200 mg bd	AZD0837 200 mg bd
VKA INR 2-3	

Measured Values

	150 mg od	300 mg od	450 mg od	200 mg bd	VKA INR 2-3
Number of Participants Analyzed	37	32	35	43	87
D-Dimer [units: ng/mL] Median (Full Range)	-46.4 (-382 to 170)	-76.9 (-613 to 29)	-45.2 (-1817 to 230)	-68.0 (-1313 to 69)	-50.3 (-3955 to 516)

6. Secondary Outcome Measure:

Measure Title	Activated Partial Thromboplastin Time (APTT)
Measure Description	Change in Activated partial thromboplastin time (APTT) from baseline to week 12 visit for VKA naïve patients while on study drug (week 12 visit-baseline)
Time Frame	12 weeks according to protocol.(baseline to week 12 visit)
Safety Issue?	Yes

Analysis Population Description
[Not Specified]

Reporting Groups

	Description
150 mg od	AZD0837 150 mg od
300 mg od	AZD0837 300 mg od
450 mg od	AZD0837 450 mg od
200 mg bd	AZD0837 200 mg bd
VKA INR 2-3	

Measured Values

	150 mg od	300 mg od	450 mg od	200 mg bd	VKA INR 2-3
Number of Participants Analyzed	35	30	34	41	0
Activated Partial Thromboplastin Time (APTT) [units: sec] Median (Full Range)	8.2 (-1 to 24)	12.3 (2 to 110)	17.4 (-79 to 52)	16.4 (2 to 60)	

7. Secondary Outcome Measure:

Measure Title	Ecarin Clotting Time (ECT)
Measure Description	Change in Ecarin clotting time (ECT) from baseline to week 12 visit for patients while on study drug (week 12 visit-baseline)
Time Frame	12 weeks according to protocol.(baseline to week 12 visit)
Safety Issue?	Yes

Analysis Population Description
[Not Specified]

Reporting Groups

	Description
150 mg od	AZD0837 150 mg od
300 mg od	AZD0837 300 mg od
450 mg od	AZD0837 450 mg od

	Description
200 mg bd	AZD0837 200 mg bd
VKA INR 2-3	

Measured Values

	150 mg od	300 mg od	450 mg od	200 mg bd	VKA INR 2-3
Number of Participants Analyzed	94	85	85	98	0
Ecarin Clotting Time (ECT) [units: sec] Median (Full Range)	33.5 (-1 to 86)	53.0 (15 to 93)	64.0 (2 to 134)	73.5 (-1 to 166)	

8. Secondary Outcome Measure:

Measure Title	Plasma Concentration of AZD0837 (Prodrug)
Measure Description	Assessment made on the week 12 visit
Time Frame	12 weeks after baseline according to protocol
Safety Issue?	No

Analysis Population Description

[Not Specified]

Reporting Groups

	Description
150 mg od	AZD0837 150 mg od
300 mg od	AZD0837 300 mg od
450 mg od	AZD0837 450 mg od
200 mg bd	AZD0837 200 mg bd
VKA INR 2-3	

Measured Values

	150 mg od	300 mg od	450 mg od	200 mg bd	VKA INR 2-3
Number of Participants Analyzed	101	104	107	112	0

	150 mg od	300 mg od	450 mg od	200 mg bd	VKA INR 2-3
Plasma Concentration of AZD0837 (Prodrug) [units: nmol/L] Median (Full Range)	199.8 (10.0 to 2334.0)	617.5 (10.0 to 5355.0)	564.5 (10.0 to 14720.0)	1143.5 (10.0 to 9644.0)	

9. Secondary Outcome Measure:

Measure Title	Plasma Concentration of AR-H067637XX (Active Metabolite)
Measure Description	Assessment made on the week 12 visit
Time Frame	12 weeks after baseline according to protocol
Safety Issue?	No

Analysis Population Description

[Not Specified]

Reporting Groups

	Description
150 mg od	AZD0837 150 mg od
300 mg od	AZD0837 300 mg od
450 mg od	AZD0837 450 mg od
200 mg bd	AZD0837 200 mg bd
VKA INR 2-3	

Measured Values

	150 mg od	300 mg od	450 mg od	200 mg bd	VKA INR 2-3
Number of Participants Analyzed	101	104	107	112	0
Plasma Concentration of AR-H067637XX (Active Metabolite) [units: nmol/L] Median (Full Range)	223.8 (10.0 to 503.9)	373.6 (10.0 to 1074.0)	454.8 (10.0 to 1490.0)	600.8 (10.0 to 1523.0)	

10. Secondary Outcome Measure:

Measure Title	Oral Clearance (CL/F) of AR-H067637XX (Active Metabolite) for C3435T Genotype TT
Measure Description	Oral clearance of AR-H067637XX in subgroup of patients with genotype TT for gene polymorphism ABCB1 C3435T
Time Frame	36 weeks according to protocol
Safety Issue?	No

Analysis Population Description
[Not Specified]

Reporting Groups

	Description
150 mg od	AZD0837 150 mg od
300 mg od	AZD0837 300 mg od
450 mg od	AZD0837 450 mg od
200 mg bd	AZD0837 200 mg bd
VKA INR 2-3	

Measured Values

	150 mg od	300 mg od	450 mg od	200 mg bd	VKA INR 2-3
Number of Participants Analyzed	34	41	27	35	0
Oral Clearance (CL/F) of AR-H067637XX (Active Metabolite) for C3435T Genotype TT [units: L/h] Median (Full Range)	39.7 (22.9 to 79.7)	42.4 (13.7 to 699)	36.3 (21.4 to 62.9)	35.6 (19.7 to 67.3)	

11. Secondary Outcome Measure:

Measure Title	Oral Clearance (CL/F) of AR-H067637XX (Active Metabolite) for C3435T Genotype TC
Measure Description	Oral clearance of AR-H067637XX in subgroup of patients with genotype TC for gene polymorphism ABCB1 C3435T
Time Frame	36 weeks according to protocol
Safety Issue?	No

Analysis Population Description
[Not Specified]

Reporting Groups

	Description
150 mg od	AZD0837 150 mg od
300 mg od	AZD0837 300 mg od
450 mg od	AZD0837 450 mg od
200 mg bd	AZD0837 200 mg bd
VKA INR 2-3	

Measured Values

	150 mg od	300 mg od	450 mg od	200 mg bd	VKA INR 2-3
Number of Participants Analyzed	73	64	64	66	0
Oral Clearance (CL/F) of AR-H067637XX (Active Metabolite) for C3435T Genotype TC [units: L/h] Median (Full Range)	39.2 (19.6 to 130.5)	39.3 (17.2 to 138.6)	37.7 (18 to 79.4)	40 (17.4 to 96.7)	

12. Secondary Outcome Measure:

Measure Title	Oral Clearance (CL/F) of AR-H067637XX (Active Metabolite) for C3435T Genotype CC
Measure Description	Oral clearance of AR-H067637XX in subgroup of patients with genotype CC for gene polymorphism ABCB1 C3435T
Time Frame	36 weeks according to protocol
Safety Issue?	No

Analysis Population Description
[Not Specified]

Reporting Groups

	Description
150 mg od	AZD0837 150 mg od
300 mg od	AZD0837 300 mg od
450 mg od	AZD0837 450 mg od
200 mg bd	AZD0837 200 mg bd

	Description
VKA INR 2-3	

Measured Values

	150 mg od	300 mg od	450 mg od	200 mg bd	VKA INR 2-3
Number of Participants Analyzed	28	21	31	30	0
Oral Clearance (CL/F) of AR-H067637XX (Active Metabolite) for C3435T Genotype CC [units: L/h] Median (Full Range)	40.9 (23.7 to 66)	41.1 (21.8 to 62.1)	43.4 (22.8 to 78)	39.6 (26.5 to 107.1)	

Reported Adverse Events

Time Frame	[Not specified]
Additional Description	[Not specified]

Reporting Groups

	Description
AZD0837 150 mg od	
AZD0837 300 mg od	
AZD0837 450 mg od	
AZD0837 200 mg bd	
VKA INR 2-3	

Serious Adverse Events

	AZD0837 150 mg od	AZD0837 300 mg od	AZD0837 450 mg od	AZD0837 200 mg bd	VKA INR 2-3
	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)
Total	12/166 (7.23%)	20/152 (13.16%)	31/157 (19.75%)	27/161 (16.77%)	50/319 (15.67%)
Blood and lymphatic system disorders					
Haemorrhagic Anaemia [A] †	0/166 (0%)	0/152 (0%)	0/157 (0%)	0/161 (0%)	1/319 (0.31%)

	AZD0837 150 mg od	AZD0837 300 mg od	AZD0837 450 mg od	AZD0837 200 mg bd	VKA INR 2-3
	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)
Cardiac disorders					
Acute Myocardial Infarction [A] †	0/166 (0%)	0/152 (0%)	1/157 (0.64%)	0/161 (0%)	0/319 (0%)
Angina Pectoris [A] †	0/166 (0%)	0/152 (0%)	1/157 (0.64%)	1/161 (0.62%)	1/319 (0.31%)
Angina Unstable [A] †	0/166 (0%)	0/152 (0%)	1/157 (0.64%)	0/161 (0%)	1/319 (0.31%)
Atrial Fibrillation [A] †	0/166 (0%)	2/152 (1.32%)	4/157 (2.55%)	0/161 (0%)	4/319 (1.25%)
Atrial Flutter [A] †	0/166 (0%)	1/152 (0.66%)	0/157 (0%)	1/161 (0.62%)	1/319 (0.31%)
Atrioventricular Block Complete [A] †	1/166 (0.6%)	0/152 (0%)	0/157 (0%)	0/161 (0%)	0/319 (0%)
Bradycardia [A] †	0/166 (0%)	0/152 (0%)	1/157 (0.64%)	1/161 (0.62%)	1/319 (0.31%)
Cardiac Failure [A] †	1/166 (0.6%)	3/152 (1.97%)	1/157 (0.64%)	1/161 (0.62%)	6/319 (1.88%)
Cardiac Failure Acute [A] †	1/166 (0.6%)	0/152 (0%)	0/157 (0%)	0/161 (0%)	0/319 (0%)
Cardiac Failure Congestive [A] †	1/166 (0.6%)	1/152 (0.66%)	1/157 (0.64%)	0/161 (0%)	1/319 (0.31%)
Coronary Artery Occlusion [A] †	0/166 (0%)	0/152 (0%)	0/157 (0%)	1/161 (0.62%)	0/319 (0%)
Myocardial Infarction [A] †	0/166 (0%)	1/152 (0.66%)	0/157 (0%)	0/161 (0%)	0/319 (0%)
Myocardial Ischaemia [A] †	0/166 (0%)	0/152 (0%)	1/157 (0.64%)	0/161 (0%)	1/319 (0.31%)
Sick Sinus Syndrome [A] †	0/166 (0%)	1/152 (0.66%)	0/157 (0%)	0/161 (0%)	1/319 (0.31%)
Ventricular Tachycardia [A] †	0/166 (0%)	0/152 (0%)	0/157 (0%)	0/161 (0%)	1/319 (0.31%)
Ear and labyrinth disorders					
Vertigo [A] †	0/166 (0%)	0/152 (0%)	1/157 (0.64%)	0/161 (0%)	0/319 (0%)
Eye disorders					
Cataract [A] †	0/166 (0%)	0/152 (0%)	0/157 (0%)	0/161 (0%)	2/319 (0.63%)
Glaucoma [A] †	0/166 (0%)	0/152 (0%)	0/157 (0%)	0/161 (0%)	1/319 (0.31%)
Vitreous Haemorrhage [A] †	0/166 (0%)	0/152 (0%)	1/157 (0.64%)	0/161 (0%)	0/319 (0%)

	AZD0837 150 mg od	AZD0837 300 mg od	AZD0837 450 mg od	AZD0837 200 mg bd	VKA INR 2-3
	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)
Gastrointestinal disorders					
Abdominal Hernia [A] †	0/166 (0%)	1/152 (0.66%)	0/157 (0%)	0/161 (0%)	0/319 (0%)
Abdominal Pain [A] †	0/166 (0%)	1/152 (0.66%)	0/157 (0%)	0/161 (0%)	0/319 (0%)
Anal Ulcer [A] †	0/166 (0%)	0/152 (0%)	0/157 (0%)	0/161 (0%)	1/319 (0.31%)
Asthenia [A] †	0/166 (0%)	0/152 (0%)	1/157 (0.64%)	0/161 (0%)	0/319 (0%)
Chest Pain [A] †	0/166 (0%)	1/152 (0.66%)	0/157 (0%)	0/161 (0%)	0/319 (0%)
Diarrhoea [A] †	0/166 (0%)	0/152 (0%)	0/157 (0%)	0/161 (0%)	1/319 (0.31%)
Gastric Ulcer [A] †	0/166 (0%)	0/152 (0%)	0/157 (0%)	0/161 (0%)	1/319 (0.31%)
Haematemesis [A] †	0/166 (0%)	0/152 (0%)	0/157 (0%)	0/161 (0%)	1/319 (0.31%)
Haematochezia [A] †	0/166 (0%)	0/152 (0%)	0/157 (0%)	1/161 (0.62%)	0/319 (0%)
Inguinal Hernia [A] †	0/166 (0%)	0/152 (0%)	0/157 (0%)	1/161 (0.62%)	0/319 (0%)
Non-Cardiac Chest Pain [A] †	0/166 (0%)	1/152 (0.66%)	0/157 (0%)	0/161 (0%)	0/319 (0%)
Periodontal Disease [A] †	0/166 (0%)	0/152 (0%)	0/157 (0%)	0/161 (0%)	1/319 (0.31%)
Rectal Haemorrhage [A] †	0/166 (0%)	0/152 (0%)	1/157 (0.64%)	0/161 (0%)	0/319 (0%)
Sudden Death [A] †	0/166 (0%)	0/152 (0%)	0/157 (0%)	0/161 (0%)	1/319 (0.31%)
Hepatobiliary disorders					
Cholelithiasis [A] †	0/166 (0%)	0/152 (0%)	0/157 (0%)	0/161 (0%)	1/319 (0.31%)
Chronic Hepatitis [A] †	0/166 (0%)	0/152 (0%)	0/157 (0%)	1/161 (0.62%)	0/319 (0%)
Immune system disorders					
Corneal Graft Rejection [A] †	0/166 (0%)	0/152 (0%)	0/157 (0%)	0/161 (0%)	1/319 (0.31%)
Hypersensitivity [A] †	0/166 (0%)	1/152 (0.66%)	0/157 (0%)	0/161 (0%)	0/319 (0%)
Infections and infestations					

	AZD0837 150 mg od	AZD0837 300 mg od	AZD0837 450 mg od	AZD0837 200 mg bd	VKA INR 2-3
	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)
Abscess Limb [A] †	0/166 (0%)	0/152 (0%)	0/157 (0%)	1/161 (0.62%)	0/319 (0%)
Appendicitis [A] †	0/166 (0%)	0/152 (0%)	0/157 (0%)	2/161 (1.24%)	0/319 (0%)
Arthritis Bacterial [A] †	1/166 (0.6%)	0/152 (0%)	0/157 (0%)	0/161 (0%)	0/319 (0%)
Erysipelas [A] †	0/166 (0%)	1/152 (0.66%)	0/157 (0%)	0/161 (0%)	0/319 (0%)
Gastroenteritis [A] †	0/166 (0%)	0/152 (0%)	0/157 (0%)	0/161 (0%)	1/319 (0.31%)
Infective Spondylitis [A] †	0/166 (0%)	0/152 (0%)	1/157 (0.64%)	0/161 (0%)	0/319 (0%)
Lower Respiratory Tract Infection [A] †	0/166 (0%)	0/152 (0%)	1/157 (0.64%)	0/161 (0%)	0/319 (0%)
Postoperative Wound Infection [A] †	0/166 (0%)	0/152 (0%)	0/157 (0%)	1/161 (0.62%)	0/319 (0%)
Pyelonephritis Acute [A] †	0/166 (0%)	0/152 (0%)	0/157 (0%)	1/161 (0.62%)	0/319 (0%)
Urinary Tract Infection [A] †	0/166 (0%)	0/152 (0%)	0/157 (0%)	0/161 (0%)	1/319 (0.31%)
Injury, poisoning and procedural complications					
Alanine Aminotransferase Increased [A] †	0/166 (0%)	0/152 (0%)	0/157 (0%)	0/161 (0%)	1/319 (0.31%)
Blood Glucose Increased [A] †	0/166 (0%)	0/152 (0%)	0/157 (0%)	0/161 (0%)	1/319 (0.31%)
Contusion [A] †	0/166 (0%)	0/152 (0%)	0/157 (0%)	0/161 (0%)	1/319 (0.31%)
Femoral Neck Fracture [A] †	0/166 (0%)	0/152 (0%)	1/157 (0.64%)	0/161 (0%)	0/319 (0%)
Haemoglobin Decreased [A] †	0/166 (0%)	0/152 (0%)	0/157 (0%)	2/161 (1.24%)	0/319 (0%)
Limb Injury [A] †	0/166 (0%)	0/152 (0%)	0/157 (0%)	1/161 (0.62%)	0/319 (0%)
Road Traffic Accident [A] †	0/166 (0%)	0/152 (0%)	0/157 (0%)	1/161 (0.62%)	0/319 (0%)
Tibia Fracture [A] †	0/166 (0%)	0/152 (0%)	1/157 (0.64%)	0/161 (0%)	0/319 (0%)
Metabolism and nutrition disorders					
Diabetes Mellitus [A] †	1/166 (0.6%)	0/152 (0%)	0/157 (0%)	1/161 (0.62%)	0/319 (0%)
Gout [A] †	0/166 (0%)	0/152 (0%)	0/157 (0%)	0/161 (0%)	1/319 (0.31%)

	AZD0837 150 mg od	AZD0837 300 mg od	AZD0837 450 mg od	AZD0837 200 mg bd	VKA INR 2-3
	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)
Musculoskeletal and connective tissue disorders					
Arthritis [A] †	0/166 (0%)	0/152 (0%)	0/157 (0%)	0/161 (0%)	1/319 (0.31%)
Back Pain [A] †	0/166 (0%)	1/152 (0.66%)	0/157 (0%)	0/161 (0%)	0/319 (0%)
Muscular Weakness [A] †	0/166 (0%)	0/152 (0%)	1/157 (0.64%)	0/161 (0%)	0/319 (0%)
Myalgia [A] †	0/166 (0%)	0/152 (0%)	0/157 (0%)	0/161 (0%)	1/319 (0.31%)
Myositis [A] †	0/166 (0%)	0/152 (0%)	0/157 (0%)	1/161 (0.62%)	0/319 (0%)
Osteoarthritis [A] †	1/166 (0.6%)	0/152 (0%)	0/157 (0%)	0/161 (0%)	0/319 (0%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)					
Basal Cell Carcinoma [A] †	0/166 (0%)	0/152 (0%)	0/157 (0%)	0/161 (0%)	1/319 (0.31%)
Bladder Cancer [A] †	0/166 (0%)	0/152 (0%)	1/157 (0.64%)	0/161 (0%)	0/319 (0%)
Brain Neoplasm [A] †	0/166 (0%)	0/152 (0%)	0/157 (0%)	0/161 (0%)	1/319 (0.31%)
Breast Cancer [A] †	0/166 (0%)	0/152 (0%)	0/157 (0%)	1/161 (0.62%)	0/319 (0%)
Colon Neoplasm [A] †	0/166 (0%)	0/152 (0%)	0/157 (0%)	1/161 (0.62%)	0/319 (0%)
Prostatic Adenoma [A] †	0/166 (0%)	0/152 (0%)	1/157 (0.64%)	0/161 (0%)	0/319 (0%)
Nervous system disorders					
Dizziness [A] †	0/166 (0%)	1/152 (0.66%)	0/157 (0%)	0/161 (0%)	0/319 (0%)
Headache [A] †	0/166 (0%)	0/152 (0%)	1/157 (0.64%)	0/161 (0%)	0/319 (0%)
Ischaemic Stroke [A] †	2/166 (1.2%)	0/152 (0%)	0/157 (0%)	0/161 (0%)	1/319 (0.31%)
Syncope [A] †	0/166 (0%)	1/152 (0.66%)	2/157 (1.27%)	2/161 (1.24%)	2/319 (0.63%)
Syncope Vasovagal [A] †	0/166 (0%)	1/152 (0.66%)	0/157 (0%)	1/161 (0.62%)	0/319 (0%)
Transient Ischaemic Attack [A] †	0/166 (0%)	0/152 (0%)	0/157 (0%)	1/161 (0.62%)	1/319 (0.31%)
Vascular Encephalopathy [A] †	0/166 (0%)	0/152 (0%)	0/157 (0%)	0/161 (0%)	1/319 (0.31%)

	AZD0837 150 mg od	AZD0837 300 mg od	AZD0837 450 mg od	AZD0837 200 mg bd	VKA INR 2-3
	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)
Vertebrobasilar Insufficiency [A] †	0/166 (0%)	0/152 (0%)	1/157 (0.64%)	0/161 (0%)	0/319 (0%)
Psychiatric disorders					
Depression [A] †	0/166 (0%)	0/152 (0%)	0/157 (0%)	0/161 (0%)	1/319 (0.31%)
Renal and urinary disorders					
Haematuria [A] †	0/166 (0%)	0/152 (0%)	1/157 (0.64%)	0/161 (0%)	0/319 (0%)
Respiratory, thoracic and mediastinal disorders					
Asthma [A] †	0/166 (0%)	0/152 (0%)	0/157 (0%)	0/161 (0%)	1/319 (0.31%)
Epistaxis [A] †	0/166 (0%)	0/152 (0%)	0/157 (0%)	0/161 (0%)	1/319 (0.31%)
Pleural Effusion [A] †	0/166 (0%)	1/152 (0.66%)	0/157 (0%)	0/161 (0%)	0/319 (0%)
Pulmonary Embolism [A] †	0/166 (0%)	0/152 (0%)	1/157 (0.64%)	0/161 (0%)	1/319 (0.31%)
Vascular disorders					
Arterial Stenosis Limb [A] †	0/166 (0%)	0/152 (0%)	1/157 (0.64%)	0/161 (0%)	0/319 (0%)
Axillary Vein Thrombosis [A] †	1/166 (0.6%)	0/152 (0%)	0/157 (0%)	0/161 (0%)	0/319 (0%)
Deep Vein Thrombosis [A] †	0/166 (0%)	0/152 (0%)	0/157 (0%)	1/161 (0.62%)	0/319 (0%)
Hypertension [A] †	0/166 (0%)	0/152 (0%)	0/157 (0%)	1/161 (0.62%)	0/319 (0%)
Hypotension [A] †	0/166 (0%)	0/152 (0%)	1/157 (0.64%)	0/161 (0%)	0/319 (0%)
Orthostatic Hypotension [A] †	0/166 (0%)	0/152 (0%)	1/157 (0.64%)	0/161 (0%)	0/319 (0%)
Peripheral Artery Aneurysm [A] †	0/166 (0%)	0/152 (0%)	0/157 (0%)	0/161 (0%)	1/319 (0.31%)
Peripheral Embolism [A] †	1/166 (0.6%)	0/152 (0%)	0/157 (0%)	0/161 (0%)	0/319 (0%)
Subclavian Vein Thrombosis [A] †	1/166 (0.6%)	0/152 (0%)	0/157 (0%)	0/161 (0%)	0/319 (0%)

† Indicates events were collected by systematic assessment.
A Term from vocabulary, MedDRA 10.0

Other Adverse Events

Frequency Threshold Above Which Other Adverse Events are Reported: 5%

	AZD0837 150 mg od	AZD0837 300 mg od	AZD0837 450 mg od	AZD0837 200 mg bd	VKA INR 2-3
	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)
Total	46/166 (27.71%)	62/152 (40.79%)	46/157 (29.3%)	59/161 (36.65%)	67/319 (21%)
Gastrointestinal disorders					
ABDOMINAL PAIN UPPER [A] †	2/166 (1.2%)	1/152 (0.66%)	8/157 (5.1%)	2/161 (1.24%)	3/319 (0.94%)
DIARRHOEA [A] †	14/166 (8.43%)	23/152 (15.13%)	12/157 (7.64%)	17/161 (10.56%)	15/319 (4.7%)
FLATULENCE [A] †	10/166 (6.02%)	11/152 (7.24%)	6/157 (3.82%)	10/161 (6.21%)	1/319 (0.31%)
NAUSEA [A] †	6/166 (3.61%)	8/152 (5.26%)	8/157 (5.1%)	9/161 (5.59%)	15/319 (4.7%)
Infections and infestations					
NASOPHARYNGITIS [A] †	10/166 (6.02%)	10/152 (6.58%)	5/157 (3.18%)	10/161 (6.21%)	20/319 (6.27%)
Nervous system disorders					
DIZZINESS [A] †	4/166 (2.41%)	9/152 (5.92%)	7/157 (4.46%)	11/161 (6.83%)	13/319 (4.08%)

† Indicates events were collected by systematic assessment.

A Term from vocabulary, MedDRA 10.0

Limitations and Caveats

[Not specified]

More Information

Certain Agreements:

Principal Investigators are NOT employed by the organization sponsoring the study.

The only disclosure restriction on the PI is that the sponsor can review results communications prior to public release and can embargo communications regarding trial results for a period that is less than or equal to 60 days from the time submitted to the sponsor for review. The sponsor cannot require changes to the communication and cannot extend the embargo.

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