Online Resource

Supplement for American Journal of Cardiovascular Drugs article:

Educational Impact on Apixaban Adherence in Atrial Fibrillation (the AEGEAN STUDY): A Randomized Clinical Trial

Gilles Montalescot, MD; Carlos Brotons, MD, PhD; Bernard Cosyns, MD, PhD, FESC; Harry J. Crijns, MD, PhD; Armando D'Angelo, MD; Ludovic Drouet, MD, PhD; Franz Eberli, MD; Deirdre A. Lane, PhD; Bruno Besse, MD*; Anthony Chan, MD, FRCSI, MFPM; Eric Vicaut, MD, PhD; Harald Darius, MD, PhD; on behalf of the AEGEAN Study Investigators

Address for correspondence

Dr. Gilles Montalescot, ACTION Study Group, Institut de Cardiologie, Centre Hospitalier Universitaire Pitié-Salpêtrière, 47 Boulevard de l'Hôpital, 75013 Paris, France.

E-mail: gilles.montalescot@aphp.fr

Phone: +33 42163006

Fax: +33 142162931

ORCID

CONTENTS

1 AEGEAN Study Investigators

1.1 Germany

Investigator		City	No. of patients recruited
Ulmer	Achim	Ludwigsburg	(37)
Axthelm	Christoph	Pirna	(33)
Weissbrodt	Matthias	Leipzig	(21)
Bott	Jochen	Berlin	(20)
Natour	Mohammed	Heidelberg	(18)
Taggeselle	Jens	Markkleeberg	(18)
Uebel	Peter	Ludwigshafen	(18)
Hagenow	Andreas	Elsterwerda	(17)
Jaeck	Ulrich	Balingen	(17)
Minnich	Joachim	Künzing	(17)
Al-Zoebi	Ayham	Wermsdorf	(16)
Stoehring	Rheinhard	Bad Homburg	(16)
Hergdt	Gunter	Obermichelbach	(15)
Hohensee	Hartmut	Dresden	(14)
Luttermann	Matthias	Wardenburg	(14)
Eissing	Volker	Papenburg	(13)
Germann	Hans	Neunkirchen	(13)
Schneider	Reinhold	Wetzlar	(13)
Schreckenberg	Andreas	Weyhe	(12)
Bauer	Florian	Spaichingen	(11)
Remppis	Rudolf	Weißenhorn	(11)
Jung	Thomas	Deggingen	(10)
Kossler-Wiesweg	Christa	Essen	(10)
Schaefer	Thomas	Kelkheim	(10)
Stalke	Jost	Berlin	(10)
Abdel-Qader	Muwafeg	Winsen	(9)
Braun	Roland	Unterschneidheim	(8)
Haas	Johannes	Bamberg	(8)
Nies	Jakob	Mammendorf	(8)
Schätzl	Roland	Grossheirath Rossbach	(8)
Wolde	Claus Henning	Heidelberg	(7)
Grosskopf	Josef	Wallerfing	(6)
Schmidt	Jürgen	Flörsheim	(6)
Wachter	Jürgen	Mannheim	(6)
Maas	Martin	Heidenau	(6)
Bosch	Ralph	Ludwigsburg	(4)
Foerster	Andreas	Berlin	(4)
Giebel	Thomas	Sinzheim	(3)
Tangerding	Gerhard	Wangen	(3)
Darius	Harald	Berlin	(2)
Jaeger	Frank-Stephan	Kassel	(2)
Naudts	Ingomar	Rodgau	(2)
Rieker	Werner	Berlin	(2)
Stenzel	Gunter	Riesa	(2)
Hartmann	Hermann Josef	Krombach	(1)
Koenemann	Jörg	Aurich	(1)

Landers	Bernhard	Mayen	(1)
Spitzer	Stefan	Dresden	(1)

1.2 France

Investigator		City	No. of patients recruited
Bayle	Sandrine	Le Coudray	(17)
Mismetti	Patrick	St Priest En Jarrez	(17)
Berneau	Jean Baptiste	Bayonne	(14)
Cayla	Guillaume	Nimes	(13)
Poulard	Jean-Ernst	Abbeville	(12)
Davy	Jean Marc	Montpellier	(11)
Georges	Jean-Louis	Le Chesnay	(11)
Messas	Emmanuel	Paris	(11)
Mansourati	Jacques	Brest	(10)
Goube	Pascal	Corbeil Essonnes	(9)
Rouanet	Francois	Bordeaux	(8)
Tibi	Thierry	Cannes	(8)
Henry	Patrick	Paris	(7)
Mirode	Anfani	Amiens	(7)
Morel	Olivier	Strasbourg	(7)
Didier Petit	Katy	Vesoul	(6)
El Mahmoud	Rami Serge	Boulogne Billancourt	(6)
Goralski	Marc	Orleans	(6)
Montalescot	Gilles	Paris	(6)
Paganelli	Franck	Marseille	(6)
Cheggour	Saida	Avignon	(5)
Guenoun	Maxime	Plan De Cuques	(5)
Lellouche	Nicolas	Creteil	(5)
Cottin	Yves	Dijon	(4)
Kacet	Salem	Lille	(4)
Mewton	Nathan	Bron	(4)
Frances	Yves	Marseille	(3)
Heiligenstein	Daniel	Thonon Les Bains	(3)
Pisapia	Andre	Marseille	(3)
Cebron	Jean-Pierre	Nantes	(2)
Deharo	Jean-Claude	Marseille	(2)
Delarche	Nicolas	Pau	(2)
Georger	Frederic	Beziers	(2)
Piot	Olivier	St-Denis	(2)
Barisic	Anne-Marie	Nice	(1)
Beygui	Farzin	Caen	(1)
Decoulx	Eric	Tourcoing	(1)
Defaye	Pascal	Grenoble	(1)
Durup	Florence	Longjumeau	(1)
Isnard	Richard	Paris	(1)
Mahé	Isabelle	COLOMBES	(1)
Sacher	Frederic	Pessac	(1)
Taieb	Jerome	Aix En Provence	(1)

1.3 Spain

Investigator		City	No. of patients recruited
Marin Ortuno	Francisco	Murcia	(21)
Arellano	Eduardo	Barcelona	(20)
Brotons	Carlos	Barcelona	(13)
Alvarez Garcia	Pere	Viladecans-Barcelona	(12)
Arrarte Esteban	Vicente Ignacio	Alicante	(12)
Roldan	Inmaculada	Madrid	(12)
Garcia Puig	Juan	Madrid	(8)
Gomez Cerezo	Jorge	San Sebastián De Los Reyes	(8)
Marco	Pascual	Alicante	(8)
Alvarez Sala	Luis	Madrid	(7)
Aguinaco Culebras	Maria Reyes	Tarragona	(6)
Calvo	Carlos	Santiago De Compostela	(3)
Roncales	Francisco	Zaragoza	(3)
Mateo	José	Barcelona	(3)
Cuixart	Lluís	Barcelona	(2)
Vilar Palop	María	Aldaya	(2)
Lobos Bejarano	José María	Madrid	(1)
Ruiz	Ricardo	Valencia	(1)

1.4 Italy

Investigator		City	No. of patients recruited
Tuttolomondo	Antonio	Palermo	(11)
Iori	Ido	Reggio Emilia	(8)
Crippa	Luciano	Milano	(7)
Oltrona Visconti	Luigi	Pavia	(7)
Ageno	Walter	Varese	(6)
Cimminiello	Claudio	Vimercate (Mi)	(6)
Di Pasquale	Giuseppe	Bologna	(6)
Mos	Lucio	San Daniele Del Friuli - Udine	(6)
Schinco	Piercarla	Torino	(6)
Bolognese	Leonardo	Arezzo	(5)
Indolfi	Ciro	Catanzaro	(5)
Fedele	Francesco	Roma	(4)
Patti	Guiseppe	Roma	(4)
Testa	Sophie	Cremona	(4)
Themistoclakis	Sakis	Mestre	(4)
Di Biase	Matteo	Foggia	(3)
Marcucci	Rossella	Florence	(3)
Piovella	Franco	Pavia	(3)
Cappelli	Roberto	Siena	(2)
Cattaneo	Marco	Milano	(2)
Di Minno	Giovanni	Napoli	(2)
Olivari	Zoran	Treviso	(2)
Di Pascoli	Loredana	Vicenza	(2)

Prisco	Domenico	Firenze	(1)
Visona	Adriana	Castelfranco Veneto (TV)	(1)

1.5 United Kingdom

Investigator		City	No. of patients recruited
Barr	Craig	Dudley	(37)
Manoj	Aravindakshan	Liverpool	(16)
Boos	Christopher	Poole	(8)
Levy	Terry	Bournemouth	(6)
Lip	Gregory Y H	Birmingham	(5)
Pell	Alastair	Airdrie Nth Lanarkshire	(5)
Hargroves	David	Ashford	(4)
Sobolewska	Jolanta	Oldham	(4)
Guyler	Paul	Westcliff-On-Sea	(3)
James	Martin	Exeter	(3)
Moriarty	Andrew	Portadown	(2)
Weir	Robin	East Kilbride	(2)
Dayer	Mark	Taunton	(1)
Natarajan	Indira	Stoke-On-Trent	(1)

1.6 Belgium

Investigator		City	No. of patients recruited
Mairesse	Georges	Arlon	(12)
Ector	Joris	Leuven	(11)
Vijgen	Johan	Hasselt	(10)
Leroy	Jean	Gilly	(9)
Gazagnes	Marie-Dominique	Bruxelles	(5)
Laloux	Patrice	Yvoir	(4)
Desfontaines	Philippe	Montegnee	(3)
Peeters	André	Bruxelles	(3)
Janssens	Luc	Bonheiden	(2)
Thijs	Vincent	Leuven	(2)
Hemelsoet	Dimitri	Gent	(1)
Xhaet	Olivier	Yvoir	(1)

1.7 Switzerland

Investigator		City	No. of patients recruited
Moccetti	Tiziano	Lugano	(4)
Hayoz	Daniel	Fribourg	(3)
Beer	Jürg. Hans	Baden	(1)
Eberli	Franz	Zürich	(1)
Linka	Andre	Winterthur	(1)
Perschak	Henry	Zürich	(1)

2 AEGEAN endpoint adjudication committee

Dr Pierre Sabouret (Pitié Hospital, Paris, France), Dr Stephane Ederhy (Saint-Antoine Hospital, Paris, France), Dr Candice Sabben (Bichat Hospital, Paris, France).

3 AEGEAN steering committee, national coordinators, and virtual clinic coordinators

3.1 Steering Committee

Gilles Montalescot (France), Carlos Brotons (Spain), Bernard Cosyns (Belgium), Harry J. Crijns (The Netherlands), Armando D'Angelo (Italy), Ludovic Drouet (France), Franz Eberli (Switzerland), Deirdre A. Lane (United Kingdom), Eric Vicaut (France), Harald Darius (Germany).

3.2 National Coordinators

Gilles Montalescot (France), Carlos Brotons (Spain), Bernard Cosyns (Belgium), Armando D'Angelo (Italy), Franz Eberli (Switzerland), Gregory Lip (United Kingdom), Harald Darius (Germany).

3.3 Virtual Clinic Coordinators

Belgium: Christian Chatelain (French speaking); Peter Verhamme (Flemish speaking)

France: Claire Bal-Dit-Sollier

Germany: Christian Hausdorf

Italy: Silvana Vigano

Spain: Gines Escolar

Switzerland: Lars Asmis and Silvana Vigano (Italian speaking); Christian Hausdorf (German speaking)

United Kingdom: Joanne Malpass

4 Definition of bleeding events

Major bleeding was defined as acute clinically overt bleeding accompanied by one or more of the following:

- A decrease in hemoglobin (Hgb) of 2 g/dl or more over a 24-hour period
- A transfusion of two or more units of packed red blood cells
- Bleeding that occurs in at least one of the following critical sites: intracranial, intraspinal, intraocular (within the corpus of the eye; thus, a conjunctival bleed is not an intraocular bleed), pericardial, intra-articular, intramuscular with compartment syndrome, retroperitoneal
- Bleeding that is fatal

Clinically relevant non-major bleeding was defined as acute clinically overt bleeding that does not satisfy additional criteria required for the bleeding event to be defined as a major bleeding event and meets at least one of the following criteria:

- Hospital admission for bleeding
- Physician-guided medical or surgical treatment for bleeding
- Change in antithrombotic treatment (anticoagulant or antiplatelet therapy)

Minor bleeding was defined as acute clinically overt bleeding not meeting the criteria for either major bleeding or clinically relevant non-major bleeding.

Fatal bleeding is defined as bleeding that is the primary cause of death or contributes directly to death.

5 Online tables and figures

Online Table 1 Procedural schedule following randomization

Procedure	**Week 4**	**Weeks 12, 24 and 36**	**Week 48 (end of treatment)**
Eligibility assessment			
Inclusion/exclusion criteria			
Medical history			
Concomitant medications	X	X	X
Safety assessment			
Physical examination	X	X	X
Vital signs	X	X	X
Assessment of signs and symptoms	X	X	X
Adverse events assessment	X	X	X
Laboratory **tests**[a]		X[b]	X
Pregnancy test (WOCBP)	X	X	X

Efficacy assessments			
Adherence **measurements**[c]		X	X
Clinical drug supplies			
Randomize		Week 24[d]	
Dispense study drug	X	X	

[a]FBC and full chemistry panel PTT and PT ratio not to be measured during follow-up.

[b]Laboratory testing required only at week 24.

[c]Adherence measurements: Electronic monitoring tool data upload.

[d]For patients who were initially randomized into the additional education program.

FBC, full blood count; PT, prothrombin time; PTT, partial thromboplastin time.

Online Table 2 Virtual clinic reminder use at 24 weeks by study group

	Primary SOC (N=583)	**Additional education program (N=579)**	**All patients (N=1162)**
Preferred communication channels, n	**4**	**554**	**558**
Phone (home)	3 (75.0)	458 (82.7)	461 (82.6)
Mobile phone	1 (25.0)	94 (17.0)	95 (17.0)
email	0	2 (0.4)	2 (0.4)
SMS	0	0	0
Type of reminder tool, n	**4**	**554**	**558**
Dose reminder	2 (50.0)	227 (41.0)	229 (41.0)
SMS alert	0	27 (4.9)	27 (4.8)
Smartphone app	0	5 (0.9)	5 (0.9)

SMS, short message service; SOC, standard of care; data presented as n (% of patients with analyzable data) unless otherwise stated

Online Table 3 Subject discontinuations

24 weeks

n (%)	**Primary SOC (N=583)**	**Additional education program (N=579)**
Reason for discontinuation		
Subject withdrew consent	17 (2.9)	20 (3.5)
Death	6 (1.0)	4 (0.7)
Lost to follow-up	0	1 (0.2)
Serious adverse event	7 (1.2)	6 (1.0)
Adverse event	15 (2.6)	11 (1.9)
>30 days of study drug interrupted	0	2 (0.3)
Inclusion/exclusion criteria	2 (0.3)	5 (0.9)
Helping hand not used	2 (0.3)	0
Helping hand not used + treatment taken	1 (0.2)	1 (0.2)
Subject decision	1 (0.2)	1 (0.2)
Medical reason	3 (0.5)	3 (0.5)

48 weeks

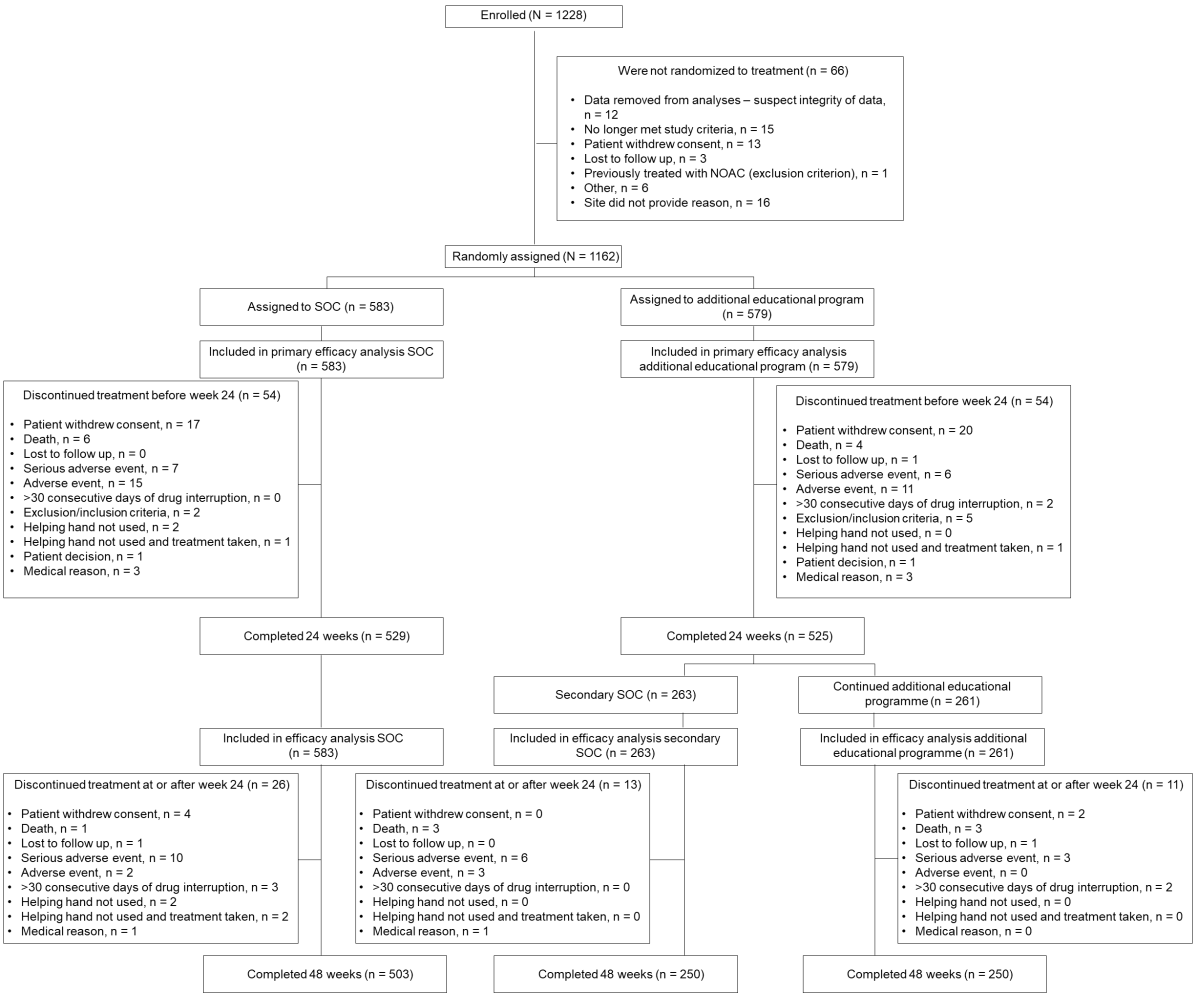
n (%)	**Primary SOC (N=583)**	**Secondary SOC (N=263)**	**Continued additional education program (N=261)**
Reason for discontinuation			
Subject withdrew consent	4 (0.7)	0	2 (0.8)
Death	1 (0.2)	3 (1.1)	3 (1.1)
Lost to follow-up	1 (0.2)	0	1 (0.4)
Serious adverse event	10 (1.7)	6 (2.3)	3 (1.1)
Adverse event	2 (0.3)	3 (1.1)	0

>30 days of study drug interrupted	3 (0.5)	0	2 (0.8)
Helping hand not used	2 (0.3)	0	0
Helping hand not used + treatment taken	2 (0.3)	0	0
Medical reason	1 (0.2)	1 (0.4)	0

Online Fig. 1 Helping Hand® electronic monitoring device (WestRock Switzerland Ltd., Sion, Switzerland), model number: 1110-01

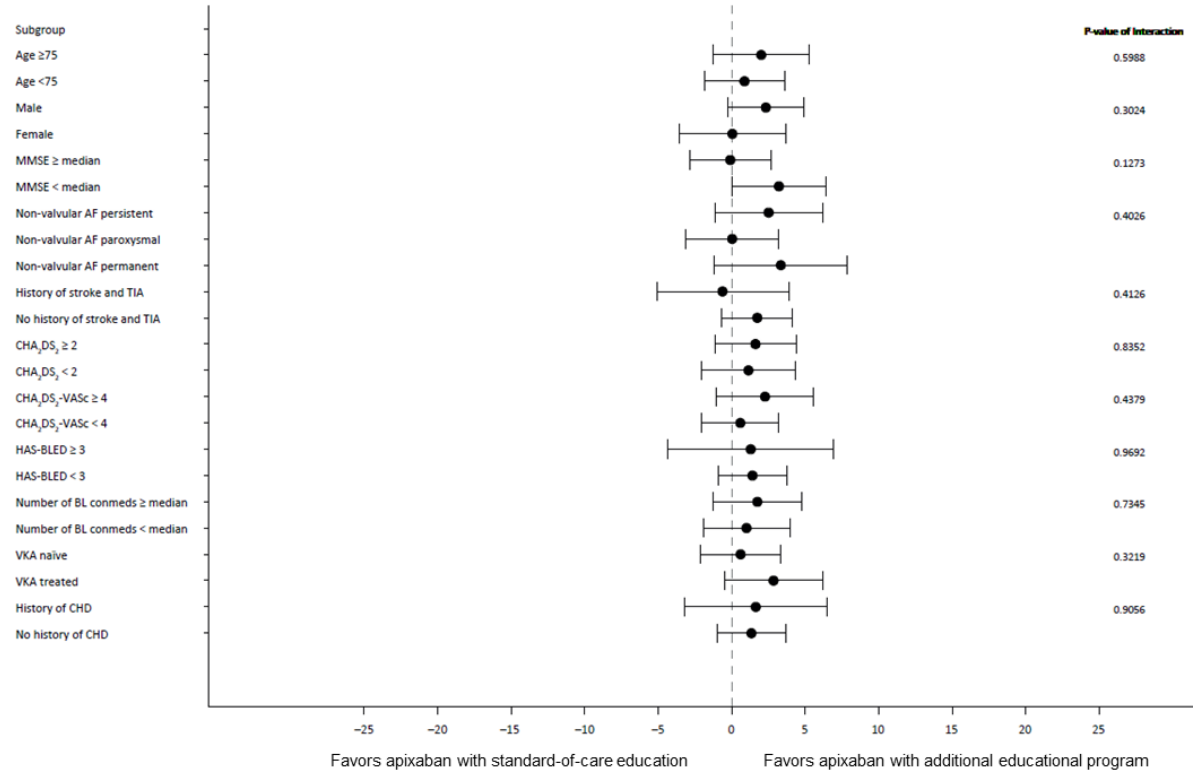
Images provided courtesy of the Aardex group (http://www.aardexgroup.com/)

Online Fig. 2 Patient flow and study populations



SOC, standard-of-care.

Online Fig. 3 Comparison between apixaban with additional educational program group (n = 579) and apixaban with SOC education group (n = 583) for implementation adherence at week 48 by subgroup (primary endpoint)



AF, atrial fibrillation; BL, baseline; CHD, coronary heart disease; conmeds, concomitant medications; MMSE, Mini Mental State Examination; SOC, standard-of- care; TIA, transient ischemic attack; VKA, vitamin-K antagonist.

Online Appendix AGEAN clinical protocol

AEGEAN

Assessment of an **E**ducation and **G**uidance program
for **E**liquis **A**dherence in **N**on-valvular atrial fibrillation

Clinical Protocol CV185220

Assessment of an Education and Guidance programme for Eliquis Adherence in Non-Valvular Atrial Fibrillation (AEGEAN)

Revised Protocol Number: 01
Incorporates amendment(s) 01

Revised version August 2013

Bristol-Myers Squibb Pfizer

PROTOCOL TITLE PAGE

Clinical Protocol CV185220

Assessment of an Education and Guidance programme for Eliquis Adherence in Non-Valvular Atrial Fibrillation (AEGEAN)

Study Director: Bruno Besse, MD
3, rue Joseph Monier - 92500 Rueil-Malmaison - France
Telephone (office): +33 1 58 83 68 64 - **Fax:** +33 1 58 83 80 15

Medical Monitor: [redacted]

24-hr Emergency Telephone Number

International: +1-248-844-7390

Bristol-Myers Squibb Research and Development

3 rue Joseph Monier
BP 325, Rueil-Malmaison Cedex - 92506, France

Avenue de Finlande 4, Building F – 1st Floor
B-1420 Braine-l'Alleud, Belgium

Pfizer Limited

Walton Oaks, Dorking Road, Tadworth
Surrey, KT20 7NS, UK

Revised Protocol Number: 01
Incorporates amendment(s) 01

Revised version August 2013

SYNOPSIS

Clinical protocol CV185220

Protocol Title: Protocol CV185220: Assessment of an Education and Guidance programme for Eliquis Adherence in Non-Valvular Atrial Fibrillation (AEGEAN).

Investigational Product(s), Dose and Mode of Administration, Duration of Treatment with Investigational Product(s): The investigational product for this trial is the patient education material for apixaban (Eliquis) adherence.
Study medication, commercial apixaban (Eliquis) tablets, 2.5 mg or 5 mg, will be taken orally two times a day (BID) for a total of 48 weeks.

Study Phase: 4

Research Hypothesis:

1. Patients treated with apixaban have a good adherence to treatment with standard of care (SOC) patient information on disease and treatment.
2. Patient adherence is enhanced by additional educational programme, such as educational package, dosing reminders, and virtual clinics.
3. Given the chronic nature of apixaban treatment for stroke prevention in atrial fibrillation (SPAF), treatment persistence will increase with adherence tools.
4. Additional educational programme for 24 additional weeks beyond the initial 24 weeks enhanced adherence.

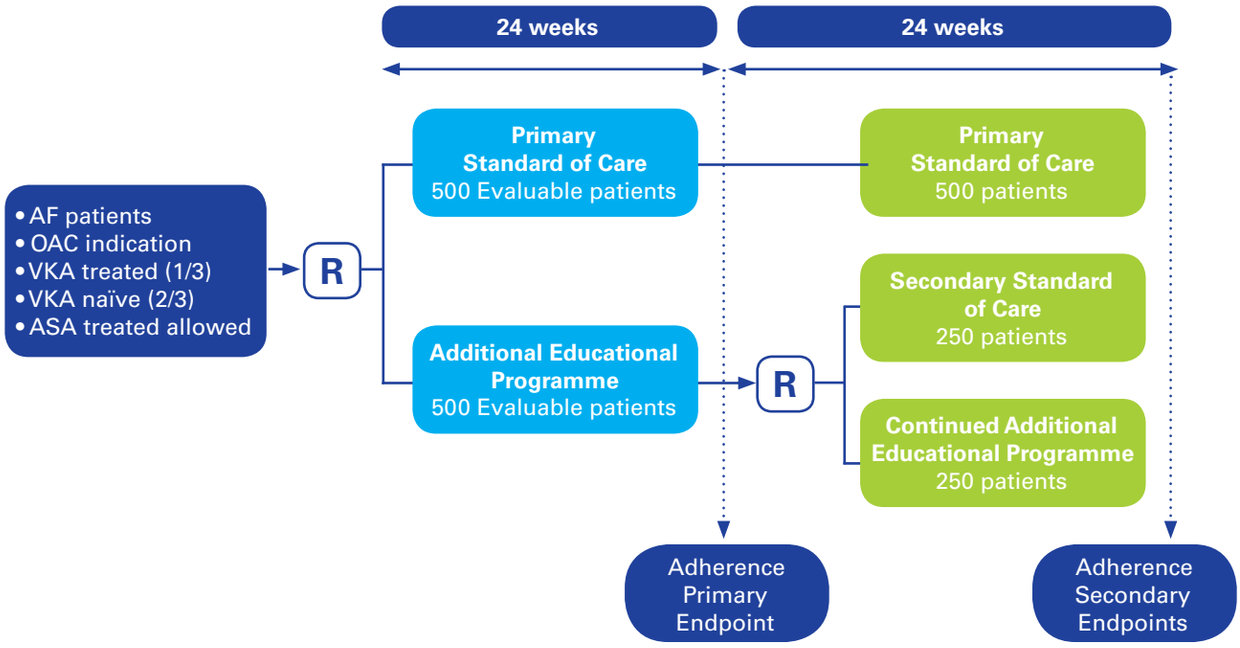
Objective: To assess the impact of educational programme on patient adherence in patients taking apixaban for SPAF at 24 weeks.

Study Design: This randomized, open-label clinical trial will study 1,112 subjects treated with apixaban for non-valvular atrial fibrillation (NVAF) for 48 weeks. Eligible subjects will be randomized 1:1 to receive either SOC information or additional education tools. After the initial 24 weeks primary endpoint period subjects in the group receiving additional education programme will be randomized 1:1 to continue receiving additional education programme or stop receiving additional education programme and revert to SOC. Patient adherence will be measured using an electronic monitoring device. At 24 weeks, the database will be locked, and an interim analysis will be conducted.

Unit of adherence: A 24-hour window where the treatment is taken as prescribed, ie, 1 tablet (5 mg or 2.5 mg, as appropriate) 2 times a day (BID). If only one dose is missed in 24 hours, it is still considered as a unit of adherence (see exception below).

Unit of non-adherence: A 24-hour window where 2 consecutive doses within 24 hours are missed. If 1 dose only is taken for several consecutive days, the first day will be considered as a unit of adherence (as above), but the subsequent days will be considered as non-adherence units. If only one dose is taken on alternate days, the second missed dose will constitute a non-adherence unit. If treatment with apixaban is withheld by the investigator during the study period, the time window during which apixaban is withheld, will not be considered for adherence. Study treatment discontinued for more than 30 consecutive days will be considered a permanent discontinuation. Adherence during a time period (eg. 24 weeks) is calculated as the percentage of adherence units within that period.
The study schematic is presented in the following figure.

Figure 3.1-1: Study Schematic



Study Population: Study subjects were >18 years of age, diagnosed with non-valvular AF with at least one risk factor for stroke, and indicated for oral anticoagulant (OAC) therapy. One third of the study population will have received prior treatment with vitamin K antagonists (VKA) and the remaining will be VKA naïve. Subjects on previous treatment with acetylsalicylic acid (ASA) for stroke prevention will be allowed.

Study Assessments and Primary Endpoint: Primary study assessment is a measurement of adherence to the study medication using an electronic monitoring device. Primary endpoint is adherence to study medication in terms of percent of adherence units over the first 24 weeks.

Statistical Methods:

Sample size determination: The study has been designed to achieve 85% power for a between group difference of 4% in the adherence at 24 weeks (percentage of days where treatment is taken at least once), assuming an intra-group standard deviation of 21.1%.

Primary analysis: The primary endpoint (adherence at 24 weeks) will be tested between the 2 study groups by the two-sample t-test performed at the 5% significance level (2-sided) with 95% confidence interval.

An interim analysis will be conducted at 24 weeks.

TABLE OF CONTENTS

1/ INTRODUCTION AND STUDY RATIONALE

1.1 Study Rationale

1.1.1 Clinical Problem and Therapeutic Landscape

Atrial Fibrillation and Stroke

Atrial fibrillation (AF) is the most common cardiac arrhythmia, accounting for approximately one third of hospitalizations attributed to cardiac rhythm disturbances and the life time risk of developing AF is 1 in 4 for adults 40 years of age or older.[1,2] During AF, electrical impulse propagation in the atria is disorganized and chaotic, with ineffective mechanical contraction. This results in remodeling of atrial anatomy, stasis of blood and activation of prothrombotic blood constituents, leading to the formation of thrombus or clot. Fragments of clot can dislodge from such thrombi and embolize to the brain to cause a stroke, or enter the systemic circulation and occlude the arterial circulation of an organ or limb to produce systemic embolism.[1]

AF is an independent risk factor for stroke. In the Framingham Heart Study (FHS), a US study that followed 5,209 men and women biennially for 34 years with objective of characterizing cardiovascular disease, AF increased stroke risk by nearly 5-fold. This increase was greater than that seen with other known cardiovascular (CV) risk factors for stroke. Even when adjusted for the CV risk factors, the increase in risk due to AF was still significantly elevated and generally increased with age (50-59 years, relative risk [RR]=4.0; 60-69 years, RR=2.6; 70-79 years, RR=3.3; and 80-89 years, RR=4.5; P<0.001 for all comparisons).[3] More than of 15% of all strokes are due to AF and such strokes are more severe than strokes not associated with AF.[4,5] Strokes in patients with AF are associated with a 70% increase in mortality, a 20% increase in the length of hospital stay, and a 40% decrease in the rate of return to home because of more severe functional impairment.[6] The outcome of such cardioembolic strokes is poor, with a mortality rate of 25% at 30 days and 50% at 1 year.[4]

Incidence of Atrial Fibrillation and Disease Burden

An estimated 2.6 million people in North America and 4.5 million people in Europe have AF. The prevalence of AF increases with age and it is estimated that in the US population AF incidence is 3.8% for ≥ 60 years and 9.0% for ≥ 80 years or more. As the US population ages, the incidence of AF in the overall population is projected to increase sharply. Similar prevalence has been reported in Europe. In a population based prospective cohort study (the Rotterdam study), the development of AF was tracked in a large (n=7,983) group of residents from the Netherlands. A steep increase in the prevalence of AF was noted with advancing age, with a prevalence of 17.8% in those 85 years or older. Prevalence of AF was reported to be higher in men than in women. The lifetime risk in those over the age of 55 was 23.8% in men and 22.2% in women. The authors concluded that the high lifetime risk to develop AF in the European population was similar to North American epidemiologic data.[7]

During the past 20 years, hospital admissions for AF have increased by 66% because of the aging population and a rising prevalence of chronic heart disease. The mortality rate in AF patients is twice that for age-matched individuals with normal sinus rhythm, reflecting, at least in part, an increase in the risk of stroke. Atrial fibrillation is an expensive public health problem. According to American Heart Association (AHA) statistics, the combined direct and indirect costs of all types of stroke in the US (with AF accounting for more than 15% of all strokes, and frequently the most debilitating strokes) were estimated to be $65.5 billion in 2008 with hospitalizations accounting for the largest share. Similar findings have been described in Europe.[8] Based on a systematic review of the literature, it was noted that costs attributable to AF had increased steeply in European countries as populations aged. For example, in the United Kingdom (UK), costs increased from £243.9 million in 1995 (1.2% of the National Health Service's [NHS's] total expenditure) to £459 million in 2000 (2.4% of NHS expenditure). These findings across Europe were driven by the cost of hospitalization. In Europe, the mean length of stay for stroke patients was noted to be 23.9 ± 26.6 days; the costs of stroke in AF patients were

significantly higher than in patients without AF: €11,799 ***vs.*** €8,817 (p<0.001).[8]

Thus, AF is a common problem with an increasing incidence. It is associated with higher risk of strokes of greater severity. Strokes have a substantial impact on both mortality and quality of life, and add significantly to the economic burden of AF. Effective treatments that reduce the risk of stroke in AF patients are desirable for both clinical and economic reasons.

Standard of Care for Stroke Prevention in Atrial Fibrillation (SPAF)

Current standard of care in long term anti-coagulation therapy is oral vitamin K antagonist (VKA) such as warfarin. It acts by inhibiting vitamin K dependent synthesis of factors FII, FVII, FIX & FX of the coagulation cascade. Vitamin K antagonists effectively reduces the risk of stroke in patients with AF, and an impressive relative risk reduction (RRR) of 62% (95% CI: 48% to 72%) when compared to placebo has been reported.[9] Warfarin has also been reported to be superior to aspirin in patients with AF and additional risk factors for stroke (RRR 36%).[10] Despite this acknowledged efficacy, warfarin and other VKAs suffer from a number of liabilities. The therapeutic range of VKAs is narrow, and dosing can be unpredictable due to genetic and environmental factors. Interactions of VKAs with food, numerous prescription, non-prescription, and herbal products are well known. The need for regular therapeutic monitoring is a barrier to effective therapy with VKAs.[11] Lack of maintenance of the INR (international normalized ratio) in the desired range may result in bleeding and the risk of intracranial haemorrhage appears to increase in the elderly, who paradoxically may benefit most from warfarin's effects to prevent ischemic stroke.[12] Warfarin is a leading cause of adverse drug events and in a number of studies done world-wide, nearly half of those who might benefit from warfarin are not presently treated with the drug, 20% because they refuse to take it. Studies have shown that in clinical practice warfarin is not always prescribed for appropriate indication and its anticoagulation effects are not always managed as well as in clinical trials. Even among those being treated with warfarin and other VKAs in well managed clinical trials, the INR is in the therapeutic range (2.0-3.0) about 60% of the time, and is not always optimal.[13] Finally, INR monitoring presents an additional cost to payers and patients; which include in addition to costs for laboratory tests, time and cost for clinicians to review of laboratory results, patient counseling, communication of dose adjustments to patients, documenting the intervention, etc.[14]

1.1.2 Apixaban for Stroke Prevention in Atrial Fibrillation (SPAF)

Apixaban (Eliquis) has marketing authorization in the European Union for use in SPAF since November 2012. This clinical study will utilize apixaban as approved for its use in the SmPC.[15] This section provides a short summary of the clinical trial experience for apixaban in SPAF.

Eliquis also has marketing authorization for use in prevention of venous thromboembolic events (VTE) in adult patients who have undergone elective hip or knee replacement surgery since 2011.

Efficacy of Apixaban Therapy in SPAF

Apixaban is a novel, orally active, selective inhibitor of the coagulation factor Xa (FXa) developed by BMS as an anticoagulant and antithrombotic agent. Apixaban (BMS562247), is a reversible and highly potent inhibitor of human FXa, with an inhibitor constant (Ki) of 0.08 ± 0.01nM, and a high degree of selectivity over other coagulation proteases and structurally related enzymes involved in digestion and fibrinolysis.

The efficacy and safety of apixaban for the prevention of stroke and systemic embolism in AF patients was demonstrated in 2 randomized, double-blind, Phase 3 trials: ARISTOTLE (apixaban *vs.* warfarin; n=18,201) in patients suitable for VKA therapy[16] and AVERROES (apixaban *vs.* aspirin; n=5,599) in patients unsuitable for VKA therapy.[17] Both studies were conducted in patients with non-valvular, persistent, paroxysmal, or permanent AF or atrial flutter, and 1 or more additional risk factors.

In the ARISTOTLE trial, the rate of the primary outcome (ischemic or hemorrhagic stroke or systemic embolism) was 1.27% per year in the apixaban group, as compared with 1.60% per year in the warfarin group (HR=0.79; P<0.001 for non-inferiority; P=0.01 for superiority).[16]

The AVERROES trial demonstrated a clear efficacy benefit in favour of apixaban and an independent Data and Safety Monitoring Board (DSMB) recommended early termination after 1.1 years of mean study participation. Rate of primary outcome events (stroke or systemic embolism) in patients assigned to apixaban was 1.6% per year, compared to 3.7% per year among those assigned to aspirin (HR=0.45; P<0.001).[18]

Adherence programme being investigated in this study has the potential to improve apixaban adherence beyond the SOC patient information, and confer outcomes benefit seen in the ARISTOTLE and AVERROES trials.

Safety Observations for Apixaban

Over the two Phase 3 studies in patients with AF, 24.4% (ARISTOTLE) and 9.6% (AVERROES) of the patients experienced adverse reactions.[15]

Common adverse reactions for apixaban were epistaxis, contusion, haematuria, haematoma, eye haemorrhage, and gastrointestinal haemorrhage.[15]

Increased incidence of bleeding events is a known risk associated with all anticoagulation therapies.

A pre-defined secondary endpoint for the ARISTOTLE trial was major bleeding events (as defined by International Society on Thrombosis and Hemostasis [ISTH]). This endpoint was met. Apixaban was superior compared to warfarin and showed a statistically lower event risk when compared to warfarin for all major bleeding events, with the exception of gastrointestinal bleeding, where it showed no statistical difference between the 2 treatment arms (see Table 1.1.2-1). The rate of death from any cause was 3.52% in apixaban group and 3.94% in the warfarin group (HR=0.89; P=0.047).

Table 1.1.2-1: ARISTOTLE: Bleeding Incidences

Outcome	Apixaban n (%)	Warfarin n (%)	HR (95% CI) P-value
Major bleeding (ISTH)	327 (2.13)	462 (3.09)	0.69 (0.60, 0.80) <0.001
Intracranial	52 (0.33)	122 (0.80)	0.42 (0.30, 0.58) <0.001
Other location	275 (1.79)	340 (2.27)	0.79 (0.68, 0.93) 0.004
Gastrointestinal	105 (0.76)	119 (0.86)	0.89 (0.70, 1.15) 0.37
Major or clinically relevant non-major bleeding	613 (4.07)	877 (6.01)	0.68 (0.61, 0.75) <0.001
GUSTO severe bleeding	80 (0.52)	172 (1.13)	0.46 (0.35, 0.60) <0.001
GUSTO moderate severe bleeding	199 (1.29)	328 (2.18)	0.60 (0.50, 0.71) <0.001
TIMI major bleeding	148 (0.96)	256 (1.69)	0.57 (0.46, 0.70) <0.001
TIMI major or minor bleeding	239 (1.55)	370 (2.46)	0.63 (0.54, 0.75) <0.001
Any bleeding	2356 (18.1)	3060 (25.8)	0.71 (0.68, 0.75) <0.001

Source: Granger, ***et al,*** 2011.16

In the AVERROES study, major bleeding occurred in 1.4% per year in the apixaban group and 1.2% per year in the aspirin group (HR=1.13; P=0.57); there were 11 cases of intracranial bleeding with apixaban and 13 with aspirin. The rate of death was 3.5% per year in the apixaban group and 4.4% per year in the aspirin group (HR=0.79; P=0.07). The risk of a first hospitalization for cardiovascular causes was reduced with apixaban as compared with aspirin (12.6% per year ***vs.*** 15.9% per year, P<0.001).[18]

1.1.3 Adherence and Treatment for Stroke Prevention in Atrial Fibrillation

Atrial fibrillation is a chronic condition and SPAF requires life-long therapy. Adherence and persistence to the treatment are critical. Patient non-adherence is highly prevalent and of great public health concern for all long term oral medications, including warfarin (see Table 1.1.3-1). Adherence is a complex issue, relating mainly to ease of use, side effects experienced, and perceived efficacy (see table below World Health Organisation [WHO] categories).[19]

Table 1.1.3-1: Reasons for Medical Non-adherence

Categories of non-adherence	Examples
Health system	Poor quality of provider-patient relationship; poor communication; lack of access to healthcare; lack of continuity of care
Disease condition	Asymptomatic chronic disease (lack of physical cues); mental health disorders (eg. depression)
Patient	Physical impairment (e.g. vision impairment or impaired dexterity); cognitive impairment; psychological/behavioural; younger age
Therapy	Complexity of regime; side effects
Social-economic	Low literacy; poor social support; high medication costs

Source: WHO, 2003.[19]

Extensive research in adherence, Ascertaining Barriers for Compliance (ABC) project, was funded by the European Community Seventh Framework Programme (FP7) with the aim of developing evidence based recommendations to inform the European policy regarding patient adherence.[20] Final report of the ABC project identified 3 components of medication adherence: initiation (occurs when the patient takes the first dose of a prescribed medication), implementation (period when a patient's actual dosing corresponds to the prescribed dosing regimen), and discontinuation (occurs when the patient stops taking the prescribed medication). Persistence is the length of time between initiation and discontinuation. The report recognised that a system based approach, with role for all stakeholders, will be required. Of several recommendations of the ABC projects, following interventions are geared towards patients and their care-givers:[20]

- Education and information to increase the knowledge about disease and treatment.
- Motivational and performance based feedback.
- Prioritize intervention when a medication is newly prescribed, a change in treatment or dosing regimen is considered, several medications are prescribed, treatment goals are not achieved, adverse reactions are anticipated or experienced, and when patient requires assistance with taking the medication.

The report also recommended a collaborative approach between patients and healthcare professionals to facilitate optimal use of medicines and patient-centered care. The report recommended that the healthcare professional and the patient should:[20]

- Discuss the patients' preferences for treatment and their health and medication related beliefs.
- Develop partnership in decision making.
- Build trust in the healthcare professional.

Adherence to OAC therapy can be challenging because of several reasons specific to management of SPAF. Importance of rigorous patient education have been recognized.[21,22]

Specifically for FXa inhibitors such as apixaban, since these treatments do not require routine efficacy monitoring, a key advantage over warfarin, there is a perception amongst some HCPs that long term adherence for apixaban may not be as good as warfarin, the current standard of care. Although FXa inhibitors are superior in efficacy and safety to warfarin, some HCPs may prefer warfarin over an FXa inhibitor because warfarin requires routine monitoring and supervision, thus potentially ensuring greater adherence. The key aim of this clinical study is to investigate the medium term implementation phase adherence (adherence during the implementation phase) of apixaban with education programme on initiation, and whether these additional educational and reminder tools will enhance adherence through innovative technology.

This Phase 4 post marketing authorisation study aims for following:

1. Ensure appropriate usage of apixaban.
2. Evaluate value of educational programme.
3. Provide information regarding how to improve apixaban adherence for the benefit of patients.
4. Support HCP objective of improving patient education.

1.2 Research Hypothesis

1. Patients treated with apixaban have a good implementation phase adherence to treatment with standard of care (SOC) patient information on disease and treatment.
2. Implementation phase adherence can be enhanced by additional educational tools, such as educational package, dosing reminders, and virtual clinics.
3. Given the chronic nature of apixaban treatment for stroke prevention in atrial fibrillation (SPAF), persistence of implementation phase adherence to the treatment will improve with adherence tools.
4. Additional educational programme for 24 additional weeks beyond the initial 24 weeks will enhance adherence.

1.3 Objectives

1.3.1 Primary objective

- To assess the impact of educational programme on implementation phase adherence in patients taking apixaban for SPAF at 24 weeks.

1.3.2 Secondary objective

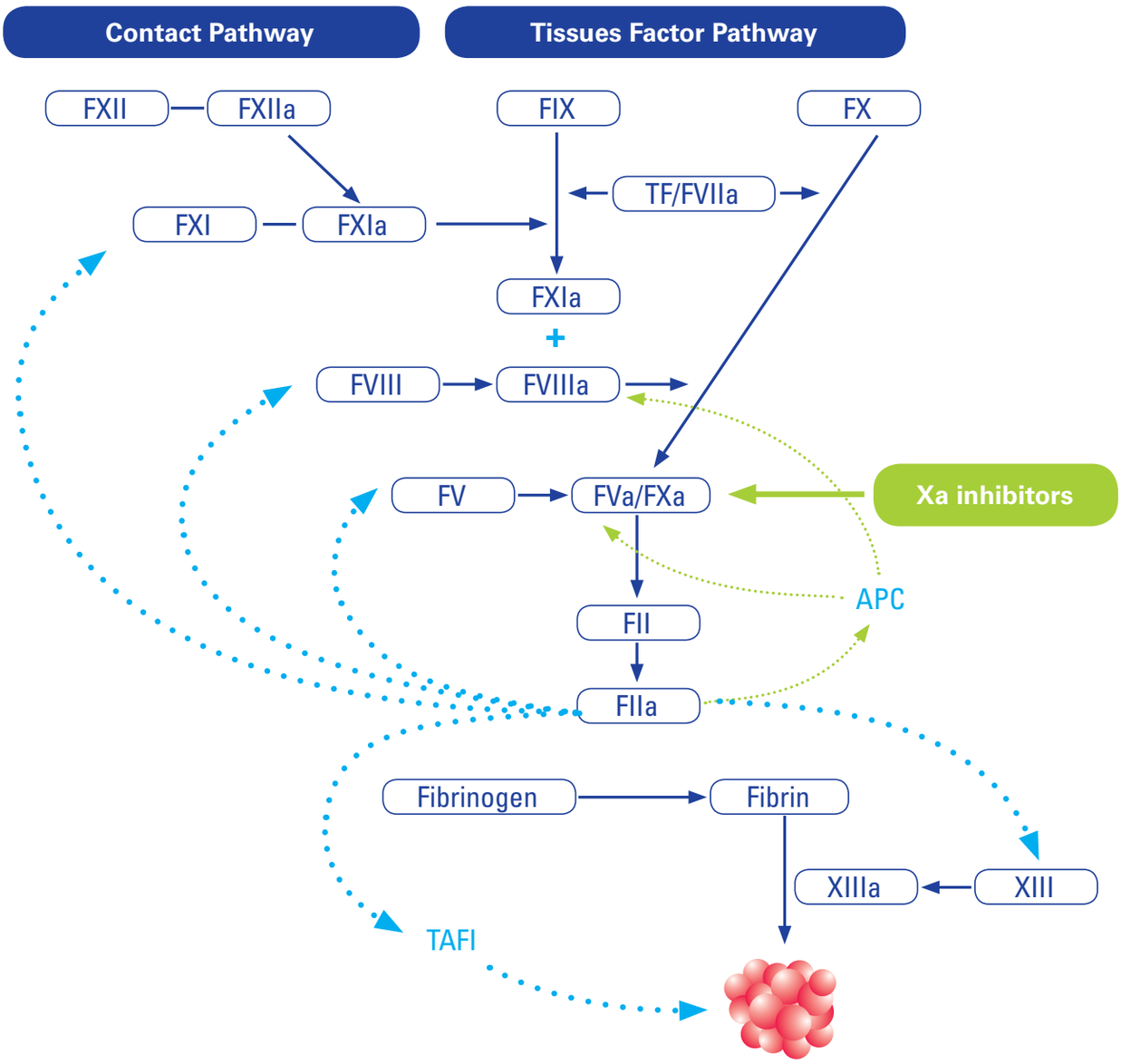
- To identify predictive risk factors linked to non-adherence in patients treated with apixaban.
- To compare implementation phase adherence to apixaban treatment with secondary SOC *versus* (1) primary SOC and (2) continued additional educational program.
- To compare implementation phase adherence to apixaban treatment at 12 weeks *vs.* 24 weeks within groups.
- To evaluate impact of educational programme on safety profile of apixaban.

1.4 Product Development Background

Apixaban is a novel, orally active, highly potent, reversible inhibitor of human FXa with an inhibitor constant (Ki) of 0.08 ± 0.01nM and a high degree of selectivity over other coagulation proteases and structurally related enzymes involved in digestion and fibrinolysis.

FXa occupies a pivotal role in the clotting cascade, converting prothrombin to thrombin. Thrombin has multiple functions, converting fibrinogen to fibrin, promoting fibrin cross-linking by activating factor XIII, providing positive feedback activation of coagulation by activating factors V, VIII, and XI, activating the protein C anticoagulant pathway, and activating thrombin activatable fibrinolysis inhibitor (TAFI) to protect the clot from premature degradation (Figure 1.4-1). Thrombin is also a powerful platelet agonist, activating platelets and recruiting additional platelets into the platelet-rich thrombus. FXa inhibition decreases conversion of prothrombin to active thrombin, thereby diminishing fibrin formation, and reducing coagulation and platelet activation.[23]

Figure 1.4-1: The Hemostatic Pathway and Site of Action of Inhibitors of Activated Factor X (FXa)



Anticoagulants act at different stages of the coagulation pathways. Warfarin and other coumarin derivatives affect the vitamin K-dependent clotting factors (II, VII, IX,X). Heparin and its derivatives (unfractionated heparin [UFH], low-molecular-weight heparin [LMWH], fondaparinux) act through an antithrombin (AT)-mediated mechanism. Apixaban directly inhibits FXa. Compared with UFH, LMWHs (including enoxaparin) have relatively more effect on inhibiting FXa than FIIa, while the pentasaccharide, fondaparinux, selectively inhibits FXa. In the OASIS-5 trial involving more than 20,000 patients with non-ST-elevation acute coronary syndromes, fondaparinux 2.5 mg once daily given by subcutaneous injection was as effective as enoxaparin in preventing thrombotic events during the treatment period, but reduced the risk of bleeding by one half.[24]

The reduction in bleeding with fondaparinux translated into fewer ischemic events and deaths at 30 days. These findings highlight the potential of FXa inhibition to be an effective and safe approach to anticoagulant therapy. Given the established utility of FXa inhibition in the prevention and treatment of venous and arterial thrombotic disease, an orally available agent that is suitable for long-term management would be desirable.

1.5 Overall Risk/Benefit Assessment

In the ARISTOTLE trial, the rate of major bleeding was 2.13% per year in the apixaban group, as compared with 3.09% per year in the warfarin group (HR=0.69; P<0.001), and the rates of death from any cause were 3.52% and 3.94%, respectively (HR=0.89; P=0.047). The rate of hemorrhagic stroke was 0.24% per year in the apixaban group, as compared with 0.47% per year in the warfarin group (HR=0.51; P<0.001). Therefore, it was concluded that, in patients with atrial fibrillation with at least one additional risk factor for stroke, apixaban was superior to warfarin in preventing stroke or systemic embolism, caused less bleeding, and resulted in lower mortality.[16]

In the AVERROES study, major bleeding occurred in 1.4% per year in the apixaban group and 1.2% per year in the ASA group (HR=1.13; P=0.57); there were 11 cases of intracranial bleeding with apixaban and 13 with ASA. The rate of death was 3.5% per year in the apixaban group and 4.4% per year in the ASA group (HR=0.79; P=0.07). The risk of a first hospitalization for cardiovascular causes was reduced with apixaban as compared with aspirin (12.6% per year *vs.* 15.9% per year, P<0.001).[18] It was concluded that in patients with atrial fibrillation for whom vitamin K antagonist therapy was unsuitable, apixaban reduced the risk of stroke or systemic embolism without significantly increasing the risk of major bleeding or intracranial hemorrhage.

Non-adherence to apixaban therapy has 2 potential effects: lack of clinical efficacy which may lead to lack of benefits to medication in relation to stroke risk reduction, whereas over adherence may potentially increase the risk of bleeding events.

2/ ETHICAL CONSIDERATIONS

2.1 Good Clinical Practice

This study will be conducted in accordance with Good Clinical Practice (GCP), as defined by the International Conference on Harmonisation (ICH) and in accordance with the ethical principles underlying European Union Directive 2001/20/EC and the United States Code of Federal Regulations, Title 21, Part 50 (21CFR50).

The study will be conducted in compliance with the protocol. The protocol and any amendments and the subject informed consent will receive Institutional Review Board/Independent Ethics Committee (IRB/IEC) approval/favorable opinion prior to initiation of the study.

All potential serious breaches must be reported to BMS immediately. A serious breach is a breach of the conditions and principles of GCP in connection with the study or the protocol, which is likely to affect, to a significant degree, the safety or physical or mental integrity of the subjects of the study or the scientific value of the study.

Study personnel involved in conducting this study will be qualified by education, training, and experience to perform their respective task(s).

This study will not use the services of study personnel where sanctions have been invoked or where there has been scientific misconduct or fraud (eg, loss of medical licensure, debarment).

2.2 Institutional Review Board/ Independent Ethics Committee

Before study initiation, the investigator must have written and dated approval/favorable opinion from the relevant IRB/IEC for the protocol, consent form, subject recruitment materials/process (eg, advertisements), and any other written information to be provided to subjects. The investigator or BMS should also provide the IRB/IEC with a copy of the Investigator Brochure or product labeling, information to be provided to subjects and any updates.

The investigator or BMS should provide the relevant IRB/IEC with reports, updates and other information (eg, expedited safety reports, amendments and administrative letters) according to regulatory requirements or institution procedures.

2.3 Informed Consent

Investigators must ensure that subjects are clearly and fully informed about the purpose, potential risks, and other critical issues regarding clinical studies in which they volunteer to participate.

In situations where consent cannot be given to subjects, their legally acceptable representatives are clearly and fully informed about the purpose, potential risks, and other critical issues regarding clinical studies in which the subject volunteers to participate.

BMS will provide the investigator with an appropriate (ie, Global or Local) sample informed consent form which will include all elements required by ICH, GCP and applicable regulatory requirements. The sample informed consent form will adhere to the ethical principles that have their origin in the Declaration of Helsinki.

Investigators must:

1. Provide a copy of the consent form and written information about the study in the language in which the subject is most proficient prior to clinical study participation. The language must be non-technical and easily understood.
2. Allow time necessary for subject or subject's legally acceptable representative to inquire about the details of the study.
3. Obtain an informed consent signed and personally dated by the subject or the subject's legally acceptable representative and by the person who conducted the informed consent discussion.
4. Obtain the IRB/IEC's written approval/favourable opinion of the written informed consent form and any other information to be provided to the subjects, prior to the beginning of the study, and after any revisions are completed for new information.

5. If informed consent is initially given by a subject's legally acceptable representative or legal guardian, and the subject subsequently becomes capable of making and communicating their informed consent during the study, then consent must additionally be obtained from the subject.
6. Revise the informed consent whenever important new information becomes available that is relevant to the subject's consent. The investigator, or a person designated by the investigator, should fully inform the subject or the subject's legally acceptable representative or legal guardian, of all pertinent aspects of the study and of any new information relevant to the subject's willingness to continue participation in the study. This communication should be documented.

The consent form must also include a statement that BMS and regulatory authorities have direct access to subject records.

The rights, safety, and well-being of the study subjects are the most important considerations and should prevail over interests of science and society.

3/ INVESTIGATIONAL PLAN

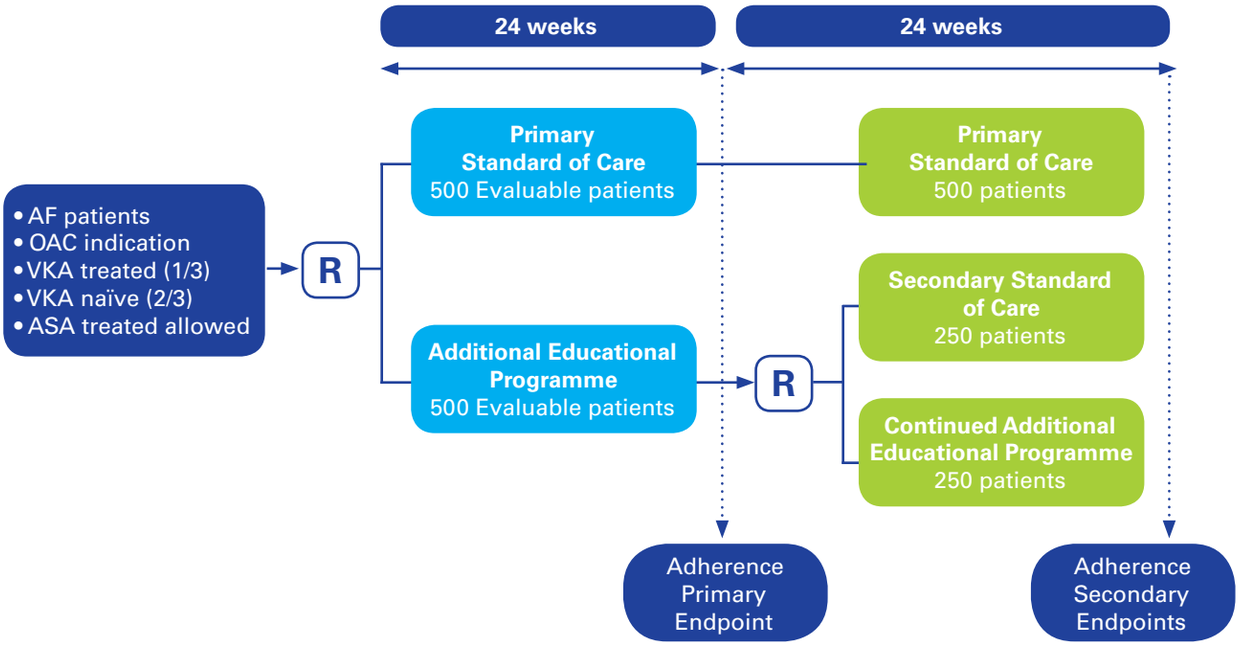
3.1 Study Design and Duration

This randomized, open-label clinical trial is designed to examine adherence to apixaban therapy with enhanced patient education programme. Approximately 1,112 subjects will be randomized with apixaban 5 mg two times daily (BID) or 2.5 mg BID for specific sub-population (see Section 4.1) in accordance with approved SmPC. Eligible patients will be initially randomized 1:1 to receive either SOC patient information or additional educational programme.

After the initial primary endpoint period of 24 weeks, subjects in the group receiving additional education programme will be randomized 1:1 for the second time to either continue receiving additional education programme or stop receiving additional education programme and revert to SOC. The 3 groups after this second randomization will be henceforth referred to as:

- Primary SOC group: those that never receive additional education programme.
- Continued additional education group: those that receive additional education programme for 48 weeks.
- Secondary SOC group: those who receive additional education programme for 24 weeks then revert to SOC after the second randomization. Study schematic is presented in Figure 3.1-1.

Figure 3.1-1: Study Schematic



An electronic monitoring device (EMD), Helping Hand®, will be dispensed to all subjects along with the study medication.

The total study duration is 48 weeks. Following the first randomization, the study visits will occur at 4 weeks, 12 weeks, 24 weeks, 36 weeks, and 48 weeks. At 24 weeks, the database will be locked, and an interim analysis will be conducted as specified in Section 8.5, Interim Analysis.

Standard of Care (SOC):

- Subject Alert card.
- Patient information provided by the investigator as per SOC.

Additional educational programme:

- Patient education leaflet (see Appendix 1): A patient leaflet explaining both the AF disease and anticoagulant treatment for stroke prevention in AF will be provided directly to the subject.
- Reminder tools: Every patient will be invited to choose one or several of the following tools:
- Dose reminders (key rings, refrigerator magnet)

- SMS (short message service) alert *service on their mobile phone*
- SmartPhone application

- Virtual clinics (Appendix 2): In order to be relevant and to take into account language and cultural differences, virtual clinics will be organized at country level using existing anticoagulant clinics staff (physicians, nurses, etc) at one specified site. Each virtual clinic centre may have different organization and use slight different content in order to fit the local habits, the general principles and call frequency (detailed in Appendix 2) will be the same for all the centres:

- The virtual clinic will call the subject within 1 week after randomisation. The main purpose of this first call will be to make sure the patient correctly understood the disease, the anticoagulant treatment and the importance of adherence. General information and advices for anticoagulant treatment will be provided and the patients will be informed that a toll-free number is available in case they have any further questions (the number of calls each patient made will be recorded).
- Follow-up calls: The main purpose is to reinforce the importance of adherence to therapy. The nurse will ask about adherence to therapy and if appropriate will advice accordingly. Subjects may call the virtual clinic as often as needed. Data from the EMD will not be available to the virtual clinic staff.

The data from the device will be uploaded at every study visit. Extent of adherence will be quantified using adherence and non-adherence units defined as follows. Adherence during the 48 weeks will be calculated as the percentage of adherence units.

- Unit of adherence: A 24-hour window when the treatment is taken as prescribed, ie, 1 tablet (5 mg or 2.5 mg, as appropriate) 2 times a day (BID). If only one dose is missed in 24 hours, it is still considered as a unit of adherence (see exception below).
- Unit of non-adherence: A 24-hour window where 2 consecutive doses within 24 hours are missed. If 1 dose only is taken for several consecutive days, the first day will be considered as a unit of adherence (as above), but the subsequent days will be considered as non-adherence units. If only one dose is taken on alternate days, every second missed dose will constitute a non-adherence unit.

Adherence during a time period (eg. 24 weeks) is calculated as the percentage of adherence units within that period.

If treatment with apixaban is withheld by the investigator during the study period, the time window during which apixaban is withheld, will not be considered for adherence.

Study treatment discontinued for more than 30 consecutive days will be considered a permanent discontinuation.

There will be no follow-up after the 48-weeks visit. The end of the study will be when the last subject completes the last study visit. There will be no follow-up for subjects who discontinue study treatment prior to end of the study, but the vital status of these patients should be obtained at the end of the theoretical follow-up phase.

3.2 Post Study Access to Therapy

At the end of the study, approximately 12 months after baseline visit, BMS **will not** continue to supply study drug to subjects. After study completion, the investigator should ensure that the subject receives appropriate standard of care to treat the condition under study.

If apixaban is not commercially available in a country when the study ends, investigators will discuss with BMS available options for continuing the treatment for their individual subjects.

3.3 Study Population

For entry into the study, all the following criteria MUST be met.

3.3.1 Inclusion Criteria

1) Signed Written Informed Consent

a) Subject must provide signed written informed consent.

2) Target Population

a) Patients with diagnosed non-valvular atrial fibrillation or atrial flutter (documented by 12-lead ECG or a Holter recording) and eligible for OAC therapy.

b) Presence of at least one of the following risk factors for stroke:

- prior stroke or transient ischaemic attack (TIA)
- age ≥ 75 years
- hypertension
- diabetes mellitus
- symptomatic heart failure (NYHA Class ≥ II)

c) Must be able to self-administer treatment.

d) Either VKA treated or VKA naïve.

i) VKA treated patients must have received the VKA treatment for ≥3 months.

ii) VKA naïve patients must not have received VKA treatment for more than 30 days within the last 12 months.

Patients who are not described by either of the above criteria (for example, a patient treated with VKA for 40 days within the last 12 months) are not eligible for the study.

e) Patients previously treated with ASA for stroke prevention are allowed (and will switch to apixaban).

f) Patients with screening Mini-mental state examination score (MMSE) more than 24 (out of 30).

g) Patient re-enrollment: This study does not permit the re-enrollment of a patient that has discontinued the study as a pre-treatment failure.

3) Age and Reproductive Status

a) Men and women ≥ 18 years of age.

b) Women of childbearing potential (WOCBP) must use method(s) of contraception based on the tables in Appendix 3. For a teratogenic study drug and/or when there is insufficient information to assess teratogenicity (preclinical studies have not been done), a highly effective method(s) of contraception (failure rate of less than 1% per year) is required. The individual methods of contraception and duration should be determined in consultation with the investigator. WOCBP must follow instructions for birth control when the half life of the investigational drug is less than 24 hours, contraception should be continued for a period of 30 days after the last dose of investigational product.

c) WOCBP must have a negative urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) within 24 hours prior to the start of study medication.

d) Women must not be breastfeeding.

e) Men who are sexually active with WOCBP must use any contraceptive method with a failure rate of less than 1% per year. The investigator shall review contraception methods and the time period that contraception must be followed. Men that are sexually active with WOCBP must follow instructions for birth control when the half life of the investigational drug is less than 24 hours, contraception should be continued for a period of 90 days after the last dose of investigational product.

f) Women who are not of childbearing potential (ie, who are postmenopausal or surgically sterile; see Section 3.3.3 for the definition of WOCBP) and azoospermic men do not require contraception.

3.3.2 Exclusion Criteria

1) Target Disease Exceptions

a) Atrial fibrillation or flutter due to reversible causes (e.g. thyrotoxicosis, pericarditis).

b) Clinically significant (moderate or severe) mitral stenosis.

c) Cardiac valvular disease requiring surgery.

2) Medical History and Concurrent Diseases

a) Conditions other than atrial fibrillation that require chronic anticoagulation (e.g., prosthetic mechanical heart valve, venous thromboembolism; also see Section 3.4, Concomitant Treatments).

b) Patient with serious bleeding in the last 6 months or with a lesion or condition at high risk of bleeding such as:

- Active peptic ulcer disease, current or recent gastrointestinal ulceration.
- Known or suspected oesophageal varices.
- Recent ischemic stroke (within 7 days).
- Recent brain or spinal injury or intracranial haemorrhage.
- Recent brain, spinal or ophthalmic surgery.
- Arteriovenous malformations.
- Vascular aneurysms.
- Major intraspinal or intracerebral vascular abnormalities.
- Documented hemorrhagic tendencies or blood dyscrasias.
- Presence of malignant neoplasms at high risk of bleeding.

c) Persistent, uncontrolled hypertension (systolic BP > 180 mm Hg, and/or diastolic BP > 100 mm Hg).

d) Active infective endocarditis.

e) Hepatic disease associated with coagulopathy and clinically relevant bleeding risk.

f) Active alcohol or drug abuse, or psychosocial reasons that make study participation impractical.

g) Severe co-morbid condition with life expectancy ≤ 1 year.

3) Physical and Laboratory Test Findings

a) Severe renal insufficiency (creatinine clearance must be calculated - Cockroft-Gault - in all patients; any patient with a calculated creatinine clearance < 15 ml/min is excluded) or patients undergoing dialysis.

b) ALT (alanine aminotransferase) or AST (aspartate aminotransferase) > 2 times upper limit of normal or a total bilirubin > 1.5 times upper limit of normal (unless an alternative causative factor [e.g., Gilbert's syndrome] is identified)

c) Haemoglobin < 9 g/dL

d) Platelet count < 100,000/mm^3

4) Allergies and Adverse Drug Reaction

a) Allergy or adverse reaction to apixaban or any of the excipients.

5) Sex and Reproductive Status

a) Women who are pregnant or breast feeding.

b) Women of child bearing potential (WOCBP, see Section 3.3.3 for definition) who are unwilling to meet the study requirements for pregnancy testing or are unwilling or unable to use an acceptable method to avoid pregnancy.

c) Sexually active fertile men not willing to use effective birth control if their partners are WOCBP.

6) Prohibited Treatments and/or Therapies

a) See Section 3.4.1 of the protocol (Prohibited and/or Restricted Treatments) for therapies which are prohibited at study entry.

b) Patients previously included or currently enrolled in clinical trials of apixaban.

c) Required treatment with ASA > 165 mg/day.

d) Simultaneous treatment with a thienopyridine (e.g., clopidogrel, ticlopidine; see Section 3.4.2.1, Acetylsalicylic acid [ASA] and Thienopyridines) or prasugrel or ticagrelor.

e) Patients receiving rivaroxaban, dabigatran, or apixaban.

f) Planned major surgery or/and invasive procedure.

g) Planned atrial fibrillation or flutter ablation procedure.

h) Planned cardioversion.

7) Other Exclusion Criteria

a) Prisoners or subjects who are involuntarily incarcerated.

b) Subjects who are compulsorily detained for treatment of either a psychiatric or physical (eg, infectious disease) illness.

c) Use of an unapproved, investigational drug or device within the past 30 days or prior participation into an apixaban clinical study.

d) Inability to comply with protocol visit and activity requirements.

e) Patients unable to self-administer study medication.

f) Patients who are hospitalized or scheduled to be hospitalized or for whom treatment is administered by a third person (eg, nurse, relatives).

g) Patients in long term residential care.

Eligibility criteria for this study have been carefully considered to ensure the safety of the study patients and that the results of the study can be used. It is imperative that patients fully meet all eligibility criteria.

3.3.3 Women of Childbearing Potential

Women of childbearing potential (WOCBP) is defined as any female who has experienced menarche and who has not undergone surgical sterilization (hysterectomy or bilateral oophorectomy) or is not postmenopausal. Menopause is defined clinically as 12 months of amenorrhea in a woman over age 45 in the absence of other biological or physiological causes. In additional, women under the age of 62 must have a documented serum follicle stimulating hormone, (FSH) level > 40 mIU/mL.

Women treated with hormone replacement therapy, (HRT) are likely to have artificially suppressed FSH levels and may require a washout period in order to obtain a physiologic FSH level. The duration of the washout period is a function of the type of HRT used:

- 1 week minimum for vaginal hormonal products, (rings, creams, gels).
- 4 week minimum for transdermal products.
- 8 week minimum for oral products.

Other parenteral products may require washout periods as long as 6 months.

3.4 Concomitant Treatments

3.4.1 Prohibited and/or Restricted Treatments

The following medications or therapies are prohibited:

1. Potent inhibitors of CYP3A4 (e.g., azole antifungals [itraconazole and ketoconazole], macrolide antibiotics [clarithromycin and telithromycin], protease inhibitors [ritonavir, indinavir, nelfinavir, atazanavir, and saquinavir], and nefazadone).
2. Other antithrombotic agents (e.g., UFH, LMWH [enoxaparin, dalteparin etc], direct thrombin inhibitors, heparin derivatives [fondaparinux], oral anticoagulants [warfarin, rivaroxaban, dabigatran etc], GP IIb/IIIa inhibitors [e.g., abciximab, eptifibatide, tirofiban]) except under the circumstances of switching therapy to apixaban, or when UFH is given at doses necessary to maintain a patent central venous or arterial catheter.

If treatment with an agent above becomes necessary during the course of the study, apixaban should be temporarily interrupted and restarted as soon as possible following discontinuation of the prohibited medication or therapy.

Restricted agents:

The administration of the following agents in subjects on study drug should be done cautiously given the increased risk of bleeding. In such cases, consideration of interruption of the study drug may be warranted; this decision should be made after a careful assessment of the risks and potential benefits.

1. Chronic (> 3 months) daily NSAIDs.

2. Cytotoxic or myelosuppressive therapy.

Patients taking a thienopyridine at the time of potential enrollment are not eligible for inclusion in the study. Patients who develop an indication for a thienopyridine during the study will discontinue from the study (see Section 3.4.2.1 Acetylsalicylic Acid and Thienopyridines).

In addition, if a subject is currently receiving an agent that is a potent inducer of CYP3A4 (e.g., rifampin), the investigator should carefully evaluate that subject's risk of thromboembolism, hence the subject's appropriateness to be enrolled into the study, as the plasma concentration of apixaban may be lower than that in subjects not receiving a potent inducer of CYP3A4.

3.4.2 Other Restrictions and Precautions

The following precautions and restrictions must be followed to preserve study integrity and subject safety:

1. Patients should comply with the prescribed dosing and visit schedule.
2. Patients should be instructed that, prior to taking any new prescriptions and/or over-the-counter medications, they should discuss this thoroughly with the Investigator to ensure the new medication is not prohibited by the study protocol.

Since apixaban is a direct inhibitor of FXa, it acts as an anticoagulant. The safety of apixaban in combination with other anticoagulants such as unfractionated heparin, low molecular weight heparin, or fondaparinux, has not been evaluated. Thus, the investigator must stop study drug to allow for its clearance from the body prior to initiating treatment with another anticoagulant or performing invasive procedures. In normal human volunteers, apixaban has a half-life of approximately 12 hours. Investigators should contact the Medical Monitor/Trial Helpline to discuss initiation of other anticoagulants for a study subject.

3.4.2.1 Acetylsalicylic Acid (ASA) and Other Anti-platelet Therapy

Investigators must stop ASA in patients taking ASA at baseline except for patients that receive ASA for another indication than AF and at a dose not exceeding 165 mg QD.

Patients taking a thienopyridine (clopidogrel or ticlopidine), ticagrelor or prasugrel at baseline are not eligible to be included in the study (see Table 3.4.2.1-1).

Table 3.4.2.1-1: Eligibility for Inclusion of Patients Taking Antiplatelet Therapy at Baseline

Baseline Antiplatelet	Indication	Eligibility	Recommended Approach
ASA	ACS, Stroke, PAD	Yes	Continued ASA therapy is strongly discouraged. If ASA is continued, the dose should not exceed 165 mg QD
Thienopyridine[a], ticagrelor and prasugrel	ACS, Stroke, PAD	No	Reassess eligibility for inclusion at completion of thienopyridine, ticagrelor and prasugrel
Dual antiplatelet therapy	ACS, Stents	No	Reassess eligibility for inclusion at completion of "dual" antiplatelet treatment

[a] Thienopyridine includes clopidogrel or ticlopidine.

Patients who develop a clear indication for antiplatelet therapy during the study will require reevaluation for continuation in the study. If open-label ASA is used, the dose should not exceed 165 mg QD and the subject should be withdrawn from the study if any other anti-platelet agent is used (see Table 3.4.2.1-2).

Table 3.4.2.1-2: Management of Patients who Develop an Indication for Antiplatelet Therapy During the Course of the Study

Possible Concomitant Treatment	Indication	Recommended Approach
ASA	ACS, Stroke, PAD	Starting open-label ASA therapy is strongly discouraged (see Section 1.4.1 for rationale). If open-label ASA is started, the dose should not exceed 165 mg QD. Continue study treatments.
Thienopyridine[a], ticagrelor and prasugrel	ACS, Stroke, PAD	Do not start thienopyridine, ticagrelor or prasugrel and continue study treatments; unless there is a clear indication, in which case the subject should be withdrawn from the study.
Dual antiplatelet therapy	ACS, Stents	Commence dual antiplatelet therapy, subject should be withdrawn from the study. See section 1.4 for rationale

[a] Thienopyridine includes clopidogrel or ticlopidine.

3.4.2.2 Oral Anticoagulants

Subjects who develop a different therapeutic indication for oral anticoagulant therapy during the trial (e.g., mechanical heart valve, acute venous thromboembolism) will discontinue study treatment for the duration of open-label oral anticoagulant therapy (see Table 3.4.2.2-1). Study treatment should be recommenced after open-label anticoagulant therapy is discontinued and the anticoagulant activity has dissipated as long as there is no contraindication.

Table 3.4.2.2-1: Management of Patients who Develop an Indication for Oral Anticoagulant Therapy During the Course of the Study

New Indication for oral anticoagulants	Strategy
Mechanical valve	Stop study treatments and start open-label anticoagulants
Acute venous thrombosis or unusual site of thrombosis	Stop study treatments and start open-label anticoagulants. Resume study drug as soon as possible if warfarin is discontinued

3.4.2.3 Cardioversion

If cardioversion is required during the trial, the investigator may maintain the patient on apixaban or switch to another AC based on the investigator's clinical experience. Transesophageal echocardiogram (TEE) is recommended.

3.5 Discontinuation of Subjects from Treatment

Subjects MUST discontinue investigational product (and non-investigational product at the discretion of the investigator) for any of the following reasons:

- Subject's request to stop study treatment.
- Any clinical adverse event (AE), laboratory abnormality or intercurrent illness which, in the opinion of the investigator, indicates that continued participation in the study is not in the best interest of the subject.
- Pregnancy.
- Termination of the study by Bristol-Myers Squibb (BMS).
- Loss of ability to freely provide consent through imprisonment or involuntarily incarceration for treatment of either a psychiatric or physical (eg, infectious disease) illness.
- Unblinding a subject for any reason (emergency or non-emergency).
- Stroke or bleeding event that, in the judgment of the investigator, is clinically significant which necessitates treatment withdrawal.
- Any clinical situation that, in the judgment of the investigator, necessitates temporary treatment discontinuation, e.g. urgent surgery or interventions, concomitant treatment with medications which either increase or decrease exposure to apixaban significantly.
- Follow the local or institutional guidance and product SmPC for requirements for interruption or discontinuation of apixaban related to jaundice or elevated liver function tests, or deterioration of renal function.
- Significant Protocol violation, especially inability to comply with protocol visit and activity requirements.

All subjects who discontinue investigational product should comply with protocol specified follow-up procedures as outlined in Section 5. The only exception to this requirement is when a subject withdraws consent for all study procedures including post-treatment study follow-up or loses the ability to consent freely (ie, is imprisoned or involuntarily incarcerated for the treatment of either a psychiatric or physical illness).

If study treatment is discontinued prior to the subject's completion of the study, the reason for the discontinuation must be documented in the subject's medical records and entered on the appropriate case report form (CRF) page.

3.6 Post Treatment Study Follow-Up

Subjects who discontinue study treatment may continue to be followed. Except for obtaining the vital status of these patients at the end of the theoretical follow-up phase, there will be no other follow-up.

3.6.1 Withdrawal of Consent

Subjects who request to discontinue study treatment will remain in the study and must continue to be followed for protocol specified follow-up procedures. The only exception to this is when a subject specifically withdraws consent for any further contact with him/her or persons previously authorized by subject to provide this information. Subjects should notify the investigator of the decision to withdraw consent from future follow-up **in writing**, whenever possible. The withdrawal of consent should be explained in detail in the medical records by the investigator, as to whether the withdrawal is from further treatment with study drug only or also from study procedures and/or post treatment study follow-up, and entered on the appropriate CRF page. In the event that vital status (whether the subject is alive or dead) is being measured, publicly available information should be used to determine vital status only as appropriately directed in accordance with local law.

3.6.2 Lost to Follow-Up

All reasonable efforts must be made to locate subjects to determine and report their ongoing status. This includes follow-up with persons authorized by the subject as noted above. Lost to follow-up is defined by the inability to reach the subject after a minimum of three documented phone calls, faxes, or emails as well as lack of response by subject to one registered mail letter. All attempts should be documented in the subject's medical records. If it is determined that

the subject has died, the site will use permissible local methods to obtain the date and cause of death.

If investigator's use of third-party representative to assist in the follow-up portion of the study has been included in the subject's informed consent, then the investigator may use a Sponsor-retained third-party representative to assist site staff with obtaining subject's contact information or other public vital status data necessary to complete the follow-up portion of the study. The site staff and representative will consult publicly available sources, such as public health registries and databases, in order to obtain updated contact information. If after all attempts, the subject remains lost to follow-up, then the last known alive date as determined by the investigator should be reported and documented in the subject's medical records.

4/ TREATMENTS

Study drugs include both Non-investigational (NIMP) and Investigational Medicinal Products (IMP) and can consist of the following:

- All products, active or placebo, being tested or used as a comparator in a clinical trial.
- Study required premedication, and
- Other drugs administered as part of the study that are critical to claims of efficacy (eg, background therapy, rescue medications).
- Diagnostic agents: (such as glucose for glucose challenge) given as part of the protocol requirements must also be included in the dosing data collection.

4.1 Study Treatments

Study treatment is open-label apixaban 5 mg tablets taken orally two times a day.

Subjects with 2 or more of the following characteristics will take apixaban 2.5 mg tablets orally twice daily.

- age ≥ 80 years.
- body weight ≤ 60 kg.
- serum creatinine ≥ 1.5 mg/dL [133 µmmol/L]

Also, subjects with severe renal insufficiency [creatinine clearance between 15-29 ml/min] will take apixaban 2.5 mg tablets orally twice daily. Subjects with reduced renal function should have their renal function monitored regularly as per local clinical practice, and may require either discontinuation of study treatment (and suitable alternative therapy initiated) or a dose reduction (for those initiated at 5 mg BID dose). Product description is presented in Table 4.1-1.

Table 4.1-1: Product Description

Product Description and Dosage Form	Potency	Primary Packaging	Secondary Packaging	Appearance	Storage Conditions	Investigational (Yes/No)
Apixaban film coated tablets	2.5 mg	Alu PVC/PVdC unit dose blister strips, each strip containing 10 film coated tablets	Carton of 2 strips	Yellow, round tablets debossed with 893 on one side and 2½ on the other side.	20°C to 25°C (68°F-77°F); excursions permitted between 15°C and 30°C (59°F-86°F)	No
Apixaban film coated tablets	5 mg	Alu PVC/PVdC unit dose blister strips, each strip containing 14 film coated tablets	Carton of 4 strips	Pink, oval tablets debossed with 894 on one side and 5 on the other side.	20°C to 25°C (68°F-77°F); excursions permitted between 15°C and 30°C (59°F-86°F)	No

4.1.1 Investigational Product

An investigational product, also known as investigational medicinal product in some regions, is defined a pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical study, including products already with a marketing authorization but used or assembled (formulated or packaged) differently than the authorized form, or used for an unauthorized indication, or when used to gain further information about the authorized form.

The investigational product should be stored in a secure area according to local regulations. It is the responsibility of the investigator to ensure that investigational product is only dispensed to study subjects. The investigational product must be dispensed only from official study sites by authorized personnel according to local regulations.

In this protocol, investigational product(s) is/are: None

In this study, the effectiveness of patient counselling materials on adherence to apixaban therapy is being compared, not the efficacy or safety of apixaban itself. Thus, in this protocol, study medication provided by BMS is not considered an investigational product. However, all conditions applicable for investigational product, such as storage, dispensation, and documentation, are required to be followed for apixaban, the study medication.

4.1.2 Non-investigational Product

Other medications used as support or escape medication for preventative, diagnostic, or therapeutic reasons, as components of the standard of care for a given diagnosis, may be considered as non-investigational products.

In this protocol, non-investigational products are: None

4.1.3 Handling and Dispensing

The product storage manager should ensure that the study drug is stored in accordance with the environmental conditions (temperature, light, and humidity) as determined by BMS. If concerns regarding the quality or appearance of the study drug arise, the study drug should not be dispensed and contact BMS immediately.

Investigational product documentation must be maintained that includes all processes required to ensure drug is accurately administered. This includes documentation of drug storage, administration and, as applicable, storage temperatures, reconstitution, and use of required processes (eg, required diluents, administration sets).

For non-investigational product, if marketed product is utilized, it should be stored in accordance with the package insert, summary of product characteristics (SmPC), or similar.

4.2 Method of Assigning Subject Identification

The patient identification (ID) will be provided by the central randomization service through screening form of electronic case report form (eCRF). The eCRF will randomly assign the subjects to 1 of the 2 study groups for the first 24 weeks and re-assign patients from the additional educational programme group at Week 24 for the forthcoming 24 weeks.

4.3 Selection and Timing of Dose for Each Subject

Patients should not have received treatment with warfarin or other VKA within 72 hours of beginning study treatment.

Apixaban will be taken as one tablet twice daily, either 5 mg or 2.5 mg. Creatinine clearance, which guides the initial dose choice, will be calculated by investigator using local laboratory results. Apixaban may be taken without regard to timing of meals.

If the patient were to vomit within 30 minutes of ingestion of the study drug, the dose should be re-administered. If the patient vomits more than 30 minutes after study drug ingestion, no additional study drug should be taken and the patient should resume study drug ingestion according to their usual schedule.

If a dose is missed, the study drug should be taken immediately and then continued with twice daily intake as before.

4.3.1 Dose Modifications

A reduced dose of apixaban will be used for patients deemed to be at increased risk of bleeding. Patients who fulfill any two of the following criteria at baseline will have their apixaban dose reduced to 2.5 mg BID at the time of randomization:

- Age ≥ 80 years.
- Body weight ≤ 60 kg.
- Serum creatinine ≥ 1.5 mg/dL (133 µmol/L).

Subjects with creatinine clearance of 15-29 mL/min should take 2.5 mg BID. Subjects with reduced renal function should have their renal function monitored regularly as per local clinical practice, and may require either discontinuation of study treatment (and suitable alternative therapy initiated) or a dose reduction (for those initiated at 5 mg BID dose).

4.3.1.1 Invasive Procedures and Surgery

The effective half-life of apixaban when administered twice daily is approximately 12 hours and it is expected that most of the anticoagulant effect will have dissipated within 24 hours after the last dose of the drug. Apixaban must be stopped for a sufficient period of time (at least 24 hours) prior to the procedure to minimize the risk of anticoagulant-related bleeding. The treating physician should be made aware that when apixaban is administered at the protocol-specified doses, routine coagulation tests such as INR/PT and aPTT are relatively insensitive measures of anticoagulant activity and are unsuitable for monitoring the anticoagulant effect of apixaban.

Apixaban should be discontinued at least 48 hours prior to elective surgery or invasive procedures with a moderate or high risk of bleeding. This includes interventions for which the probability of clinically significant bleeding cannot be excluded or for which the risk of bleeding would be unacceptable.

Apixaban should be discontinued at least 24 hours prior to elective surgery or invasive procedures with a low risk of bleeding. This includes interventions for which any bleeding that occurs is expected to be minimal, non-critical in its location or easily controlled.

If surgery or invasive procedures cannot be delayed, appropriate caution should be exercised, taking into consideration an increased risk of bleeding. This risk of bleeding should be weighed against the urgency of intervention.

Apixaban should be restarted after the invasive procedure or surgical intervention as soon as possible provided the clinical situation allows and adequate haemostasis has been established.

It is anticipated that bridging anticoagulation will not be required in patients who temporarily discontinue study medications but any decision to use unfractionated heparin (UFH) or low molecular weight heparin (LMWH) during interruption of study medication will be at the discretion of the investigator.

Emergency Procedures

The study medication should be temporarily discontinued for patients requiring the use of anticoagulants (UFH, LMWH, direct thrombin inhibitors, fondaparinux), thrombolytics, or surgery or other invasive procedures that are associated with an increased risk of bleeding. The use of concomitant antiplatelet therapies is discussed in Section 3.4, Concomitant Treatments.

The treating physician should be made aware that when apixaban is administered at the protocol-specified doses, routine coagulation tests such as INR/PT and aPTT are relatively insensitive measures of anticoagulant effect and are unsuitable for monitoring the anticoagulant effect of apixaban. Study medication should be restarted as soon as possible following stabilization after an acute event.

In event of an overdose, note that there is no antidote for apixaban. Overdose of apixaban may result in a higher risk of bleeding. In the event of haemorrhagic complications, treatment must be discontinued and the source of bleeding investigated. The initiation of appropriate treatment, e.g., surgical haemostasis or the transfusion of fresh frozen plasma should be considered.

4.4 Blinding/Unblinding

Not applicable.

4.5 Treatment Compliance

Adherence to the study treatment is the primary outcome for this trial. Adherence data from the EMD will be uploaded from the EMD to study BMS data collection website at 24-week and 48-week study visits. At each study visit the subjects will receive treatment adherence oriented counselling as described in Section 3.1, Study Design and Duration. Any subject who discontinues apixaban for more than 30 days will be discontinued from the study.

4.6 Destruction and Return of Study Drug

4.6.1 Destruction of Study Drug

If study drugs (those supplied by BMS or sourced by the investigator) are to be destroyed on site, it is the investigator's responsibility to ensure that arrangements have been made for the disposal, procedures for proper disposal have been established according to applicable regulations, guidelines and institutional procedures, and appropriate records of the disposal have been documented. The unused study drugs can only be destroyed after being inspected and reconciled by the responsible BMS Study Monitor.

4.6.2 Return of Study Drug

Study drug will not be returned to BMS. All unused and/or partially used study drug may be destroyed on site providing the site has an applicable standard operating procedure on file.

5/ STUDY ASSESSMENTS AND PROCEDURES

5.1 Flow Chart/Time and Events Schedule

Table 5.1A: Screening Procedural Outline

Procedure	Screening Visit	Baseline Visit (within 10 days of screening)[a]	Notes
Eligibility Assessments	X	X	
Informed Consent	X		
Inclusion/Exclusion Criteria	X	X	
Medical History	X	X	
Concomitant Medications	X	X	
Safety Assessments	X	X	
Physical Examination	X		
Targeted Physical Examination		X	
Vital Signs	X	X	
Assessment of Signs and Symptoms	X	X	
Adverse Events Assessment	X	X	
Laboratory Tests[b]	X	X	At screening
Urine Pregnancy Test	X	X	
Education regarding adherence to study medication[c]		X	
Clinical trial supplies			
Randomize		X	
Dispense Study Drug		X	Those supplied by BMS

[a] Baseline visit may occur on the same day as the screening visit, and no later than 10 days after the screening visit.
[b] FBC and full chemistry panel and INR/ACT. INR/ACT values during the last 3 months to be recorded for VKA treated patients switching to apixaban. Laboratory tests within three months prior to the screening visit are allowed.
[c] Only for the intervention group.

Table 5.1B: Short-term Procedural Outline

Procedure	During Treatment Visit 2 (4 weeks)	During Treatment Visits 3, 4, and 5 (12, 24, and 36 weeks)	End of Treatment Visit 6 (48 weeks)	Notes
Eligibility Assessments				
Inclusion/Exclusion Criteria				
Medical History				
Concomitant Medications	X	X		
Safety Assessments				
Physical Examination	X	X	X	
Vital Signs	X	X	X	
Assessment of Signs and Symptoms	X	X	X	
Adverse Events Assessment	X	X	X	
Laboratory Tests[a]		X[b]	X	
Pregnancy Test (WOCBP)	X	X	X	As defined by SOC
Efficacy Assessments				
Adherence measurements[c]		X	X	
Clinical Drug Supplies				
Randomize		Week 24[d]		
Dispense Study Drug	X	X		

[a] FBC and full chemistry panel PTT and PT ratio not to be measured during follow-up.
[b] Laboratory testing required only at Visit 4 (Week 24).
[c] Adherence measurements: Electronic monitoring tool data upload.
[d] For patients who were initially randomized into the additional education program.

5.2 Study Materials

The following study supplies will be provided:

- Subject Alert Card and Eliquis prescriber guide.
- Material with guidelines for additional patient tools.
- EMD (Helping Hand) and operating manual.
- Emergency card.
- Pregnancy test kits.

5.3 Safety Assessments

5.3.1 Imaging Assessment for the Study

Not applicable.

Bleeding assessments will be conducted as outlined in Section 5.3.2.

5.3.2 Bleeding Assessment

Acute clinically overt bleeding is defined as new onset, visible bleeding or signs or symptoms suggestive of bleeding that is confirmed by imaging techniques which can detect the presence of blood (e.g., US, CT, MRI).

The definition of major bleeding described below is adapted from the International Society on Thrombosis and Hemostasis (ISTH) definition. Detailed information regarding the severity and treatment for bleeding will be collected separately.

Major bleeding is defined as acute clinically overt bleeding that is accompanied by one or more of the following:

- A decrease in hemoglobin (Hgb) of 2 g/dL or more over a 24-hour period.
- A transfusion of 2 or more units of packed red blood cells.
- Bleeding that occurs in at least one of the following critical sites: intracranial, intraspinal, intraocular (within the corpus of the eye; thus, a conjunctival bleed is not an intraocular bleed), pericardial, intra-articular, intramuscular with compartment syndrome, retroperitoneal.
- Bleeding that is fatal.

Clinically relevant non-major bleeding is defined as acute clinically overt bleeding that does not satisfy additional criteria required for the bleeding event to be defined as a major bleeding event and meets at least one of the following criteria:

- Hospital admission for bleeding.
- Physician guided medical or surgical treatment for bleeding.
- Change in antithrombotic treatment (anticoagulant or antiplatelet) therapy.

Minor bleeding is defined as acute clinically overt bleeding not meeting the criteria for either major bleeding or clinically relevant non-major bleeding.

Fatal bleeding is defined as bleeding that is the primary cause of death or contributes directly to death.

Data about major bleeding events will be collected with the mandatory bleeding assessment form. (Appendix 4).

5.3.2.1 Treatment Guidelines for Bleeding/Suspected Bleeding

There is no antidote to Eliquis. Overdose of apixaban may result in a higher risk of bleeding. In the event of haemorrhagic complications, treatment must be discontinued and the source of bleeding investigated. The initiation of appropriate treatment, e.g., surgical haemostasis or the transfusion of fresh frozen plasma should be considered.

Patients with bleeding or suspected bleeding should undergo confirmatory laboratory or other testing as indicated clinically (e.g., US, CT, MRI). The date and time of the onset of the bleeding event will be recorded on the eCRF.

5.3.3 Laboratory Assessments

Full blood count and chemistry panel are the laboratory tests required for this study. INR will be measured for VKA treated patients as specified in the SmPC. The tests should be performed in local laboratories.

Hematology Profile:

1. Hematocrit
2. Hemoglobin
3. Red Blood Cell Count
4. MCV
5. MCHC
6. MCH
7. White Blood Cell Count
8. Platelet Count
9. INR (INR values during the last 3 months for patients that switch from VKA to be retrospectively recorded)
10. Activated Clotting Time (ACT)

Chemistry:

1. BUN (Urea)
2. Chloride
3. Bicarbonate
4. Creatinine
5. Glucose
6. Potassium
7. Sodium
8. ALP
9. ALT
10. AST
11. Direct Bilirubin
12. Total Bilirubin
13. GGT (gamma-glutamyltransferase)

Result of urine pregnancy tests are required to be reported on the CRF at screening and at subsequent visit when indicated. Additional laboratory testing as required by the local standard of care should be conducted at the investigator's discretion.

5.4 Efficacy Assessments

Data on treatment adherence will be uploaded from the EMD and will be recorded in BMS clinical database. No other efficacy data will be collected for this study. Additional procedures and assessments may be performed as part of standard of care and should remain in the subjects' medical records. These data should not be provided to BMS unless specifically requested.

5.4.1 Primary Efficacy Assessment

Primary study assessment is measurement of implementation phase adherence to the study medication at 24-weeks using an electronic monitoring device. Adherence data from the EMD will be uploaded at 24-weeks and 48-weeks visits. Adherence units will be computed as described in Section 3.1, Study design and Duration.

5.4.2 Secondary Efficacy Assessments

Secondary study assessment is measurement of implementation phase adherence to the study medication at 12-weeks and 48-weeks using an electronic monitoring device.

5.5 Pharmacokinetic Assessments

Not applicable.

5.6 Biomarker Assessments

Not applicable.

5.7 Outcomes Research Assessments

Not applicable.

5.8 Other Assessments

Not applicable.

5.9 Results of Central Assessments

Not applicable.

6/ ADVERSE EVENTS

An ***Adverse Event (AE)*** is defined as any new untoward medical occurrence or worsening of a preexisting medical condition in a clinical investigation subject administered an investigational (medicinal) product and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (such as an abnormal laboratory finding), symptom, or disease temporally associated with the use of investigational product, whether or not considered related to the investigational product.

The causal relationship to study drug is determined by a physician and should be used to assess all adverse events (AE). The casual relationship can be one of the following:

Related: There is a reasonable causal relationship between study drug administration and the AE.

Not related: There is not a reasonable causal relationship between study drug administration and the AE.

The term "reasonable causal relationship" means there is evidence to suggest a causal relationship.

Adverse events can be spontaneously reported or elicited during open-ended questioning, examination, or evaluation of a subject. (In order to prevent reporting bias, subjects should not be questioned regarding the specific occurrence of one or more AEs.)

6.1 Serious Adverse Events

A ***Serious Adverse Event (SAE)*** is any untoward medical occurrence that at any dose:

- results in death.
- is life-threatening (defined as an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe).
- requires inpatient hospitalization or causes prolongation of existing hospitalization (see NOTE below).
- results in persistent or significant disability/ incapacity.
- is a congenital anomaly/birth defect.
- is an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the subject or may require intervention [eg, medical, surgical] to prevent one of the other serious outcomes listed in the definition above). Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization.) Potential drug induced liver injury (DILI) is also considered an important medical event. (See Section 6.6 for the definition of potential DILI).

Suspected transmission of an infectious agent (eg, pathogenic or non-pathogenic) via the study drug is an SAE.

Although pregnancy, overdose, cancer, and potential drug induced liver injury (DILI) are not always serious by regulatory definition, these events must be handled as SAEs. (See Section 6.1.1 for reporting pregnancies).

NOTE:

The following hospitalizations are not considered SAEs in BMS clinical studies:

- a visit to the emergency room or other hospital department < 24 hours, that does not result in admission (unless considered an important medical or life-threatening event)
- elective surgery, planned prior to signing consent
- admissions as per protocol for a planned medical/ surgical procedure
- routine health assessment requiring admission for baseline/trending of health status (eg, routine colonoscopy)
- medical/surgical admission other than to remedy ill health and planned prior to entry into the study. Appropriate documentation is required in these cases
- admission encountered for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (eg, lack of housing, economic inadequacy, caregiver respite, family circumstances, administrative reason)

6.1.1 Serious Adverse Event Collection and Reporting

Following the subject's written consent to participate in the study, all SAEs, whether related or not related to study drug, must be collected, including those thought to be associated with protocol-specified procedures. All SAEs must be collected that occur during the screening period and within 30 days of discontinuation of dosing.

The investigator should report any SAE that occurs after these time periods and that is believed to be related to study drug or protocol-specified procedure.

An SAE report should be completed for any event where doubt exists regarding its seriousness.

If the investigator believes that an SAE is not related to study drug, but is potentially related to the conditions of the study (such as withdrawal of previous therapy, or a complication of a study procedure), the relationship should be specified in the narrative section of the SAE Report Form.

SAEs, whether related or not related to study drug, and pregnancies must be reported to BMS (or designee) within 24 hours. SAEs must be recorded on the SAE Report Form; pregnancies on a Pregnancy Surveillance Form (electronic or paper forms). When using paper forms, the reports are to be transmitted via email or confirmed facsimile (fax) transmission to:

SAE Email Address: Refer to Contact Information list.

SAE Facsimile Number: Refer to Contact Information list.

For studies capturing SAEs through electronic data capture (EDC), electronic submission is the required method for reporting. The paper forms should be used and submitted immediately, only in the event the electronic system is unavailable for transmission. When paper forms are used, the original paper forms are to remain on site.

SAE Telephone Contact (required for SAE and pregnancy reporting): Refer to Contact Information list.

If only limited information is initially available, follow-up reports are required. (Note: Follow-up SAE reports should include the same investigator term(s) initially reported.)

If an ongoing SAE changes in its intensity or relationship to study drug or if new information becomes available, a follow-up SAE report should be sent within 24 hours to the BMS (or designee) using the same procedure used for transmitting the initial SAE report.

All SAEs should be followed to resolution or stabilization.

6.2 Non-serious Adverse Events

A ***Non-serious adverse event*** is an AE not classified as serious.

6.2.1 Non-serious Adverse Event Collection and Reporting

The collection of non-serious AE information should begin at initiation of study drug. Non-serious AE information should also be collected from the start of a placebo lead-in period or other observational period intended to establish a baseline status for the subjects.

Non-serious AEs should be followed to resolution or stabilization, or reported as SAEs if they become serious (see Section 6.1.1). Follow-up is also required for non-serious AEs that cause interruption or discontinuation of study drug and for those present at the end of study treatment as appropriate. All identified non-serious AEs must be recorded and described on the non-serious AE page of the CRF (paper or electronic).

Completion of supplemental CRFs may be requested for AEs and/or laboratory abnormalities that are reported/identified during the course of the study.

6.3 Laboratory Test Result Abnormalities

The following laboratory test result abnormalities should be captured on the non-serious AE CRF page or SAE Report Form (paper or electronic) as appropriate:

- Any laboratory test result that is clinically significant or meets the definition of an SAE.
- Any laboratory test result abnormality that required the subject to have study drug discontinued or interrupted.
- Any laboratory test result abnormality that required the subject to receive specific corrective therapy.

It is expected that wherever possible, the clinical rather than laboratory term would be used by the reporting investigator (eg, anemia *versus* low hemoglobin value).

6.4 Pregnancy

If, following initiation of the investigational product, it is subsequently discovered that a study subject is pregnant or may have been pregnant at the time of investigational product exposure, including during at least 6 half lives after product administration, the investigational product will be permanently discontinued in an appropriate manner (eg, dose tapering if necessary for subject safety). Protocol-required procedures for study discontinuation and follow-up must be performed on the subject unless contraindicated by pregnancy (eg, x-ray studies). Other appropriate pregnancy follow-up procedures should be considered if indicated.

The investigator must immediately notify BMS (or designee) Medical Monitor of this event and complete and forward a Pregnancy Surveillance Form to BMS (or designee) within 24 hours and in accordance with SAE reporting procedures described in Section 6.1.1.

Follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome and, where applicable, offspring information must be reported on the Pregnancy Surveillance Form.

Any pregnancy that occurs in a female partner of a male study participant should be reported to BMS. Information on this pregnancy will be collected on the Pregnancy Surveillance Form.

NOTE: Since in this study the effectiveness of patient counselling materials on adherence to apixaban therapy is being compared, study medication (apixaban) provided by BMS is not considered an investigational product. However, standard pregnancy related procedures in this section are applicable to the study medication.

6.5 Overdose

All occurrences of overdose must be reported as SAEs (see Section 6.1.1 for reporting details).

6.6 Potential Drug Induced Liver Injury (DILI)

Wherever possible, timely confirmation of initial liver-related laboratory abnormalities should occur prior to the reporting of a potential DILI event. All occurrences of potential DILIs, meeting the defined criteria, must be reported as SAEs (see Section 6.1.1. for reporting details).

Potential drug induced liver injury is defined as

1. AT (ALT or AST) elevation > 3 times upper limit of normal (ULN) and
2. Total bilirubin > 2 times ULN, without initial findings of cholestasis (elevated serum alkaline phosphatase), and
3. No other immediately apparent possible causes of AT elevation and hyperbilirubinemia, including, but not limited to, viral hepatitis, pre-existing chronic or acute liver disease, or the administration of other drug(s) known to be hepatotoxic.

6.7 Other Safety Considerations

Any significant worsening noted during interim or final physical examinations, electrocardiograms, x-rays, and any other potential safety assessments, whether or not these procedures are required by the protocol, should also be recorded as a non-serious or serious AE, as appropriate, and reported accordingly.

7/ DATA MONITORING COMMITTEE AND OTHER EXTERNAL COMMITTEES

7/ DATA MONITORING COMMITTEE AND OTHER EXTERNAL COMMITTEES

Not applicable.

8/ STATISTICAL CONSIDERATIONS

8.1 Sample Size Determination

The study will randomize approximately 1,112 subjects, 556 in each group, so that assuming a dropout rate of 10%, sample size of approximately 1000 (2 x 500) will be available for the primary analysis.

The total sample size has been calculated for a two-sample t-test performed at the two-sided 5% significance level on the percentage of days with a correct execution of the apixaban dosing regimen over 24 weeks.

The standard deviation retained in the calculation is the intra-group standard deviation of the adherence at 32 weeks (percentage of days with a correct warfarin dose during 32 weeks) seen in the IN-RANGE study.[25]

This study has been designed to achieve 85% power for a between group difference of 4% in the percentage of days with a correct execution of the dosing regimen during 24 weeks, assuming an intra-group standard deviation of 21.1%.

8.2 Populations for Analyses

- The primary efficacy data set will consist of all randomized subjects. Subjects will be categorized to the group to which they were assigned by the eCRF, regardless of the counseling actually received.
- A secondary data set, the evaluable subject data set, will exclude data from subjects with protocol deviations expected to affect the primary efficacy endpoint. Such protocol deviations will be pre-specified in the statistical analysis plan.
- For the primary efficacy endpoint, analyses will be performed using the evaluable subject data set as well as the primary efficacy data set. For the secondary efficacy endpoints, analyses will be performed using the primary efficacy data set.
- For the primary and secondary safety endpoints, analyses will be performed using data from all randomized subjects who receive any study drug.

8.3 Endpoints

8.3.1 Primary Endpoint(s)

The primary endpoint for this study is the percentage of days with a correct execution of the apixaban dosing regimen during 24 weeks. This endpoint will be compared between the two study groups: SOC information or additional education.

8.3.2 Secondary Endpoint(s)

The secondary endpoints are as follows:

- Within each study group, percentage of days with a correct execution of the apixaban dosing regimen during the 12 to 24 weeks period compared with during the first 12 weeks.
- Adherence to apixaban dosing regimen during the 24 to 48 weeks in continued additional education group, secondary SOC group, and primary SOC group.
- Risk factors indicative of non-adherence at 24 and 48 weeks.
- Serious adverse events and other AEs, including major bleeding (ISTH).

8.3.3 Exploratory Endpoint(s)

Not applicable.

8.4 Analyses

8.4.1 Demographics and Baseline Characteristics

Frequency distribution and summary statistics for demographic and baseline variables will be presented by treatment group and for all subjects combined. Key demographic and baseline variables to be summarized include: geographic region, age, gender, height, weight, body mass index, vital signs (systolic blood pressure, diastolic blood pressure, and heart rate), VKA naïve or experienced, risk factor type, number of risk factors, smoking history, baseline medications, atrial fibrillation type and onset.

The summaries will be tabulated for all randomized subjects and also for subjects included in the evaluable subject dataset.

8.4.2 Efficacy Analyses

Primary Analysis: The primary endpoint (implementation phase adherence at 24 weeks), calculated as the percentage of days with a correct execution of the apixaban dosing regimen during this period (24 weeks) will be tested by the two-sample ttests performed at the 5% significance level (two-sided) with 95% confidence interval. The difference between groups will be provided with the 95% confidence interval.

Secondary Analyses:

1. Within each group, a linear regression approach will be used to identify predictors of non-adherence within baseline characteristics. Possible predictors include MMSE scores, age, number of concomitant medications, UK standard occupational classification, and previous experience with VKA (yes *vs.* no). The model will explain log(-log(proportion of days with incorrect execution of apixaban dose regimen during 24 weeks) by a linear combination of the possible predictors. These analyses will be performed for the adherence over the 24 first weeks (considering 2 study groups) and repeated for the adherence over the 48 weeks (considering 3 study groups). These analyses will be performed for the adherence over the 24 first weeks (considering 2 study groups) and repeated for the adherence over the 48 weeks (considering 3 study groups).
2. Within each study group, the percentage of days with a correct execution of the apixaban dosing regimen during the first 12 weeks and the percentage of days during the 12 to 24 week period will be compared using a paired t-test.
3. The proportion over time within each group of «persistent» patients (patients having not permanently discontinued the treatment) will be graphically presented (using Kaplan-Meier estimates).
4. The proportion over time within each group of «adherent» patients («persistent» and executing correctly the apixaban dosing regimen, as defined in Section 3.1, Study Design and Duration) will be graphically presented.

The percentage of days with a correct execution of the apixaban dosing regimen during the second period (24 to 48 weeks) will be compared between the 3 study groups (primary SOC group, continued additional education group, and secondary SOC group) using a oneway ANOVA. If the global test is statistically significant, the secondary SOC group will compared to (1) the primary SOC group and (2) continued additional education group. (Corrected p-value using the Dunnett multiple comparison test will also provided.)

8.4.3 Safety Analyses

The term "treatment period" refers to the period between the first administration of study drug and two days after the last administration of study drug. This period will be the basis for the summaries of safety.

The incidence of AEs and of marked abnormalities in clinical laboratory tests will presented in the overall population and by study group. All AEs that are serious or that result in discontinuation of study drug will be described in depth.

Changes from baseline in laboratory parameters will be summarized at each measurement time point by study group.

8.4.4 Other Analyses

Not applicable.

8.5 Interim Analyses

The database will be locked after 24 weeks, and an interim analysis of the data will be conducted.

9/ STUDY MANAGEMENT

9.1 Compliance

9.1.1 Compliance with the Protocol and Protocol Revisions

The study shall be conducted as described in this approved protocol. All revisions to the protocol must be discussed with, and be prepared by, BMS. The investigator should not implement any deviation or change to the protocol without prior review and documented approval/favorable opinion from the IRB/IEC of an amendment, except where necessary to eliminate an immediate hazard(s) to study subjects.

If a deviation or change to a protocol is implemented to eliminate an immediate hazard(s) prior to obtaining IRB/IEC approval/favourable opinion, as soon as possible the deviation or change will be submitted to:

1. IRB/IEC for review and approval/favourable opinion
2. Bristol-Myers Squibb
3. Regulatory Authority(ies), if required by local regulations

Documentation of approval signed by the chairperson or designee of the IRB(s)/IEC(s) must be sent to BMS.

If an amendment substantially alters the study design or increases the potential risk to the subject: (1) the consent form must be revised and submitted to the IRB(s)/IEC(s) for review and approval/favourable opinion; (2) the revised form must be used to obtain consent from subjects currently enrolled in the study if they are affected by the amendment; and (3) the new form must be used to obtain consent from new subjects prior to enrollment.

If the revision is an administrative letter, investigators must inform their IRB(s)/IEC(s).

9.1.2 Monitoring

Representatives of BMS must be allowed to visit all study site locations periodically to assess the data quality and study integrity. On site they will review study records and directly compare them with source documents, discuss the conduct of the study with the investigator, and verify that the facilities remain acceptable.

Certain CRF pages and/or electronic files may serve as the source documents.

In addition, the study may be evaluated by BMS internal auditors and government inspectors who must be allowed access to CRFs, source documents, other study files, and study facilities. BMS audit reports will be kept confidential.

The investigator must notify BMS promptly of any inspections scheduled by regulatory authorities, and promptly forward copies of inspection reports to BMS.

9.1.3 Investigational Site Training

Bristol-Myers Squibb will provide quality investigational staff training prior to study initiation. Training topics will include but are not limited to: GCP, AE reporting, study details and procedure, electronic CRFs, study documentation, informed consent, and enrollment of WOCBP.

9.2 Records

9.2.1 Records Retention

The investigator must retain all study records and source documents for the maximum period required by applicable regulations and guidelines, or institution procedures, or for the period specified by BMS, whichever is longer. The investigator must contact BMS prior to destroying any records associated with the study.

BMS will notify the investigator when the study records are no longer needed.

If the investigator withdraws from the study (eg, relocation, retirement), the records shall be transferred to a mutually agreed upon designee (eg, another investigator, IRB). Notice of such transfer will be given in writing to BMS.

9.2.2 Study Drug Records

It is the responsibility of the investigator to ensure that a current disposition record of study medication (those supplied by BMS) is maintained at each study site where EMDs, patient education materials, and apixaban 2.5 mg and 5 mg tablets are inventoried and dispensed.

Records or logs must comply with applicable regulations and guidelines and should include:

1. Amount received and placed in storage area
2. Amount currently in storage area
3. Label ID number or batch number
4. Amount dispensed to and returned by each subject, including unique subject identifiers
5. Amount transferred to another area/site for dispensing or storage
6. Non-study disposition (eg, lost, wasted)
7. Amount destroyed at study site, if applicable
8. Amount returned to BMS
9. Retain samples for bioavailability/bioequivalence, if applicable
10. Dates and initials of person responsible for study medication dispensing/accountability, as per the Delegation of Authority Form

BMS will provide forms to facilitate inventory control if the investigational site does not have an established system that meets these requirements.

9.2.3 Case Report Forms

An investigator is required to prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the investigation on each individual treated or entered as a control in the investigation. Data that are derived from source documents and reported on the CRF must be consistent with the source documents or the discrepancies must be explained. Additional clinical information may be collected and analyzed in an effort to enhance understanding of product safety. CRFs may be requested for AEs and/or laboratory abnormalities that are reported or identified during the course of the study.

For sites using the BMS electronic data capture tool, electronic CRFs will be prepared for all data collection fields except for fields specific to SAEs and pregnancy, which will be reported on the paper or electronic SAE form and Pregnancy Surveillance form, respectively. Spaces may be left blank only in those circumstances permitted by study-specific CRF completion guidelines provided by BMS.

The confidentiality of records that could identify subjects must be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirement(s).

The investigator will maintain a signature sheet to document signatures and initials of all persons authorized to make entries and/or corrections on CRFs.

The completed CRF, including any paper or electronic SAE/pregnancy CRFs, must be promptly reviewed, signed, and dated by the investigator or qualified physician who is a subinvestigator and who is delegated this task on the Delegation of Authority Form. For electronic CRFs, review and approval/signature is completed electronically through the BMS electronic data capture tool. The investigator must retain a copy of the CRFs including records of the changes and corrections.

Each individual electronically signing electronic CRFs must meet BMS training requirements and must only access the BMS electronic data capture tool using the unique user account provided by BMS. User accounts are not to be shared or reassigned to other individuals.

9.3 Clinical Study Report and Publications

A Signatory Investigator will be selected to sign the clinical study report.

The data collected during this study are confidential and proprietary to BMS. Any publications or abstracts arising from this study require approval by BMS prior to publication or presentation and must adhere to BMS's publication requirements as set forth in the approved clinical trial agreement (CTA). All draft publications, including abstracts or detailed summaries of any proposed presentations, must be submitted to BMS at the earliest practicable time for review, but at any event not less than 30 days before submission or presentation unless otherwise set forth in the CTA. BMS shall have the right to delete any confidential or proprietary information contained in any proposed presentation or abstract and may delay publication for up to 60 days for purposes of filing a patent application.

10/ GLOSSARY OF TERMS

Term	Definition
Adverse Reaction	An adverse event that is considered by either the investigator or BMS as related to the study medication
Unexpected Adverse Reaction	An adverse reaction, the nature or severity of which is not consistent with the applicable product information (eg, Investigator Brochure for an unapproved study medication)

11/ LIST OF ABBREVIATIONS

11/ LIST OF ABBREVIATIONS

ABC	Ascertaining Barriers for Compliance project
ACT	Activated clotting time
AE	Adverse event
AF	Atrial fibrillation
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BID	Two times a day (twice daily)
BMI	Body Mass Index
BMS	Bristol-Myers Squibb
CRF	Case report form
CTA	Clinical trial agreement
CV	Cardiovascular
EMD	Electronic monitoring device
FHS	Framingham Heart Study
FP7	European Community Seventh Framework Programme
GGT	Gamma-glutamyltransferase
INR	International normalized ratio
IRB/IEC	Institutional Review Board/Independent Ethics Committee
ISTH	International Society on Thrombosis and Hemostasis
MMSE	Mini-Mental State Examination
NYHA	New York Heart Association
OAC	Oral anticoagulant
SAE	Serious adverse event
SmPC	Summary of Product Characteristics
SPAF	Stroke prevention in atrial fibrillation
TIA	Transient ischemic attack
UK	United Kingdom
VKA	Vitamin K antagonists

12/ REFERENCES

12/ REFERENCES

1 Fuster V, Ryden LE, Cannom DS, *et al.* 2011 ACCF/AHA/HRS focused updates incorporated into the ACC/AHA/ESC 2006 guidelines for the management of patients with atrial fibrillation: a report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines. *Circulation.* Mar 15 2011;123(10):e269-367.

2 Lloyd-Jones DM, Wang TJ, Leip EP, *et al.* Lifetime risk for development of atrial fibrillation: the Framingham Heart Study. *Circulation.* Aug 31 2004;110(9):1042-1046.

3 Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation as an independent risk factor for stroke: the Framingham Study. *Stroke.* Aug 1991;22(8):983-988.

4 Lin HJ, Wolf PA, Kelly-Hayes M, *et al.* Stroke severity in atrial fibrillation: the Framingham Study. *Stroke.* 1996;27:1760-1764.

5 Dulli DA, Stanko H, Levine RL. Atrial fibrillation is associated with severe acute ischemic stroke. *Neuroepidemiology.* Mar-Apr 2003;22(2):118-123.

6 Jørgensen HS; Nakayama H, Reith J, Raaschou HO, Olsen TS. Acute Stroke With Atrial Fibrillation: The Copenhagen Stroke Study. *Stroke.* 1996;27:1765-1769.

7 Heeringa J, van der Kuip DAM, Hofman A, *et al.* Prevalence, incidence and lifetime risk of atrial fibrillation: the Rotterdam study. *Eur Heart J.* 2006;27:949-953.

8 Wolowacz SE, Samuel M, Brennan VK, Jasso-Mosqueda JG, Van Gelder IC. The cost of illness of atrial fibrillation: a systematic review of the recent literature S.E. *Europace.* 2011;13:1375-1385.

9 Hart RG, Benavente O, McBride R, Pearce LA. Antithrombotic therapy to prevent stroke in patients with atrial fibrillation: a meta-analysis. *Ann Intern Med.* 1999;131(7):492-501.

10 van Walraven C, Hart RG, Singer DE, *et al.* Oral anticoagulants vs aspirin in nonvalvular atrial fibrillation: an individual patient meta-analysis. *JAMA.* 2002; 288(19):2441-2448.

11 Holbrook AM, Pereira JA, Labiris R, *et al.* Systematic overview of warfarin and its drug and food interactions. *Arch Intern Med.* 2005;165(10):1095-1106.

12 Hylek EM, D'Antonio J, Evans-Molina C, Shea C, Henault LE, Regan S. Translating the results of randomized trials into clinical practice: the challenge of warfarin candidacy among hospitalized elderly patients with atrial fibrillation. *Stroke.* 2006;37(4):1075-1080.

13 Howitt A, Armstrong D. Implementing evidence based medicine in general practice: audit and qualitative study of antithrombotic treatment for atrial fibrillation. *Brit Med J.* May 15 1999;318(7194):1324-1327.

14 McCormick D, Gurwitz JH, Goldberg RJ, *et al.* Prevalence and quality of warfarin use for patients with atrial fibrillation in the long-term care setting. *Arch Intern Med.* Nov 12 2001;161(20):2458-2463.

15 Eliquis, Summary of Product Characteristics. European Medicines Agency. Available at http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002148/WC500107728.pdf Accessed 6 December 2012.

16 Granger CB, Alexander JH, McMurray JJ, *et al.* Apixaban versus warfarin in patients with atrial fibrillation. *N Engl J Med.* Sep 15 2011;365(11):981-992.

17 Eikelboom JW, O'Donnell M, Yusuf S, *et al.* Rationale and design of AVERROES: apixaban versus acetylsalicylic acid to prevent stroke in atrial fibrillation patients who have failed or are unsuitable for vitamin K antagonist treatment. *Am Heart J.* Mar 2010;159(3):348-353 e341.

18 Connolly SJ, Eikelboom J, Joyner C, *et al.* Apixaban in patients with atrial fibrillation. *N Engl J Med.* Mar 3 2011;364(9):806-817.

19 Adherence to long-term therapies: evidence for action. World Health Organization, Switzerland, 2003.

20 Ascertaining Barriers for Compliance: policies for safe, effective and cost-effective use of medicines in Europe, Final Report of the ABC Project. June 2012. Available at: http://abcproject.eu/img/ABC%20Final.pdf Accessed on 7 November 2012.

21 Tay KH, Lip GY, Lane DA. Anticoagulation variability: is it the physician, patient or hospital? *J Intern Med.* 2009;265(3):303-6.

22 Borg Xuereb C, Shaw RL, Lane DA. Patients' and health professionals' views and experiences of atrial fibrillation and oral-anticoagulant therapy: a qualitative meta-synthesis. *Patient Educ Couns.* 2012;88(2):330-7.

23 Hall JE, Guyton AC, eds. Guyton and Hall Textbook of Medical Physiology. 10th ed. Philadelphia, PA: Saunders Elsevier; 2000.

24 Yusuf S, Mehta SR, Chrolavicius S, *et al.* Comparison of fondaparinux and enoxaparin in acute coronary syndromes. *New England Journal of Medicine.* 2006;354(14):1464-76.

25 Parker CS, Chen Z, Price M, *et al.* Adherence to warfarin assessed by electronic pill caps, clinician assessment, and patient reports: results from the IN-RANGE study. *J Gen Intern Med.* 2007;1254-9.

EUEL134702-01 09/13 432HQ13NP01172