Statistical Analysis Plan

Protocol B0661025/CV185-267

A PHASE IV TRIAL TO ASSESS THE EFFECTIVENESS OF APIXABAN COMPARED WITH USUAL CARE ANTICOAGULATION IN SUBJECTS WITH NON-VALVULAR ATRIAL FIBRILLATION UNDERGOING CARDIOVERSION

Statistical Analysis Plan
(SAP)

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TABLE OF CONTENTS

1. AMENDMENTS FROM PREVIOUS VERSION(S)

2. THIS AMENDS VERSION 2 FROM OCT 15 2015 INTRODUCES ADDITIONAL SENSITIVITY ANALYSES AS REQUESTED BY THE EXECUTIVE COMMITTEE. INTRODUCTION

Apixaban is a novel, orally active, selective inhibitor of the coagulation factor Xa (FXa) developed by Bristol-Myers Squibb (BMS) and Pfizer as an anticoagulant and antithrombotic agent. Apixaban is a reversible and highly potent inhibitor of human FXa with a high degree of selectivity over other coagulation proteases and structurally related enzymes involved in digestion and fibrinolysis.

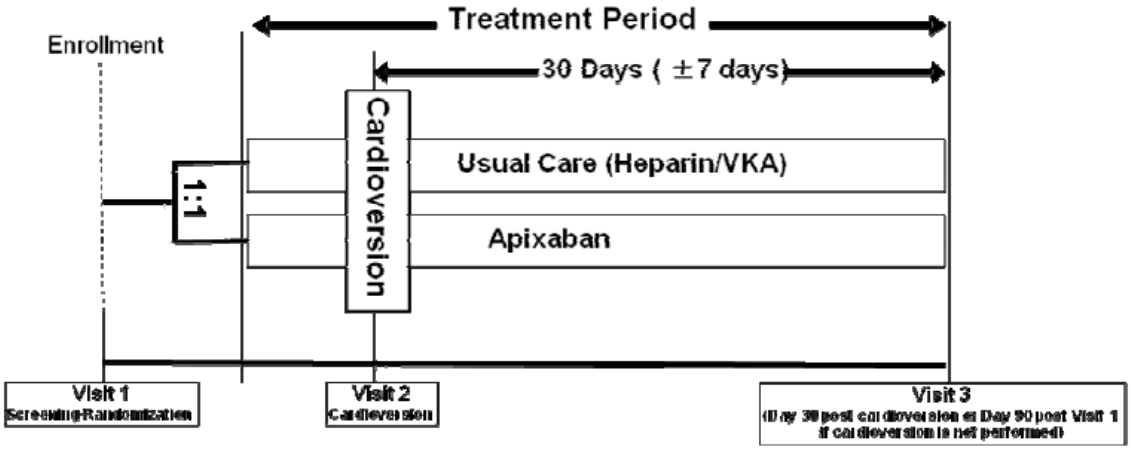
2.1. Study Design

This is a randomized, active controlled, parallel-group, open label study. Approximately 1500 subjects will be randomized 1:1 to apixaban or usual care (parenteral heparin and/or oral anticoagulation with Vitamin K antagonist (excluding other novel oral anticoagulants)). Following randomization, endpoints will be collected during the 30 days following the early cardioversion or during the 90 days post randomization if cardioversion is not performed within that time frame.

A schematic diagram below (Figure 1) shows the design of the study:

Figure 1 Study Design Schematic

Figure 1 Study Design Schematic



The Schedule of Activities table provides an overview of the protocol visits and procedures. Refer to Study Procedures and Assessments sections of the protocol for detailed information on each procedure and assessment required for compliance with the protocol.

The investigator may schedule visits (unplanned visits) in addition to those listed on the schedule of activities, in order to conduct evaluations or assessments required to protect the wellbeing of the subject.

Table 1 Schedule of Activities

Procedure	Visit 1 Enrollment Screening/Randomization[a]	Visit 2 Cardioversion	Visit 3 Follow-Up (30 days post cardioversion (Visit 2) or up to 90 days following Visit 1)
Visit Windows			±7 days
Informed Consent	X		
Obtain Alternative Contact	X		
Inclusion/Exclusion	X		
Demographics	X		
Medical History	X		
CHA_2DS_2-VASc score [b]	X		
Local Laboratory Parameters	X	X	X
Randomization	X		
Cardioversion [c]		X	
Endpoint Assessments [d]		X	X
Dispense Study Drug	X	X	
Collect Study Drug		X	X
Study Drug Compliance Check		X	X
Adverse Event Assessment		X	X

[a] Screening/Randomization could occur on the same day
[b] CHA_2DS_2-VASc - Congestive heart failure, hypertension, age, diabetes, stroke, vascular disease, age, sex category risk score
[c] Cardioversion details (timing, type, attempts, and rhythm status) and use of image guidance
[d] Endpoints; stroke, systemic embolism, major bleeding, clinically relevant non-major bleeding, all cause death, and length of in-hospital stay

2.2. Study Objectives and Endpoints

The study objective is to assess the occurrence of clinical endpoints in non-valvular AF subjects (i.e., without rheumatic mitral valve disease, a prosthetic mechanical heart valve, or mitral valve repair) indicated for early cardioversion and treated with apixaban or usual care (parenteral heparin and/or oral anticoagulation with Vitamin K antagonist (excluding other NOACs)).

Clinical Endpoints

- *Stroke.*
- *Systemic embolism.*
- *Major Bleeding.*
- *Clinically Relevant Non-Major Bleeding.*
- *All cause death.*

Additional information will also be collected on:

- *Cardioversion details: timing, type, attempts, and rhythm status*
- *Length of in-hospital stay.*
- *Use of image guidance e.g., TEE/TOE or CT.*

This protocol will use independent adjudication of disease-related clinical endpoints.

3. INTERIM ANALYSES, FINAL ANALYSES AND UNBLINDING

This study will use an Independent Review Committee (IRC) independent of the sponsor study team. The IRC, in collaboration with the sponsor (Pfizer/BMS) and the Executive Committee will create a Charter including the interim analysis plan .

The sponsor study team will monitor blinded data trends in accordance with the Safety Review Plan. The IRC will be responsible for ongoing monitoring of the safety of subjects in the study according to the Charter. The recommendations made by the IRC to alter the conduct of the study will be forwarded to Executive Committee and the sponsor (Pfizer/BMS) for final decision. The sponsor will forward such decisions, which may include summaries of aggregate analyses of endpoint events and of safety data which are not endpoints, to regulatory authorities, as appropriate.

The final analysis will be executed after the database release.

4. HYPOTHESES AND DECISION RULES

4.1. Statistical Hypotheses

This is a descriptive study, and there is no formal pre-defined hypothesis testing.

Baseline demographics, endpoints, AEs and SAEs will be reported as per Pfizer/BMS reporting standards and consistent with the therapeutic area standards. Number of observations and proportions will be given for categorical or binary variables, number of observations, mean, standard deviation, median minimum and maximum will be given for continuous variables; time-to-event data will be displayed using Kaplan-Meier techniques; hazard ratio will be calculated.

4.2. Statistical Decision Rules

No decision rules will be set, this is a descriptive study.

5. ANALYSIS SETS

Adverse events and adjudicated bleeding endpoints (Major Bleeding and Clinically Relevant Non-Major Bleeding) will be reported based on the Safety Analysis set. All other data will be reported based on the Full Analysis Set as-randomized (using a strict intent-to-treat criterion), irrespective of the actual treatment or compliance.

5.1. Full Analysis Set

The Full Analysis Set contains all randomized subjects. It will be used under the intent to treat principle (subjects will be categorized to the treatment group to which they were assigned by the IVRS, regardless of the treatment actually received).

5.2. 'Per Protocol' Analysis Set

N/A

5.3. Safety Analysis Set

The Safety Analysis Set (as-treated) will consist of all treated subjects (randomized subjects who received at least one dose of study drug). For the purpose of safety analyses, subjects will be categorized according to the treatment received; subject that received both treatments will be counted as apixaban. The reporting will be done as per Pfizer/BMS reporting standards and BMS CT SOP 109.

5.4. Other Analysis Sets

Prevention-evaluable analyses datasets will be created in order to exclude subjects identified at visit 2 through imaging as already having a thrombus; if multiple evaluations took place over time for a subject, only the first one will be used.

The Full Prevention-Evaluable Analysis Set is obtained by excluding thrombus-positive subjects from the Full Analysis Set. The Safety Prevention-Evaluable Analysis Set is obtained by removing subjects with thrombus from the Safety Analysis Set. The sets of Thrombus Positive-Full Analysis Set and Thrombus Positive-Safety are the complements of the Full Prevention Evaluable and Safety Prevention-evaluable subjects.

The Modified Full Analysis Set is the subset of the Full Analysis Set of subjects that received at least one study drug dose.

5.5. Treatment Missallocations

N/A

5.6. Protocol Deviations

All significant protocol deviations including eligibility deviations, use of prohibited concomitant medications, subjects receiving the incorrect study drug, or other deviations-as deemed significant by the project team will be identified (either from the project database or RightrackII) prior to database release, then listed and summarized by deviation type and randomized treatment group after database release. The Clinical team will provide before the database lock a list of prohibited medications.

5.6.1. Deviations Assessed Prior to Randomization

N/A

5.6.2. Deviations Assessed Post-Randomization

N/A

6. ENDPOINTS AND COVARIATES

Clinical Endpoints

- *Stroke.*
- *Systemic embolism.*
- *Major Bleeding.*
- *Clinically Relevant Non-Major Bleeding.*
- *All cause death.*

6.1. Efficacy Endpoint(s)

N/A

6.2. Safety Endpoints

N/A

6.3. Other Endpoints

Additional information will also be collected on cardioversion detail, length of in-hospital stay and usage of image guidance:

- Cardioversion details: timing, type, attempts, and rhythm status;
- Length of in-hospital stay (in hours);
- Use of image guidance e.g., TEE/TOE or CT;

6.4. Covariates

We have identified a number of baseline variables of interest:

- Age (continuous, in years),
- Hypertension (checkmark, Yes/No),
- Low Left Ventricular Function (≤40%),
- Diabetes (Yes/No),
- Duration of Arrhythmia (in hours)

No imputation for missing data will be made on these covariates.

We will explore the effect of the above-mentioned covariates on all the clinical endpoints. Univariate analyses (one predictor at a time) and multivariate analyses (including all covariates from above and treatment effect) will be performed for the above mentioned covariates on each of the clinical endpoints using Cox proportional hazards models. Interaction tests between covariates and allocated treatment will be conducted.

7. HANDLING OF MISSING VALUES

Safety data will be handled according to the BMS safety data conventions (described in "Analysis of Safety Data - Reference to BMS CT SOP 109". This document includes descriptions on how to analyze AE data as well as how to handle partial dates, missing dates, and unknown end dates when analyzing safety data.

For the analyses of clinical endpoints, imputation of missing or partial dates for efficacy and bleeding events will follow the convention outlined in "Analysis of Safety Data - Reference to BMS CT SOP 109".

8. STATISTICAL METHODOLOGY AND STATISTICAL ANALYSES

8.1. Statistical Methods

8.1.1 Analyses for Continuous Data

Frequencies, means, standard deviations, and medians will be reported by treatment arms.

8.1.2 Analyses for Time-to-Event Data

Summaries will include tabular and graphical summaries of Kaplan-Meier estimates by treatment arm as well as hazard ratios of the treatment effect or other covariates, their 95% confidence intervals and p-values.

8.1.3 Analyses for Binary Endpoints

For binary endpoints, 95% exact confidence intervals of each event rate will be reported by treatment group. The relative risk (risk ratios) will also be reported. In the SAS language we will use the RELRISK with FMSCORE method option in the EXACT statement of PROC FREQ in order to provide exact unconditional confidence limits for the relative risk.

Other binary data comparisons will be made using Fisher's exact test.

8.2. Statistical Analyses

N/A

8.2.1. Analysis of Primary Endpoints

N/A

8.2.2. Analysis of Secondary Endpoints

N/A

8.2.3. Analysis of Safety Data

Safety data will be analyzed according to the BMS safety data conventions (described in "Analysis of Safety Data - Reference to BMS CT SOP 109".

8.2.4. Analyses of Clinical Endpoints

- *Stroke.*
- *Systemic embolism.*
- *Major Bleeding.*
- *Clinically Relevant Non-Major Bleeding.*
- *All cause death.*

The following time periods will be defined for reporting clinical endpoints:

- Pre-cardioversion
- Post-cardioversion
- ALL: entire duration (include 30 days follow-up after cardioversion).

The characterization of stroke, systemic embolism and death will be done based on the adjudicated endpoints during the study (according to an intention-to-treat paradigm). Analysis of these endpoints will be based on the full analysis set.

The characterization of bleeding will be done with a focus on adjudicated major bleeding and clinically relevant non-major bleeding during the treatment period (according to a safety paradigm). Analysis of these endpoints will be based on the safety analysis set.

The clinical endpoint summaries will include descriptive statistics of individual event rates and their exact 95% confidence intervals; however exact risk ratios and corresponding p-values comparing the treatment arms will also be presented without any formal testing.

Sensitivity analysis: If the TEE/TOE or CT procedures will identify subjects with thrombus (thrombus-positive), sensitivity analyses of all clinical endpoints will be run on a dataset obtained by removing those subjects from the Full Analysis Set. The dataset from which thrombus-positive (as per investigator's assessment) subjects were excluded will be labeled as Full Prevention-Evaluable;its complementary set of Thrombus Positive-ITT will be analyzed for the endpoints of Stroke, Systemic Embolism, and Death. Sensitivity analyses of bleeding events will also be run on a dataset (labeled as Safety Prevention-Evaluable Analysis Set) obtained by removing subjects with thrombus (as per investigator's assessment) from Safety analysis set; its complementary set of Thrombus Positive-Safety will be analyzed for the bleeding endpoints.

The Modified Full Analysis set will be analyzed for the endpoints of Stroke, Systemic Embolism, and Death.

Subgroup analyses: Clinical endpoints and safety (AEs, SAEs) will be reported for each subgroup of interest. Subgroups of interest are (please note that bleeding endpoints are based on the safety analysis set while the others are based on the full analysis set):

- "Early Cardioversion" (defined as cardioversion that occurs within 7 days from randomization),
- Image Guidance (TEE/TOE or CT),
- age (< 65 years old, ≥ 65 years old)
- gender.
- For the clinical endpoints (stroke/embolism/death), also analyze by (first) cardioversion status: 'Interventional cardioversion', no cardioversion, or 'Spontaneous cardioversion'
- For clinical endpoints, breakdown summaries by Apixaban initial dose levels (loading dose vs. no loading dose) will be produced.

We will display graphically the Kaplan-Meier product-limit estimators of the time to

- Composite of first adjudicated stroke or systemic embolism,
- First Major bleeding event,
- Composite of first major bleeding and clinically relevant non-major bleeding
- All cause death.

8.2.5. Other analyses:

The full analysis set will be used to summarize data on cardioversion details, length of in-hospital stay and usage of image guidance.

- Cardioversion details will be summarized by number of attempts (a separate table will be presented for each number of attempts).
    - The summary for first attempt will be based on the full analysis set. Timing of cardioversion will be the time from randomization to the first attempt only, with time to first attempt censored at the last day of follow-up if an attempt has not been made.
    - The hazards ratio (and p-value) will be calculated for time from randomization to the first attempt at cardioversion, comparing image guided to non-image guided subjects.
    - The second attempt will be summarized based on the subset of the full analysis set that already had the first cardioversion, etc.

  - For each attempt we will summarize the number and proportion of subjects with cardioversion attempts and the number and proportion with each rhythm status.
  - Demog/baseline tables will be subset for 1) subjects with no cardioversion attempt, 2) subjects with one cardioversion attempt, and 3) subjects with 2 or more cardioversion attempts

- Length of in-hospital stay is defined as the number of hours from hospital admission to hospital discharge following cardioversion. The date and time of all hospital admissions and discharges following cardioversion will be captured within the CRF at Visit 2 and 3. Frequency of hospital stay, mean and median duration will be summarized by treatment arm.

- Early cardioversion is defined as cardioversion that occurred within the first 7 days after randomization. Frequency and proportions will be reported by treatment arm.

Routine hemoglobin and serum creatinine will be recorded within the CRF from Visit 1 to Visit 3. The data will be presented in listings without imputations and displaying even multiple findings per visit. The lab data will not be summarized.

Compliance for apixaban will be reported and summarized overall. The compliance formula is: #tablets taken / (#of days*2+L) where L=1 if loading dose was given and 0 otherwise.

INR will be summarized for the usual care arm. Rosendaal's linear interpolation methodology will be used to determine the proportion of time in specified INR range and time to therapeutic range (i.e. time from randomization to the first INR greater than or equal to 2.

Time to withdrawal will be analyzed and displayed as a KM figure.

For the adjudicated TEEs, we will report the concordance/discordance between investigator's assessment and the adjudicator's assessment, without regard to treatment arm. Details of the adjudicated TEEs will be included in a listing, as well as details of the investigator's initial TEE assessment.

Demogs/baseline characteristics will be summarized for the following groups: 10 mg load vs no load, 5 mg load vs. no load, 10 mg load vs 5 mg load

Demogs/baseline characteristics will be compared for spontaneous vs. interventional cardioversion within the Apixaban arm.

Demogs/baseline characteristics will be compared for spontaneous vs. interventional cardioversion within the usual care arm.

Demogs/baseline characteristics will be compared for spontaneous vs. interventional cardioversion in the two treatment arms combined.

Demogs/baseline characteristics will be compared for electrical vs. pharmacological vs. both cardioversion within the Apixaban arm.

Demogs/baseline characteristics will be compared for electrical vs. pharmacological vs. both cardioversion within the usual care arm.

Demogs/baseline characteristics will be compared for electrical vs. pharmacological vs. both cardioversion in the two treatment arms combined.

Demogs/baseline characteristics will be compared for subjects with thrombus vs. subjects without thrombus.

The following analyses/comparisons will be performed for each of the clinical endpoints; the Full Ananlysis Set will be used for stroke, systemic embolism, and for death, while the safety dataset will be used for the bleeding endpoints;

for the following Apixaban groups: 10 mg load vs no load, 5 mg load vs. no load, 10 mg load vs 5 mg load

for spontaneous vs. interventional cardioversion within the Apixaban arm.

for spontaneous vs. interventional cardioversion within the usual care arm.

for spontaneous vs. interventional cardioversion in the two treatment arms combined.

for electrical vs. pharmacological vs. both cardioversion within the Apixaban arm.

for electrical vs. pharmacological vs. both cardioversion within the usual care arm.

for electrical vs. pharmacological vs. both cardioversion in the two treatment arms combined.

for subjects with thrombus vs. subjects without thrombus.

References

N/A

APPENDICES

Appendix 1. DATA DERIVATION DETAILS

Appendix 1.1. Definition of Protocol Deviations that Relate to Statistical Analyses/Populations

N/A

Appendix 1.2. Definition of Analysis Populations/Sets

N/A

Appendix 1.3. Further Definition of Endpoints

N/A

Appendix 2. STATISTICAL METHODOLOGY DETAILS

N/A

Appendix 2.1. Further Details of Interim Analyses

N/A

Appendix 2.2. Further Details of the Statistical Methods

N/A