Boehringer Ingelheim

Advisory Committee Briefing Document

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Dosage Form, Strength:	DE 150 BID and DE 110 BID	
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LIST OF ABBREVIATIONS

ACC	American College of Cardiology
ACCP	American College of Chest Physicians
ACE	Angiotensin-Converting Enzyme
ACS	Acute Coronary Syndrome
ACT	Activated Clotting Time
AE(s)	Adverse Event(s)
AF	Atrial Fibrillation
AHA	American Heart Association
ALT	Alanine Aminotransferase (=SGPT)
AP	Alkaline Phosphatase
aPTT	Activated Partial Thromboplastin Time
ARB	Angiotension Receptor Blocker
AReS	Automated Randomization System
ASA	Acetylsalicylic Acid
AST	Aspartate Aminotransferase (=SGOT)
AUC	Area under the Plasma-Concentration Time Curve
BI	Boehringer Ingelheim
BID	*bis in die* (twice daily)
BMI	Body Mass Index
BP	Blood Pressure
BRPM	Blinded Report Planning Meeting
$C_{2,ss}$	Plasma Concentration at 2 hours after Drug Administration at Steady State
C_{max}	Maximum Concentration in Plasma
CABG	Coronary Artery Bypass Graft
CAD	Coronary Artery Disease
CBD	Common Bile Duct
$CHADS_2$	Cardiac Failure, Hypertension, Age, Diabetes, Stroke (Doubled)
CHF	Congestive Heart Failure
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
CK-MB	Creatinine Kinase-MB (muscle brain)
CML	Clinical Monitor Local
CNS	Central Nervous System
Conc	Concentration
COX2	Cyclo-oxgygenase-2
$C_{pre,ss}$	Trough Plasma Concentration at Steady-State
CRA	Clinical Research Associate
CrCl	Creatinine Clearance
CRF	Case Report Form
CTP	Clinical Trial Protocol
CV	Coefficient of Variation
CYP	Cytochrome P

DE	dabigatran etexilate
DE 50	dabigatran etexilate 50 mt
DE 110	dabigatran etexilate 110 mg
DE 150	dabigatran etexilate 150 mg
DE 300	dabigatran etexilate 300 mg
DILI	Drug-Induced Liver Injury
DM	Diabetes mellitus
DQRM	Data Quality Review Meeting
DSMB	Data Safety Monitoring Board
E_{max}	Maximum Effect
$E_{pre,ss}$	Predose Effect at Steady State Immediately before Administration of the Next Dose
EC50	The Drug Dose Required to Attain 50% of the maximum Effect
ECG(s)	Electrocardiogram(s)
ECT	Ecarin Clotting Time
e.g.	Latin expression ‘exempli gratia’
ESC	European Society of Cardiology
EU	European Union
FAS	Full Analysis Set
FDA	Food and Drug Administration
GCP	Good Clinical Practice
gCV	Geometric Coefficient of Variation
GI	Gastrointestinal
gMean	Geometric Mean
gp	Glycoprotein
h	hour
HBc	Hepatitis B Core
HBsAg	Hepatitis B Surface Antigen
HCV	Hepatitis C Virus
HPMC	Hydroxyl, Propyl-methyl Cellulose
i.e.	Latin expression ‘id est'
i.v.	Intravenous
ICH	Intra-cranial Hemorrhage
IND	Investigational New Drug
INR	International Normalized Ratio
ITT	Intent to Treat
IVRS	Interactive Voice Response System
kg	kilograms
KM	Kaplan Meier
LFT	Liver Function Test
LIMR	Lankenau Medical Research
LMWH	Low molecular weight heparin
MBE	Major Bleeding Event
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram

mL	milliliter
MI	Myocardial Infarction
NC	National Coordinators
NCB	Net Clinical Benefit
NDA	New Drug Application
ng	nanogram
NIH	National Institute of Health
NIM	Non-inferiority margin
NYHA	New York Heart Association
NSAID(s)	Non-steroidal Anti-inflammatory Drug(s)
OS	Orthopedic Surgery
PD	Pharmacodynamic
PE	Pulmonary Embolism
PETRO	**P**revention of **E**mbolic and **T**h**RO**mbotic Events
P-gp	P-glycoproteins
pH	Hydrogen ion concentration
PHRI	Population Health Research Institute
PK	Pharmacokinetic(s)
PPI	Proton Pump Inhibitors
PPS	Per Protocol Set
PROBE	Prospective Randomized Open trial with Blinded Evaluation of Outcomes
PT	Prothrombin Time
QD	Every day
SAE(s)	Serious Adverse Event(s)
SAF	Safety Analysis Set
SD	Standard Deviation
SE	Standard Error
SEE	Systemic Embolic Event
SOC	System Organ Class
SPAF	**S**troke **P**revention in **A**trial **F**ibrillation
ss	Steady State
TIA	Transient Ischemic Attack
TID	*ter in die* (three times daily)
TT	Thrombin Time
TTR	time in therapeutic range
UCR	Uppsala Clinical Research Centre
UFH	Unfractionated heparin
ULN	Upper Limit of Normal
US	United States
VKA	Vitamin K Antagonist
VTE	Venous Thrombosis Event

1. EXECUTIVE SUMMARY

New Drug Application (NDA) 22-512, submitted by Boehringer Ingelheim Pharmaceuticals, Inc. (BI) requests approval for the use of dabigatran etexilate 110 and 150 mg capsules. The Food and Drug Administration (FDA) has requested that Boehringer Ingelheim participate in a review of this application by the Cardiovascular and Renal Drugs Advisory Committee. This briefing document is intended to support that review.

The proposed doses of dabigatran etexilate are 150 mg twice daily (BID) and 110 mg BID for chronic use, with the DE 110 mg BID dose recommended only for use in those 80 years of age and older for:

The prevention of stroke and systemic embolism in patients with atrial fibrillation.

This document will summarize the information necessary to make a risk-benefit assessment of the use of two doses of dabigatran etexilate as an oral anticoagulant in subjects with atrial fibrillation, based largely, but not solely upon comparisons of two blinded doses of dabigatran etexilate to open-label warfarin (target INR 2.0 – 3.0) in the large Phase III trial, "**R**andomized **E**valuation of **L**ong term anticoagulant therap**Y**" (**RE-LY**) (U09-3249-01). This document and the presentations to the committee will address the following key areas in the dabigatran etexilate development program: development objectives, clinical pharmacology and non-clinical safety data, brief summary of DE development in non-**S**troke **P**revention in **A**trial **F**ibrillation (**SPAF**) indications, Phase II SPAF data and Phase III SPAF dose selection, the Phase III trial design and its results including efficacy, safety, pharmacokinetics, and dose-response information and finally a risk benefit assessment and overall summary and conclusions.

The nomenclature used throughout the remainder of this document to identify different dosing regimens of dabigatran etexilate is provided below.

Full text for dabigatran dosing	**Dosing Nomenclature**
Dabigatran etexilate	DE
Dabigatran etexilate 50 mg twice daily	DE 50 BID
Dabigatran etexilate 110 mg twice daily	DE 110 BID
Dabigatran etexilate 150 mg twice daily	DE 150 BID
Dabigatran etexilate 300 mg twice daily	DE 300 BID
Dabigatran etexilate 150 mg once daily	DE 150 QD
Dabigatran etexilate 220 mg once daily	DE 220 QD
Dabigatran etexilate 300 mg once daily	DE 300 QD

1.1 BACKGROUND, MEDICAL NEED AND DEVELOPMENT OBJECTIVES

The clinical development program for dabigatran etexilate in the SPAF indication was designed to establish that fixed doses of DE administered without the need for monitoring could be an alternative to warfarin in patients with atrial fibrillation (AF) for whom warfarin therapy can be considered. Efficacy in several non-SPAF indications has also been explored in a series of clinical trials.

Atrial fibrillation is the most common arrhythmia in clinical practice, accounting for approximately one third of hospitalizations for cardiac rhythm disturbances. An estimated 2.3 million people in North America and 4.5 million people in Europe have AF (R03-1232**)**. The incidence of AF increases by age and so for those between 80 and 90 years of age the prevalence of AF is about 9% according to data from the Framingham Study (R07-0034). The risk of stroke is increased approximately 5-fold in patients with AF (P09-01180**)**. Up to 15% of all strokes are due to AF and strokes in those with AF are more severe than strokes in those without AF (R96-0252**)**. During the past 20 years, hospital admissions for AF have increased by 66% (R03-1232**)** due to the aging of the population and a rising prevalence of chronic heart disease. The mortality rate in AF patients is twice that of age-matched individuals with normal sinus rhythm reflecting, at least in part, an increase in the risk of stroke (P09-01180**)**.

For over 50 years, Vitamin K antagonists (VKAs) such as warfarin have been the only oral anticoagulants available for use as a long-term treatment to prevent strokes in patients with AF. Aspirin (ASA) may be used for patients with AF, but ASA is much less effective than warfarin and is therefore currently recommended only for AF patients at low risk of stroke in the American College of Chest Physicians (ACCP) guidelines (R10-0658**)**.

Six historical placebo-controlled trials in subjects with AF were conducted with warfarin between 1989 and 1992. A meta-analysis of these 6 historical trials using a fixed effects model showed that the relative risk reduction of stroke by warfarin was 62% (95% CI: 0.48, 0.72); this transformed to a hazard ratio of 0.38 (95% CI: 0.28, 0.52) for warfarin compared to placebo (P99-02978).

Therefore, warfarin has been proven to be highly effective in preventing strokes; however, because of the difficulty of its management (i.e., periodic monitoring of anticoagulation, dietary restrictions, medication restrictions, concern about bleeding risk that can lead to patients having prothrombin time International Normalized Ratio (INR) around the low end of the target therapeutic range), many eligible AF patients do not receive warfarin treatment for stroke prevention or they receive an inadequate warfarin dose. For example, a registry of patients discharged from hospital revealed that only 54% of eligible AF patients received warfarin (P06-07839). Likewise, surveys indicated that many patients with AF cannot or will not take warfarin. Only 10% of patients with known AF who presented with an acute ischemic stroke had a therapeutic INR on admission, and even in those AF patients with a prior history of stroke or transient ischemic attack (TIA), only 18% had a therapeutic INR on admission (R10-0768).

More recent epidemiological studies have provided evidence that untreated AF results in high rates of stroke (R09-4831). The estimated annual incidence of stroke in the non-treated AF population ranges from 2-5% in moderate risk patients to 5-10% in high risk patients. (ACC/American Heart Association (AHA)/European Society of Cardiology (ESC) AF Guideline, P06-08196).

1.2 CLINICAL PHARMACOLOGY

Dabigatran is a potent, competitive, reversible direct thrombin inhibitor. It inhibits thrombin-dependent conversion of fibrinogen to fibrin, thus preventing the formation of thrombi. Dabigatran inhibits free thrombin, fibrin-bound thrombin, clot-bound thrombin and thrombin-induced platelet aggregation. Dabigatran is not absorbed via the oral route. However, dabigatran etexilate, a small molecule prodrug which does not exhibit any anticoagulant activity, is orally bioavailable. After oral administration, dabigatran etexilate is rapidly absorbed and converted to dabigatran by esterase-catalysed hydrolysis in the liver.

The pharmacokinetic profile of DE is characterized by maximum plasma concentrations at approximately 2 hours after oral administration, a bi-exponential distribution phase and a terminal half-life of 11 hours in the elderly. Steady state is attained by the third day of treatment with BID DE. The total and peak exposure have been shown to increase linearly and are dose proportional after single and multiple oral dosing of DE in a dose range between 10 to 400 mg and 50 to 400 mg BID, respectively. Due to its physicochemical properties, the oral bioavailability of dabigatran etexilate in hard capsules is 6.5% and there is a moderate intersubject variability, ranging between 31.4% and 53.5% for area under the concentration-time curve in plasma at steady state ($AUC_{\tau,ss}$) in healthy volunteers.

Dabigatran is mainly (80-85%) eliminated in the unchanged form via glomerular filtration. Approximately 20% of dabigatran is excreted as glucuronides. There are effects of age, creatinine clearance, gender, and body weight on dabigatran plasma concentrations. Ethnicity did not have any major effect on the disposition kinetics or on the pharmacodynamics of dabigatran.

Administration of DE as capsule formulation together with a high-fat meal does not result in relevant changes of the mean bioavailability of dabigatran. Dabigatran is neither a substrate nor an inhibitor or inducer of cytochrome P450 enzymes.

The prodrug dabigatran etexilate, but not the active moiety dabigatran, is a substrate of the efflux transporter P-glycoprotein (P-gp). In Phase I studies, P-gp inhibitors such as ketoconazole or verapamil increased dabigatran plasma concentrations by about 2.5- and 1.5-fold, respectively. However, in the RE-LY trial, P-gp inhibitors only modestly increased the mean plasma concentrations of dabigatran up to a maximum of 20% and had little- or no effect on bleeding. The modest effect on dabigatran pharmacokinetics documented in RE-LY may have been because subjects were not required to maintain the strict regimentation of when they took medications in relation to each other or to food as was done in the Phase I studies which were designed to estimate maximum potential drug-drug interactions.

There is a close correlation between dabigatran plasma concentrations and its pharmacodynamic effects (e,g., changes in ecarin clotting time, thrombin time, and activated partial thromboplastin time [aPTT]) in all populations studied, resulting in reproducible dose-dependent prolongation in clotting times with rapid onset and offset of these effects.

There was a relationship between dabigatran trough plasma concentration and effect (stroke/SEE) detected in RE-LY subjects receiving DE. This exposure-effect association was dependent on age and the type of stroke, with a stronger relationship in elderly subjects and with the classification of ischemic stroke/SEE only. There also was an association of higher dabigatran plasma concentrations and the occurrence of major and any bleeding events. The median dabigatran plasma concentration in subjects with adjudicated major or any (minor+major) bleeding were on average about 50% and 20%, respectively, higher than those with no reported bleeding event. ASA or clopidogrel when administered with DE (but also warfarin) increased the risk of major bleeding approximately two-fold.

1.3 OVERALL DABIGATRAN DEVELOPMENT

Numerous Phase I trials in healthy volunteers explored the pharmacokinetics of dabigatran and its potential for drug-drug and drug-food interactions.

Seven Phase II and III trials evaluated the potential of DE to prevent venous thromboembolic events (VTE) in subjects undergoing major orthopedic surgery. They included over 10,000 randomized subjects; over 6,000 of these subjects were randomized to DE. The duration of treatment in this population was short and ranged from 5 to 35 days.

One Phase III trial for the treatment of venous thromboembolic events (proximal deep vein thrombosis with and without pulmonary emboli) included over 2500 subjects; approximately half were randomized either to double-blind, double dummy warfarin or to DE (U09-1400-01).

A single Phase II trial in acute coronary syndrome (ACS) included ~1800 subjects; over 1400 were allocated to one of 4 different doses of DE with all subjects on a background regimen of ASA and clopidogrel (U10-1294-02).

All Phase III studies for the prevention of VTE and all-cause mortality following orthopedic surgery (OS; OS includes total knee replacement and total hip replacement) were randomized, double-blind clinical trials. These clinical trials compared once daily DE at doses of 150 or 220 mg or only 220 mg with enoxaparin. Based upon data from this clinical program, DE gained regulatory approval in over 70 countries, including Europe and Canada, for the prevention of VTE in subjects undergoing elective total hip and knee replacement surgery. Additional regulatory authority submissions in other countries are planned, including an NDA submission in the United States for this indication.

The demonstration that DE was a safe and effective anticoagulant during short-term treatment supported the development of DE for stroke prevention in subjects with AF.

In the SPAF program, 3 Phase II trials and a single Phase III trial randomized a total of 18,789 subjects, of whom 12,635 were randomized to DE. Two Phase II SPAF trials targeted an exposure of 12 weeks; the third Phase II trial followed over 150 of these subjects in an open-label manner for over 4 years to obtain long-term safety information. The Phase III trial (RE-LY) followed 18,113 subjects for a median duration of 2.0 years (Table 1.3: 1).

Table 1.3: 1 SPAF Development Program

Study ID	Study Design	Treatment Groups	No. Subjects Randomized	Study Duration/ Exposure
1160.49 **(Phase II)** U07-3126	Randomized, parallel group, open-label warfarin and dabigatran doses	DE 110 mg BID DE 150 mg BID Warfarin, adjusted dose	Total = 174	12 weeks
1160.20 "PETRO" **(Phase II)** U06-1615-02	Randomized, parallel group, open-label for warfarin and ASA, double-blind for dabigatran doses	DE 50-300mg+ASA 81-325 mg DE 50 mg BID DE 150 mg BID DE 300 mg BID DE 50 mg BID+ASA 81 mg DE 150 mg BID+ASA 81 mg DE 300 mg BID+ASA 81 mg DE 50 mg BID+ASA 325 mg DE 150 mg BID+ASA 325 mg DE 300 mg BID+ASA 325 mg Warfarin, adjusted dose	 N = 58 N = 99 N = 98 N = 20 N = 34 N = 33 N = 27 N = 33 N = 30 N = 70 Total = 502	12 weeks
1160.42 "PETRO" Extension **(Phase II)** U09-3247-01	Open-label long-term follow-up	DE 150 mg QD* DE 150 mg BID* DE 300 mg QD* DE 300 mg BID*	(extension of "PETRO" 1160.20) N = 98 N = 89 N = 50 N = 124 Total = 361	Up to 5 years
1160.26 **"RE-LY"** **(Phase III)** U09-3249-01	Randomized, parallel group, open-label warfarin, double-blind dabigatran doses	DE 110 mg BID DE 150 mg BID Warfarin, adjusted dose	N = 6015 N = 6076 N = 6022 Total = 18,113	3 years/ median f/u: 24 months median duration: 1.8 yrs subjects exposed: > 6 months =10,549 >12 months = 9,924 >24 months = 6,383

* For Study 1160.42, treatments are those at enrolment into the study. Most subjects changed regimens at least once during the trial and all were receiving 300 mg/day at the end of the trial.

1.4 PHASE II SPAF RESULTS AND PHASE III DOSE SELECTION

A 12-week Phase II trial in 502 atrial fibrillation subjects at moderate- to high risk of stroke explored the safety and efficacy of dabigatran etexilate at doses of 50, 150 or 300 mg twice

daily, with or without aspirin, compared to warfarin alone (INR of 2-3; **P**revention of **E**mbolic and **Th**ro**mbo**tic Events in Patients with Persistent Atrial Fibrillation (**PETRO**), (U06-1615-02). This study established that bleeding rates of warfarin alone and dabigatran etexilate 150 mg BID were similar over 12 weeks of treatment. In addition, the suppression of D-dimer in the 150 mg BID dose was similar to warfarin, while that of the 50 mg BID dose was not. There were too few strokes to reach meaningful conclusions about the efficacy for this endpoint, although during the extension study doses of 150 mg/day or lower appeared to be less effective in stroke prevention. The 300 mg BID dose had excessive bleeding in the presence of ASA (PETRO), (U06-1615-02). Long-term follow-up of the subjects on 300 mg BID without ASA also identified excess bleeding in subjects not on ASA and that dose regimen was subsequently terminated for safety reasons with all subjects converted to a 300 mg total daily dose or removed from the trial (PETRO extension, U09-3247-01).

The orthopedic surgery Phase II program (**B**oehringer **I**ngelheim **S**tudy in **Th**ro**mbo**sis, **BISTRO II**, 1160.19, U06-1997) evaluated once daily dosing versus twice daily dosing of dabigatran etexilate compared to enoxaparin and found similar efficacy and safety results comparing a total daily dose of DE 300 mg. The peak/trough ratio was approximately 6/1 versus 2/1 for once daily compared to twice daily dosing. Additionally, pharmacokinetic modelling from this study also suggested that Day 1 peak plasma concentrations correlated best with the occurrence of bleeding.

These data taken together led to the decision to use only bid dosing regimens in RE-LY so as to minimize peaks in plasma concentration and to ensure higher trough levels.

Based on the data from bleeding events and from pharmacodynamic (D-dimer) and anticoagulant effects (aPTT) in the Phase II SPAF and other trials, a dose of 300 mg/day was chosen as the target dose for stroke prevention. However, the precision of this dose selection was limited by the 6-fold range of the tested doses in the SPAF Phase II program, the necessary use of minor bleed rates in AF subjects rather than major bleeds (i.e., too few major bleeds) to model safety, and the uncertainty about extrapolating efficacy data from short-term exposure in a surgical subject population. A second target dose of 220 mg/day was therefore selected. This decision was based upon the following factors:

- The observed rates of bleeding on DE 150 BID and the other DE doses compared to warfarin in the Phase II SPAF program
- The effectiveness of DE in Phase II trials of VTE prevention in orthopedic surgery
- The finding that DE effects on aPTT with a dose DE 150 mg BID were greater than those observed for ximelagatran 36 mg BID, a dose that appeared effective in stroke prevention (SPORTIF III and SPORTIF V), while the modelled effect of DE 110 BID on aPTT was similar to that of ximelagatran 36 mg BID.

1.5 PHASE III SPAF - RE-LY

Design

The RE-LY study was a randomized, parallel group, active-controlled, non-inferiority trial of 2 blinded doses of DE (DE 110 BID and DE 150 BID) compared with open-label warfarin in subjects with non-valvular AF. The trial was designed to evaluate whether the fixed doses of DE 110 BID and DE 150 BID without anticoagulant monitoring were non-inferior to adjusted-dose warfarin (target INR of 2.0 to 3.0) in the prevention of stroke and systemic embolism (SE) in AF subjects with at least 1 additional risk factor for stroke. The study was designed so that half of the subjects were warfarin-naïve; the other half were warfarin-treatment experienced. The trial design, by virtue of inclusion of two blinded doses of DE, allowed for a definitive evaluation of the dose-response relationship for DE for both bleeding and efficacy, as well as 2 independent comparisons to warfarin. The design prespecified the primary efficacy comparison to be between each DE dose and warfarin for non-inferiority, including use of the Hochberg procedure to adjust for multiplicity of testing. Subsequent comparison for the superiority of each DE dose to warfarin after non-inferiority was achieved was prespecified in the trial statistical analysis plan which was finalized prior to un-blinding of the trial. It is well known that superiority can be tested statistically after having established non-inferiority without adjusting the type one error (α). The subsequent testing of superiority follows the closed testing procedure. The results of this study are the primary basis for the proposed marketing application of DE for SPAF.

RE-LY was a non-inferiority study with a **P**rospective **R**andomized **O**pen **B**linded **E**nd-point (**PROBE**) design. The open-label design was selected as it could evaluate both agents as they currently are- or would be used in clinical practice. For example, treatment interruptions could reflect actual clinical use and develop data to support bridging strategies and transition to- and from other anticoagulants. The open-label design of RE-LY was discussed at multiple meetings of a group of academic advisors who supported its use. A special protocol assessment was obtained for the RE-LY study from FDA. The FDA preferred a double-blind study design but did not rule out an open-label design.

There were multiple measures put in place to ensure the robustness and reliability of the results of RE-LY. Some of the more important of these include the following:
(1) data management was external to the sponsor and was managed by an independent academic group with firewalls to protect the integrity of the study, (2) adjudication was performed with procedures to ensure adjudicators were unaware of treatment group assignments and the selected outcomes were of clinical importance (i.e., stroke, death, SEE, myocardial infarction [MI], pulmonary embolism [PE], major bleeding), (3) stroke and bleeding questionnaires were used at every visit to decrease ascertainment bias and subjects in all treatment groups had a similar number of visits to the study centers, (4) screening of free text fields on CRF such as hospitalization forms, reported adverse events (AEs) and serious adverse events (SAEs) were done to identify subjects with findings that could be indicative of an outcome event.

For the non-inferiority hypothesis to be tested with the high degree of confidence in the results, it was necessary that certain items were addressed: (1) processes were in place to

prevent ascertainment bias, (2) there was consistency in the results across subgroups, and (3) the comparator, warfarin, was administered with a degree of INR control at least as good as historical clinical trials. The study results demonstrated: (1) the primary efficacy outcome on warfarin occurred at an annual rate similar to that observed in contemporary trials, and; the control of INR was comparable to other recent trials (ACTIVE-W, SPORTIF III and V, AMADEUS), (2) outcome events (eg, strokes and bleeding) were demonstrated to be dependent on INR control in the warfarin group and were demonstrated to be dose dependent in the blinded DE groups, (3) efficacy and safety results were consistent across a large number of subgroups, (4) higher risk groups had more outcome events, as expected.

Results

RE-LY included 18,113 subjects (randomized 1:1:1; 2 blinded doses of DE [DE 110 BID or DE 150 BID] or open-label warfarin) with target INR for warfarin at 2.0-3.0. The study was conducted in 44 countries. RE-LY included 36.1% of subjects from either the United States or Canada. The average age was 71.5 years, 70.0% were white and 63.6% were males. Approximately one quarter had diabetes mellitus (23%) and just over a quarter had a history or coronary artery disease (28%) with about one third (32%) having a history of heart failure. The median creatinine clearance was 68.4 mL/min. At baseline, subjects had paroxysmal (32.0%), persistent (32.8%), or permanent (35.2%) AF. Warfarin-naïve subjects comprised 50% of the population as did warfarin experienced subjects.

The population studied in RE-LY included the entire spectrum of subjects that are recommended to receive oral anticoagulant therapy by current guidelines (AHA/ACCP/ACC), rather than being restricted to only very high risk subjects (i.e., [$CHADS_2$] scores of ≥3 or those with multiple risk factors such as those having had a prior stroke and >75 years of age). RE-LY subjects had the following baseline $CHADS_2$ scores: 0 (2.5%), 1 (29.4%), 2 (35.6%) or ≥3 (32.4%) (NDA Amendment; Table 15.1.4: 17). RE-LY also included a large number of subjects for whom guidelines recommend either aspirin (ASA) or warfarin (i.e., $CHADS_2$, score=1).

The RE-LY subjects were well-treated for their concomitant medical conditions. In particular, baseline mean entry blood pressures were 131.0/77.0 mmHg and baseline concomitant medications were administered with 51.0%, 44.8% and 23.9% of subjects receiving diuretics, angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs), respectively, while 79% of subjects had a history of hypertension. These entry blood pressure values were lower than other recent trials in the AF population and support the premise that the RE-LY subjects were receiving comprehensive, guideline-driven care. Subjects in RE-LY were receiving the following medications at study entry: beta blockers (62.9%), digoxin (29.2%), statins (44.5%) and ASA (39.5%). These medications are consistent with existing treatment guidelines for subjects with AF and coronary artery disease (CAD).

Overall, 17,360 (96.2%) of the 18,040 treated subjects completed the study; 78.1% completed on study medication and 18.1% completed follow-up but stopped study medication prematurely in RE-LY (Table 1.5: 1). Only 24 (0.1%) treated subjects had an unknown final

vital status. A higher frequency of subjects completed the study on medication in the warfarin group compared to the DE 110 BID and DE 150 BID groups. There were no differences in the disposition of those who did not complete the study.

Table 1.5: 1 Disposition of Subjects - Overall Population

	DE 110 N (%)	DE 150 N (%)	Warfarin N (%)	Total N (%)
Enrolled (screened)				20377
Not entered				2264
Entered (randomized)	6015	6076	6022	18113
Not Treated (randomized)	32	17	24	73
Completed follow-up	14	7	5	26
Withdrew consent or lost to follow-up or other	18	10	19	47
Treated (randomized)	5983 (100.0)	6059 (100.0)	5998 (100.0)	18040 (100.0)
Completed study	5780 (96.6)	5824 (96.1)	5756 (96.0)	17360 (96.2)
Completed on study medication	4610 (77.1)	4627 (76.4)	4849 (80.8)	14086 (78.1)
Completed follow-up but stopped study medication prematurely	1170 (19.6)	1197 (19.8)	907 (15.1)	3274 (18.1)
Outcome events	421 (7.0)	431 (7.1)	333 (5.6)	1185 (6.6)
Serious AEs not related to outcome events	194 (3.2)	196 (3.2)	148 (2.5)	538 (3.0)
Subject preference	393 (6.6)	408 (6.7)	331 (5.5)	1132 (6.3)
Elevated liver function test result	25 (0.4)	16 (0.3)	11 (0.2)	52 (0.3)
Hospitalization	139 (2.3)	148 (2.4)	154 (2.6)	441 (2.4)
Adverse Event	296 (4.9)	325 (5.4)	192 (3.2)	813 (4.5)
Other	444 (7.4)	492 (8.1)	371 (6.2)	1307 (7.2)
Premature discontinuation from study	203 (3.4)	235 (3.9)	242 (4.0)	680 (3.8)
Sites closed for cause	25 (0.4)	27 (0.4)	27 (0.4)	79 (0.4)
Withdrew consent	126 (2.1)	144 (2.4)	136 (2.3)	406 (2.3)
Lost to follow-up	17 (0.3)	31 (0.5)	40 (0.7)	88 (0.5)
Other	35 (0.6)	33 (0.5)	39 (0.7)	107 (0.6)
Final vital status unknown	5 (0.1)	8 (0.1)	11 (0.2)	24 (0.1)

Subjects may be counted in more than one of the subclasses.
Outcome events include: stroke, systemic emboli, myocardial infarction, pulmonary emboli, transient ischemic attack (TIA), bleeding and death (U09-3249-01, Section 9.5.1.4)
Hospitalization could have been for elective procedures or those not otherwise specified.
The subjects identified above as "lost to follow-up" are those with this status in their CRF, although additional information on their vital status may have been available.
Source data: NDA Sequence 0155; Tables 2.21.3.7

The warfarin overall mean INR time in therapeutic range was 64.4%, a rate comparable to recent trials such as SPORTIF III and V and ACTIVE-W. The INR control (TTR) was 66.9% for US/Canada, similar to the TTR in Western Europe. Half of the RE-LY subjects were warfarin-naive, a larger proportion than other recent large AF trials. Naïve subjects have lower TTRs for the initial treatment period compared to warfarin-experienced subjects. The warfarin-experienced cohort in RE-LY had a 67.2% time in therapeutic range compared to

61.8% for naïve subjects (NDA amendment Table 15.1.5: 11). When assessing overall INR control by increasing the size of the INR range of interest beyond the interval of 2.0 – 3.0, the results demonstrate progressively better overall INR control for warfarin-treated subjects. The percent of time in the INR range 1.8 – 3.2 was 78.8% and in the INR range 1.5-4.0 was 93.1% (NDA Amendment Tables 15.1.5: 24 and 15.1.5: 27). These data establish that the use of warfarin in RE-LY was similar to all recent large clinical trials and at least as good as historical clinical trials.

The primary endpoint, stroke/SEE and its components are presented for all treatment groups in the Table 1.5: 2, which is an intention-to-treat analysis.

Table 1.5: 2 Yearly Event Rate for Primary Endpoint - Stroke/SEE

	DE 110 BID N (%)	**DE 150 BID N (%)**	**Warfarin N (%)**
Subjects randomized	6015	6076	6022
Subject-years	11899	12033	11794
Subjects with stroke/SEE	183 (1.54)	134 (1.11)	202 (1.71)
Stroke	171 (1.44)	122 (1.01)	186 (1.58)
Ischemic stroke	152 (1.28)	103 (0.86)	134 (1.14)
Hemorrhagic stroke	14 (0.12)	12 (0.10)	45 (0.38)
Stroke of uncertain classifications	7 (0.06)	9 (0.07)	10 (0.08)
SEE	15 (0.13)	13 (0.11)	21 (0.18)

Each subject with an event was counted once for the composite endpoint and once for each component of the composite endpoint. In case of recurrent events, only the first event was considered.
Patient-years = sum (date of study termination – date of randomization +1) of all randomized subjects / 365.25.
Yearly event rate (%) = No. of subjects with event/subject-years * 100
Source: NDA Amendment; Table 15.2.1.1: 1

Compared to warfarin, both DE doses prevent hemorrhagic strokes to a similar extent. The relative benefit of DE 150 BID on ischemic stroke compared to warfarin is smaller than the relative effect on hemorrhagic stroke but the absolute reduction in ischemic strokes is approximately the same. Both doses of DE are clearly non-inferior to warfarin with the DE 150 BID dose superior to warfarin for the prevention of stroke/SEE (Table 1.5: 3).

The primary statistical analysis used the Hochberg procedure to adjust for multiple comparisons; 97.5% confidence intervals were assessed for the superiority comparison of DE 150 BID and warfarin. DE 150 mg was superior to warfarin (Table 1.5: 3).

Table 1.5: 3 Hazard Ratios and CIs for Primary Endpoint - Stroke/SEE

	DE 110 BID vs Warfarin	**DE 150 BID vs Warfarin**
Hazard ratio (SE)	0.90 (0.09)	0.65 (0.07)
95% CI	0.74, 1.10	0.52, 0.81
97.5% CI	0.71, 1.13	0.51, 0.83
P-value for non-inferiority using 1.46	<0.0001	<0.0001
P-value for superiority	<0.0001	<0.0001

Source: NDA Amendment; Table 15.2.1.1: 3, Table 15.2.1.1: 4, Table 15.3.5.4: 4

Multiple sensitivity analyses were conducted on the primary endpoint and all confirmed the non-inferiority of both doses of blinded DE to warfarin and the superiority of DE 150 BID to open-label warfarin. These analyses included the following: (1) analysis based on only the first 450 events, (2) an analysis with a non-inferiority margin determined on a logarithmic rather than a linear scale (1.38 vs 1.46), (3) analyses of warfarin-naïve- and warfarin-experienced subjects considered separately, (4) on treatment-only analysis censoring subjects after treatment discontinuation, (5) DE treatment group comparisons to only well controlled warfarin subjects (mean TTR $\geq$ 65% and $\geq$ 68%).

There were no significant by-treatment interactions for any subgroup analysis of the primary endpoint. Stroke rates generally increased with increasing age and decreasing renal function. The hazard ratios remained similar in all key subgroups with DE 150 BID superior to warfarin and DE 110 BID similar to warfarin.

However, at the age of 80, the stroke/SEE yearly rate was comparable for both double-blind doses of DE and lower than the rate in the warfarin group (DE 110 BID: 1.88%; DE 150 BID: 1.78%; warfarin: 2.72%; NDA Sequence 0132): there was a relationship between dabigatran plasma levels and the occurrence of stroke.

The results for both secondary composite endpoints (stroke/SEE and all-cause death and Stroke, SEE, PE, MI and vascular death) showed the same pattern as for the primary endpoint, namely, the yearly event rate of the composite endpoint was numerically lower than warfarin for both DE doses with the DE 150 BID superior to warfarin.

There were 1371 deaths during the study. Sixty four percent were adjudicated as vascular deaths. All-cause deaths decreased 9% and 12% for DE 110 BID and DE 150 BID versus warfarin, respectively. Vascular deaths decreased 10% and 15% for DE 110 BID and DE 150 BID, respectively, compared to warfarin. The DE 150 BID vs warfarin comparison has a nominal p value slightly below 0.05 (Table 15.2.2.2: 1). The most common causes of vascular death were cardiovascular sudden death and pump failure. The differences in the number of deaths between the DE and warfarin groups were mainly due to fewer strokes and fatal bleeds in the DE groups. Causes of non-vascular death were similar between all treatment groups with cancer and respiratory failure most common (Table 15.3.2.4: 1).

Other adjudicated efficacy endpoints included MI, PE, transient ischemic attack (TIA) and hospitalizations. There were no statistically significant between-group differences for any of these endpoints other than hospitalization occurring less frequently on DE 110 BID compared to warfarin. PEs occurred infrequently (<0.2%/year) with a maximum difference of 7 total cases between treatment groups. TIAs occurred at <1.0%/year with lower occurrence rates for both DE doses compared to warfarin. The frequency of MIs was low (<1.0%/year) with about a 0.2% excess annual rate in both DE groups compared to warfarin. The reason for the observed imbalance in MI frequency between the DE and warfarin groups is not apparent. Approximately 20% of MIs occurred after subjects discontinued study therapy with an imbalance against DE persisting, even off study drug for > 90 days. There was no evidence of a rebound effect when discontinuing DE.

Safety

All major prespecified categories of bleeding occurred less frequently on both doses of DE compared to warfarin except for non-life-threatening major bleeds when comparing DE 150 BID and warfarin (Table 1.5: 4).

Table 1.5: 4 Yearly Event Rate of Bleeding - RE-LY Study

	DE 110 BID N (%)	DE 150 BID N (%)	Warfarin N (%)
Adjudicated Bleeds			
Number of subjects	6015	6076	6022
Subject-years	11899	12033	11794
Major bleeds (%/year)	342 (2.87)	399 (3.32)	421 (3.57)
Life threatening MBEs	147 (1.24)	179 (1.49)	218 (1.85)
Other MBEs	218 (1.83)	248 (2.06)	226 (1.92)
ICH[1]	27 (0.23)	38 (0.32)	90 (0.76)
Minor bleeds[2]	1566 (13.16)	1787 (14.85)	1931 (16.37)
Any bleeds[2]	1754 (14.74)	1993 (16.56)	2166 (18.37)

[1] ICH includes subdural and subarachnoid bleeds in addition to intracerebral bleeds.
[2] Investigator-reported bleeding events. Minor bleeds were not adjudicated.
In case of a recurrent event of the same category, the first event was considered.
Subject-years = sum (date of study termination - date of randomization +1) of all randomized subjects / 365.25.
Yearly event rate (%) = # of subjects with event / subject-years * 100.
Source data: NDA Amendment; Table 15.3.2.1: 1, Table 15.3.2.1: 2

Gender, prior VKA use and ethnicity did not appear to influence the time to first major bleed or the yearly event rate across all treatment groups. As previously observed for anticoagulants, elderly subjects, subjects with renal dysfunction and those with higher CHADS2 scores had a higher risk of bleeding in RE-LY across all treatment groups including warfarin.

Major bleeds within a critical area or organ occurred at twice as often with warfarin treatment compared with DE (15.1%, 14.2%, and 30.2% of major bleeds for DE 110 BID, DE 150 BID, and warfarin, respectively) (Table 7.3.1: 4, NDA Amendment Tables 15.3.2.1: 2 and 15.3.2.1: 7). Over twice the number of symptomatic intracranial bleeds occurred with warfarin compared with either DE treatment. For all categories of symptomatic bleeding into a critical area/organ, fewer events occurred for DE compared to warfarin with one exception. Additionally, more fatal bleeds were associated with the use of warfarin (NDA Amendment Table 15.3.2.1: 7).

DE treatment resulted in a higher incidence of major GI bleeds (1.14%/year for DE 110 BID, 1.57%/year for DE 150 BID, and 1.07%/year for warfarin) and any GI bleeds (5.41%/year for DE 110 BID, 6.13%/year for DE 150 BID, and 4.02%/year for warfarin) than warfarin (Table 7.3.1: 6 and NDA Amendment 15.3.2.2.8: 1).

Overall, in subjects with moderate renal dysfunction (CrCl 30-50 mL/min), bleeding rates for the both DE doses were comparable to warfarin.

In those over the age of 80, major bleed rates were higher on dabigatran. The DE 110 BID dose had lower bleed rates than DE 150 BID. (DE 110 BID: 5.25%; DE 150 BID 6.24%; warfarin 4.70%; NDA Sequence 0132, Table 2.9). There was a significant between-treatment interaction for yearly major bleed rates with or without other covariates in the model (p=0.0038; NDA Sequence 0132, Table 2.10). In subjects over 75, there were more GI bleeds on DE. In patients under 65, there were more GI bleeds on warfarin. Absolute rates increased with age.

RE-LY subjects treated with DE 150 BID had a higher risk of discontinuation of study medication due to MBEs compared with DE 110 BID and warfarin subjects for the first 18 months of treatment but after this time, the risk was generally similar.

INR control in the warfarin treatment group was related to major bleeding with better levels of INR control on warfarin associated with fewer major bleeds. However, when looking at the post-randomization identified groups with INR TTR $\geq$ 65% and INR TTR $\geq$ 68%, DE 110 BID was still superior to warfarin with fewer major bleeds while DE 150 had both lower bounds of the 95% CI that included 1.00.

The use of ASA nearly doubled the rate of major bleeds for all treatment groups with no differential impact of treatment.

Increased dabigatran plasma levels were associated with an increased bleeding risk. Subjects with major bleeds had, on average, a 50% greater dabigatran plasma level than those with no bleeding.

Overall AEs

The AEs reported in RE-LY were not unexpected, considering the enrolled study population. This study was in an elderly population (mean age was 71.5 years at baseline) treated with an anticoagulant, receiving multiple concomitant medications, and often having multiple concomitant illnesses. All AEs were presented using the safety dataset (on treatment) (Table 1.5: 5).

The overall incidence of reported AEs was similar across the 3 treatment groups, although slightly higher in both DE groups (DE 110 BID [78.6%] DE 150 BID [78.3%] compared to warfarin [75.9%]; NDA Amendment, Table 15.3.2.6: 1). For overall AEs, the SOCs with the highest incidence of AEs for both dabigatran-treated subjects and for warfarin-treated subjects were GI disorders, infections and infestations, and general disorders (NDA Amendment, Table 15.3.2.6: 30). The most frequently occurring AEs (in MedDRA preferred terms) for DE 110, DE 150, and warfarin-treated subjects, respectively, were dyspnea (8.3%, 8.7%, 9.2%), dizziness (7.6%, 7.6%, 9.2%), and peripheral edema (7.5%, 7.3%, 7.6%). Warfarin-treated subjects had the highest incidence in all of these AEs (NDA Amendment, Table 15.3.2.6: 30).

Dyspepsia, nausea and GI bleeding were the most common AEs leading to discontinuation, having higher frequencies for both DE groups compared to warfarin.

GI AEs were reported the most frequently for DE 110, DE 150 and warfarin (34.6%, 34.5%, 24.1%, respectively; NDA Amendment, Table 15.3.2.6: 30). The most frequently reported GI AEs (preferred terms) for DE 110, DE 150, and warfarin groups, respectively, were diarrhea (5.9%, 6.1%, and 5.5%) and dyspepsia (6.2%, 5.7%, and 1.4%). Less frequently occurring was the incidence of bronchitis 4.4%, 4.6%, 4.8% and hypertension at 4.2%, 3.9%, and 4.4% (for DE 110, DE 150, and warfarin groups, respectively (NDA Amendment, Table 15.3.2.6: 30).

Deaths were discussed earlier in the efficacy results. Deaths were reported for 1371 subjects during the study, of which 64% were adjudicated as vascular deaths.

The incidence of SAEs was similar across all treatment groups (DE 110 BID [21.1%], DE 150 BID [21.3] warfarin [22.6]); although fatal SAEs, life-threatening AEs, and events that required hospitalization were more common with warfarin – with similar rates in both DE groups. No definitive relationship was determined between DE dose and the overall incidence of specific AEs or SAEs other than bleeding-related events (NDA Amendment Tables 15.3.2.6: 2 and 15.3.2.6: 4). Two AEs with small differences by dose included dyspnea (DE 110 BID 8.3% vs DE 150 BID 8.7%) and anemia (DE 110 BID 3.0% vs. DE 150 BID 3.4%) (NDA Amendment, Table 15.3.2.6: 30).

DE subjects had a lower incidence of fatal AEs, life-threatening AEs, and events that required hospitalization when compared to warfarin subjects – with similar rates in both DE groups (NDA Amendment, Table 15.3.2.6: 1).

Table 1.5: 5 Summary of Adverse Events (safety set)

	DE 110 BID N (%)	DE 150 BID N (%)	Warfarin N (%)
Number of subjects	5983 (100.0)	6059 (100.0)	5998 (100.0)
Any AE	4703 (78.6)	4746 (78.3)	4551 (75.9)
SAEs	1263 (21.1)	1290 (21.3)	1357 (22.6)
Fatal*	107 (1.8)	100 (1.7)	122 (2.0)
Immediately life-threatening	50 (0.8)	46 (0.8)	64 (1.1)
Disability/incapacitating	575 (9.6)	532 (8.8)	592 (9.9)
Required hospitalization	1073 (17.9)	1090 (18.0)	1178 (19.6)
Prolonged hospitalization	95 (1.6)	71 (1.2)	89 (1.5)
Other	215 (3.6)	252 (4.2)	230 (3.8)
Preferred terms for SAEs (incidence ≥ 0.9% in any treatment)**			
Congestive heart failure	83 (1.4)	58 (1.0)	73 (1.2)
Cardiac failure	51 (0.9)	62 (1.0)	65 (1.1)
Pneumonia	74 (1.2)	70 (1.2)	62 (1.0)
Atrial fibrillation	64 (1.1)	55 (0.9)	74 (1.2)
Gastrointestinal hemorrhage	38 (0.6)	55 (0.9)	41 (0.7)
Other significant AEs according to ICH	775 (13.0)	875 (14.4)	586 (9.8)
AEs leading to death*	121 (2.0)	110 (1.8)	135 (2.3)
AEs leading to discontinuation of trial drug	1138 (19.0)	1243 (20.5)	939 (15.7)
Preferred terms for discontinuations (incidence ≥ 0.7% in any treatment **)			
Anemia	43 (0.7)	61 (1.0)	39 (0.7)
Dyspepsia	57 (1.0)	57 (0.9)	2 (0.0)
Gastrointestinal hemorrhage	39 (0.7)	55 (0.9)	37 (0.6)
Dyspnea	37 (0.6)	43 (0.7)	33 (0.6)
Nausea	41 (0.7)	42 (0.7)	20 (0.3)
Severe AEs	1724 (28.8)	1749 (28.9)	1707 (28.5)
Preferred terms for severe AEs (incidence ≥ 1.0% in any treatment **)			
Pneumonia	103 (1.7)	95 (1.6)	111 (1.9)
Cardiac failure congestive	118 (2.0)	93 (1.5)	110 (1.8)
Cardiac failure	79 (1.3)	91 (1.5)	116 (1.9)
Atrial fibrillation	96 (1.6)	92 (1.5)	110 (1.8)
Syncope	60 (1.0)	53 (0.9)	57 (1.0)
Dyspnea	82 (1.4)	84 (1.4)	89 (1.5)
Related AEs	1244 (20.8)	1335 (22.0)	950 (15.8)
Preferred terms for severe AEs (incidence ≥ 1.0% in any treatment **)			
Dyspepsia	187 (3.1)	178 (2.9)	7 (0.1)
Nausea	58 (1.0)	73 (1.2)	12 (0.2)
Abdominal pain	65 (1.1)	69 (1.1)	8 (0.1)
Anemia	49 (0.8)	68 (1.1)	45 (0.8)
Diarrhea	69 (1.2)	67 (1.1)	11 (0.2)
Epistaxis	66 (1.1)	67 (1.1)	107 (1.8)
Hematuria	50 (0.8)	60 (1.0)	64 (1.1)

A subject may be counted in more than one seriousness criterion. MedDRA Version 12.0 used for reporting AEs.
Percentages are calculated using total number of subjects per treatment as the denominator.
*Deaths/fatalities due to AEs were reported only if investigator considered the AE related to study treatment.
**Preferred terms are in descending order by incidence for DE 150
Source: NDA Amendment; Table 15.3.2.6: 1, Table 15.3.2.6: 2, Table 15.3.2.6: 4, Table 15.3.2.6: 5, Table 15.3.2.6: 8, Table 15.3.2.6: 9

Both DE groups had a higher incidence of AEs considered related to treatment. With similar incidences of AEs leading to discontinuations, AEs considered to be treatment- related by the investigators were reported at higher frequencies with DE treatment for the events dyspepsia, nausea and abdominal pain when compared to warfarin treatment.

In general, the AE safety profile for the commonly reported AEs demonstrated that DE was comparable to warfarin, with the exception of gastrointestinal AEs, which were reported more frequently with DE treatment.

Another direct thrombin inhibitor, ximelagatran, was reported to have an increased incidence of elevations of liver function tests and potential Hy's Law cases associated with its use, especially during its SPAF development program which included two Phase III warfarin comparative studies. This observation for another drug resulted in increased monitoring of liver function tests during the dabigatran SPAF clinical development program. Warfarin is a drug that is generally not considered to be hepatotoxic. There were generally fewer subjects with occurrences of elevations of ALT and AST at specified levels (i.e., > 3 x ULN, > 5 x ULN, > 10 x ULN; > 20 x ULN) on either DE dose compared to warfarin. There were also about half the number of reported potential Hy's Law cases in either DE group than in the warfarin group. There were readily available explanations for almost all potential Hy's Law cases (i.e., pancreatic cancer, cholelithiasis, etc.). One DE case and two warfarin cases were considered possibly drug related, when these cases were classified by an independent blinded academic expert reviewer who evaluated all potential Hy's Law cases. Dabigatran has been shown to have a similar or better hepatic safety profile than warfarin. In summary, given the following, (1) warfarin is used without LFT monitoring, (2) liver function monitoring in RE-LY detected the same or fewer abnormalities with DE use compared with warfarin use; monitoring of hepatic function during the administration of DE is not necessary.

One important aspect of the design of RE-LY was that both doses of DE were blinded, while warfarin treatment was open-label. This allowed a comparison of the impact of temporary treatment interruptions on both the DE and warfarin groups in a manner consistent with how DE will be used for the SPAF indication. Use of a double-blind double dummy approach would not have allowed development of such information. Discontinuation of DE for between 1 and 5 days was recommended in the protocol depending upon the type of procedure planned and the anticipated bleeding risk. Temporary interruptions for a surgery or procedure occurred in 4623 (25.6%) subjects (NDA Sequence 0132, Table 17.1) and of these subjects, more than half were from the US or Canada. Most temporary interruptions were for surgery and/or diagnostic procedures. Over 90% of the treatment interruptions were for elective procedures. More subjects in the DE groups were managed without bridging anticoagulant therapy as compared to subjects in the warfarin group (79.3% and 77.4% for DE 110mg bid and DE 150 mg bid, respectively, vs. 65.7% for warfarin; NDA Sequence 0132, Tables 17.2, 17.8, and 17.9). Strokes, MIs and bleeding events occurred at comparable frequencies in all treatment groups within the 30 days after reinitiating study medications following a temporary treatment interruption. Sufficient information is available to recommend strategies to manage DE treatment interruptions for elective, urgent and emergency situations, whether or not short term bridging anticoagulant therapy (e.g., UFH and/or LMWH) is needed.

Summary and Conclusion

Dabigatran has been demonstrated to be an effective anticoagulant in animal models of arterial and venous thrombosis. It has a constant relationship between its pharmacokinetics (plasma levels) and pharmacodynamic responses (aPTT, thrombin time, ecarin clotting time) in animals and in multiple populations (i.e., healthy volunteers, subjects undergoing orthopaedic surgery, subjects being treated for deep vein thrombosis and/or pulmonary embolism and subjects with atrial fibrillation).

Preclinical studies have identified no target organ toxicity of dabigatran etexilate, but an exaggerated pharmacologic effect of the active drug, dabigatran, is seen when it is given at pharmacologically excessive doses. Therefore, bleeding has been seen in long and short term animal safety studies. Dabigatran etexilate is neither mutagenic nor carcinogenic.

Two blinded doses of DE were selected for inclusion in the Phase III RE-LY study. This decision was made based upon pharmacokinetic, pharmacodynamic (i.e., D-dimer, aPTT), safety (bleeding) and efficacy data from DE Phase II studies as well as published data from another direct thrombin inhibitor, ximelagatran. This strategy also allowed the comparison of both blinded dabigatran doses to open-label warfarin as well as a blinded comparison of the two dabigatran etexilate dose strengths to assess the dose-response relationship for both safety (i.e., bleeding) and efficacy and to strengthen the reliability and robustness of the trial design.

The INR control (TTR was 64.4% for warfarin overall and 66.9% in USA/Canada) was comparable to recent warfarin trials (SPORTIF III and V, ACTIVE-W, AMADEUS).

RE-LY, a study in 18,113 subjects, unequivocally demonstrated that DE 150 BID significantly reduced the risk of the primary efficacy endpoint, stroke and systemic embolism and additionally reduced the risk of intracranial hemorrhage compared to warfarin. DE 150 BID also decreased the incidence of ischemic strokes, hemorrhagic strokes, vascular mortality and all bleeding events (all nominal p-values <0.05), with a comparable overall rate of major bleeding to warfarin, although there were more major and total GI bleeds on DE 150 BID than on warfarin. DE 110 BID was non-inferior to warfarin for reducing the risk of stroke and systemic embolism, while major bleeding, life-threatening bleeding, intracranial bleeding and any bleeding were all significantly reduced by this lower dose compared to warfarin. For those over the age of 80, DE 110 BID had similar efficacy to DE 150 BID with less bleeding and therefore had a better benefit/risk profile than both DE 150 BID and warfarin, and is thus most appropriate for use in this population. These results were robust with all sensitivity and subgroup analyses essentially having similar results.

More subjects discontinued both blinded DE doses compared to open-label warfarin, although there was no dose response relationship for any specific AEs. GI AEs such as dyspepsia and nausea occurred more frequently in DE subjects but there were no other important differences in the reported AEs between the treatment groups. There was no difference in the incidence of SAEs between treatment groups.

The clinical development program for dabigatran etexilate in the SPAF indication has shown that fixed doses of DE administered without the need for monitoring is an alternative to warfarin in the entire group of AF subjects for whom warfarin therapy can be considered.

2. BACKGROUND

2.1 EPIDEMIOLOGY OF ATRIAL FIBRILLATION

Atrial fibrillation (AF) is the most common arrhythmia in clinical practice, accounting for approximately one third of hospitalizations for cardiac rhythm disturbances. An estimated 2.3 million people in North America and 4.5 million people in the European Union have paroxysmal or persistent AF (R03-1232). The incidence of AF increases with age and this increase becomes larger over the age of 80 years (R03-1233). The prevalence of AF is approximately 9% in those between the ages of 80 and 90 years (R03-1233).

The mortality rate in AF subjects is twice that of age-matched individuals with a normal heart rhythm reflecting, at least in part, an increase in the risk of stroke (R09-4892). The risk of stroke is increased approximately 5-fold in subjects with AF (R96-0252) (Figure 2.1: 1). Up to 15% of all strokes are due to AF (AF strokes are more severe than other etiologies (P06-08196).

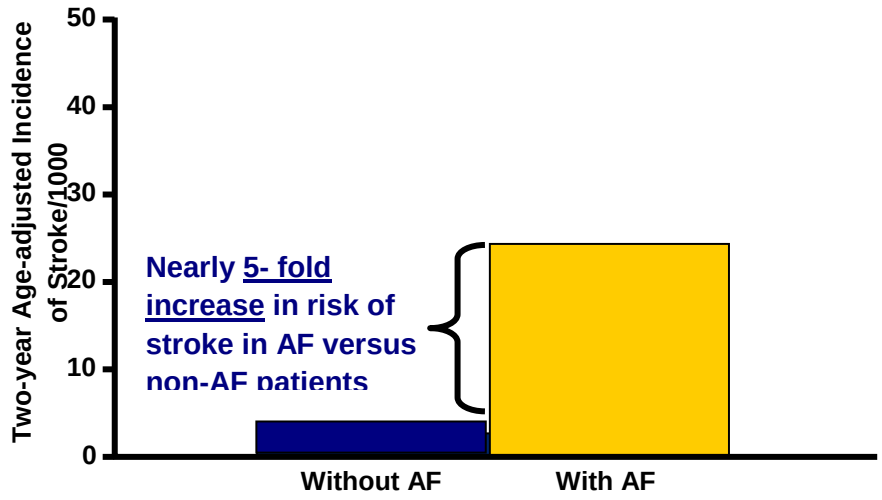


Figure 2.1: 1 Incidence of Stroke According to Presence or Absence of AF Adjusted for Age

Source: P09-01180

Most of the strokes in AF subjects are cardioembolic in origin. Thrombi form because of stagnation of blood in the fibrillating left atrium. Fragments can then dislodge from these thrombi and travel to the brain to cause a stroke or to the systemic circulation to produce an embolism.

The outcome of cardioembolic strokes is poor with a mortality rate of 25% at 30 days (P09-01180) and 50% at one year (R09-4892). The high mortality rate reflects the fact that strokes in AF subjects are more severe than those that occur in subjects with sinus rhythm. This concept is highlighted by the facts that strokes in AF subjects 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 (R09-4885). Because of the high risk of disabling and fatal stroke in subjects with AF and the healthcare expenditures associated with long-term care of these subjects, antithrombotic therapy is used to reduce the risk of stroke in AF subjects. Stroke in subjects with AF can be a serious, life-threatening, debilitating condition. During the past 20 years, hospital admissions for AF have increased by 66%[2] due to the aging of the population and more frequent diagnosis.

AF is an expensive public health problem—Medicare costs of newly incident AF cases identified through an initial hospitalization were approximately $108,000 annually per subject (R10-1345). According to American Heart Association statistics, the combined direct and indirect cost of stroke in the US was estimated to be $65.5 billion in 2008 (P09-01180). The annual cost burden of stroke due to AF is at least $9.8 billion per year. The majority of costs were due to high hospitalization rates and the need for rehabilitation and long-term care.

Key points:

- AF is a leading cause of ischemic stroke: subjects with AF have an approximately five-fold increase in the risk of stroke with worse severity and outcomes compared with those in sinus rhythm

- Severe strokes, such as those more frequently associated with AF, have a significant impact on quality of life and add significantly to the economic burden of the disease

2.2 CURRENT TREATMENTS FOR ATRIAL FIBRILLATION

For over 50 years, Vitamin K antagonists (VKAs) such as warfarin have been the only oral anticoagulants available for long-term treatment, such as for stroke prevention in subjects with AF. Additionally, aspirin (ASA) is used for subjects with AF, but ASA is much less effective than warfarin in AF subjects and is therefore currently used only for low risk subjects as per ACCP guidelines (P08-08090). Several recent trials have further explored other treatment options for patients with AF. ACTIVE-A was conducted in subjects with AF for whom VKA therapy was unsuitable and the ASA/clopidogrel treatment group demonstrated a reduced risk of major vascular events, especially stroke, compared to ASA alone, but also increased the risk of major hemorrhage; the ACTIVE-W (P06-06455) study was discontinued prematurely due to the superior efficacy of warfarin in stroke prevention compared to ASA/clopidogrel. The AMADEUS trial of idraparinux, a long acting Factor Xa inhibitor, failed in a Phase III trial due to excessive bleeding when compared to warfarin (P08-01644).

Current guidelines for the management of subjects with AF recommend the use of anticoagulation therapy (ASA and/or VKA) for subjects with AF at a moderate- to high risk of stroke. ASA has been shown to be superior to placebo in preventing strokes. However warfarin has been shown to be superior to ASA alone or when used together with clopidogrel.

2.3 UNMET MEDICAL NEED

Warfarin has been proven to be highly effective in preventing strokes; however, because of the difficulty of its management (i.e., periodic monitoring of anticoagulation, dietary restrictions, medication restrictions, concern about bleeding risk that can lead to patients having INRs around the low end of the target therapeutic range), many eligible AF patients do not receive warfarin treatment for stroke prevention or they receive an inadequate warfarin dose. For example, a registry of patients discharged from hospital revealed that only 54% of eligible AF patients received warfarin (P06-07839). Likewise, surveys indicated that many patients with AF cannot or will not take warfarin. In support of this concept, only 10% of patients with known AF who presented with an acute ischemic stroke had a therapeutic INR on admission; and even in those AF patients with a prior history of stroke or transient ischemic attack (TIA), only 18% had a therapeutic INR on admission.

Figure 2.3: 1 Survey of Patients in Clinical Practice - Percent of Warfarin Use in AF

Source: P06-07839

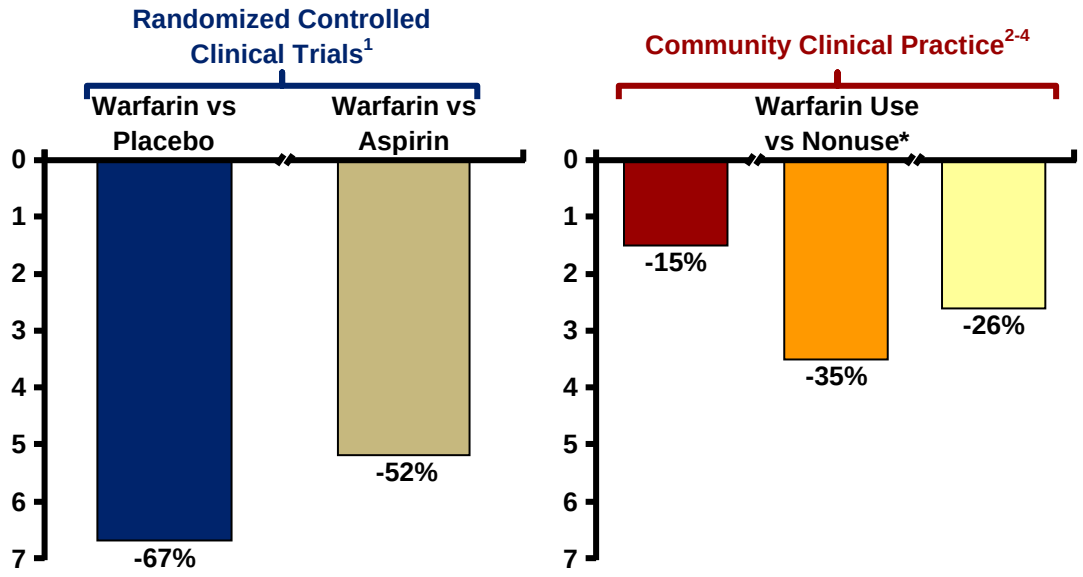


Figure 2.3: 2 Relative Risk Reduction in Two Randomized Clinical Trials vs. Three Clinical Practice Communities

Source: Left Panel - P99-02978, Right Panel - R06-2314, R10-1343, R10-1342

There is currently an unmet medical need in managing AF patients at risk of stroke. Due to the limitations of VKAs, a significant number of diagnosed patients living with AF are at a risk of stroke and are either not receiving appropriate anticoagulant therapy or are not treated at all. Therefore, there are multiple product profiles that would offer viable alternatives to warfarin. These include:

- similar efficacy and safety to warfarin and with better convenience
- better efficacy with similar safety profile to warfarin
- similar efficacy with a better safety profile than warfarin
- better efficacy, better safety, and better convenience

The ideal new alternative for warfarin would have better efficacy, better safety, and better convenience.

3. OVERVIEW OF PRECLINICAL DATA

Dabigatran is a potent, competitive, reversible direct thrombin inhibitor. It inhibits thrombin dependent conversion of fibrinogen to fibrin, thus preventing the formation of thrombus. Dabigatran inhibits free thrombin, fibrin-bound thrombin and thrombin-induced platelet aggregation. Dabigatran is very poorly absorbed via the oral route. However, dabigatran etexilate, a small molecule prodrug which has been shown not to have anticoagulant activity, is orally bioavailable. After oral administration, dabigatran etexilate is rapidly absorbed and converted to dabigatran by esterase-catalyzed hydrolysis in plasma and in the liver

3.1 DABIGATRAN CHEMICAL STRUCTURE

The chemical structure of the free base form of dabigatran etexilate and the active substance, dabigatran can be found in Section 4.2.2.

3.2 PHARMACOLOGY AND TOXICOLOGY

Dabigatran is a classical competitive inhibitor of the active site of serine proteases. It has a high affinity for the active site of thrombin, with a dissociation constant (Ki) of 4.5 nM. Trypsin was inhibited with a Ki of 50.3 nM. For all other proteases, (factor Xa, factor VIIa/tissue factor complex, factor XIa, plasma kallikrein, plasmin, 2-chain urokinase, tissue-type plasminogen activator, activated protein C, granulocyte elastase, and C1s esterase), inhibition was 1000-fold to 100,0000-fold higher than for thrombin.

In-vivo and *ex-vivo* animal studies have demonstrated antithrombotic efficacy and anticoagulant activity of dabigatran after intravenous administration and of dabigatran etexilate after oral administration in various animal models of venous and arterial thrombosis.

Multiple animal toxicology studies were conducted and the longer durations were in lifetime toxicology studies in rats (2 years) and mice (18 months). There was no evidence for a tumorigenic potential of dabigatran up to maximum doses of 200 mg/kg (free base equivalent). Teratology studies were performed with up to 200 mg/kg (free base equivalent) in rats and rabbits. A slight effect on the morphogenesis of foetuses was observed in rats at 200 mg/kg (free base equivalent). No teratogenic effects were noted in rabbits.

In the fertility study in rats, no toxicologically remarkable parental findings were noted. With respect to litter parameters, a slight decrease in corpora lutea and an increase in pre-implantation loss led to a decrease in the mean number of implantations in the 200 mg/kg (free base equivalent) dose group. All observed adverse events were attributed to exaggerated pharmacologic activity (anticoagulant activity) of dabigatran that resulted in bleeding.

There was no evidence for any adverse effects on the liver in any of the animal safety or toxicology studies that were conducted including in Rhesus monkeys. The available individual animal data (clinical chemistry, organ weights, gross and histopathology) were also analyzed in accordance with 4.1 of the CHMP Draft “Reflection paper on non-clinical

evaluation of drug-induced liver injury (DILI)" from 24 June 2010 (R10-1326) since another direct thrombin inhibitor, ximelagatran was associated with hepatotoxicity in humans.

4. CLINICAL PHARMACOLOGY

4.1 SUMMARY

The pharmacokinetics (PK) and pharmacodynamics (PD) of DE were investigated in numerous clinical pharmacology studies and multiple Phase II and III studies including subjects with atrial fibrillation. There was a consistent correlation of dabigatran plasma concentrations and its pharmacodynamic activity, resulting in reproducible dose-dependent prolongations in clotting times with rapid onset and offset of these effects.

Phase I studies were conducted in healthy Caucasian and Japanese volunteers, as well as in the elderly, those with graded degrees of renal impairment, and those with hepatic insufficiency. A thorough QT study which evaluated therapeutic and supratherapeutic doses of DE also has been completed. In addition, a battery of drug-drug interaction studies has been performed including evaluations of P-gp inhibitors, inducers, and substrates.

The pharmacokinetic profile of dabigatran etexilate (DE) is characterized by maximum plasma concentrations at approximately 2 hours after oral administration, a bi-exponential distribution phase and a terminal half-life of about 11 h in healthy elderly($\geq$ 65 years) volunteers. Steady state is attained on Day 3 of treatment with BID dosing. The total and peak exposure have been shown to increase linearly and are dose proportional after single and multiple oral dosing of DE in a dose range between 10-400 mg single dose and 50 to 400 mg TID, respectively. Accordingly, after the two studied DE doses in the RE-LY trial (DE 110 BID and DE 150 BID), plasma concentrations of dabigatran were dose proportional.

Due to its physicochemical properties the oral bioavailability of dabigatran etexilate is low (6.5%) and exhibits a moderate to high intra- and intersubject variability. However, in chronically treated AF subjects, the intra-subject variability of dabigatran trough levels was moderate (38.9%).

Dabigatran is mainly (80-85%) eliminated in the unchanged form via glomerular filtration. There are effects of age, creatinine clearance, and gender on dabigatran plasma concentrations. Ethnicity did not have any major effect on the disposition kinetics or on the pharmacodynamics of dabigatran.

Administration of DE, as the capsule formulation to be marketed, together with a high-fat meal does not result in relevant changes of the mean bioavailability of dabigatran.

Dabigatran and dabigatran etexilate are neither substrates nor inhibitors or inducers of cytochrome P450 enzymes. Dabigatran is not a substrate, inducer or inhibitor of the efflux transporter P-glycoprotein (P-gp). However, dabigatran etexilate, the pro-drug is a substrate but not an inducer or inhibitor of P-gp.

Phase I studies were designed to observe maximal effects of P-gp inhibitors on dabigatran bioavailability by their administration in a fasted state 1 hour before dabigatran etexilate dosing to ensure high levels of P-gp inhibition, especially in the gut. Three studies demonstrated that ketoconazole, subchronic verapamil, and amiodarone increased dabigatran

plasma concentrations by about 2.5-fold, 1.5-fold, and 1.5- fold, respectively. In the RE-LY study, P-gp inhibitors, which had been shown to result in approximately 50% increases in dabigatran Cmax and AUC in Phase I studies (verapamil and amiodarone), only modestly increased the mean plasma concentrations of dabigatran up to a maximum of 20% (verapamil: 20% and amiodarone: 13%).

Pre-dosing of the potent P-gp inducer rifampicin at a dose of 600 mg QD for 7 days decreased dabigatran AUC and Cmax by 66% and 67%, respectively. There were too few subjects in RE-LY that received rifampicin to make conclusions regarding their concomitant use.

In the 18,113 randomized subjects of the RE-LY Phase III study, an age-adjusted plasma level vs ischemic stroke curve had a dose-response relationship with higher plasma concentrations associated with a lower ischemic stroke risk. There was a clear association of higher dabigatran plasma concentrations and the occurrence of major and any bleeding events. The median dabigatran plasma concentration in subjects with adjudicated major or any (minor+major) bleeding were on average about 50% and 20% higher, respectively, than in subjects who did not have any reported bleeding event.

There was a relationship between stroke/SEE and dabigatran plasma concentration that was more pronounced for ischemic stroke risk alone. There was a strong association between increased bleeding and increasing age in all treatment groups in RE-LY. This relationship was independent of dabigatran plasma concentration, although there also is a relatively strong relationship between increasing dabigatran plasma concentration and the risk of bleeding. Since plasma concentration after a given dose of DE are higher in the elderly, the totality of these data support the use of the lower DE dose (DE 110 BID) in those subjects over the age of 80 years.

4.2 HUMAN PHARMACOKINETICS AND ADME CHARACTERISTICS

4.2.1 Absorption and Distribution

Following oral administration to healthy volunteers, DE (BIBR1048) is rapidly converted by esterase-catalyzed hydrolysis to dabigatran (BIBR953). Peak plasma concentrations of dabigatran occur 1-2 hours after drug administration in the fasted condition. Plasma concentrations of dabigatran (AUC and Cmax) have been shown to increase linearly in proportion to dose following single oral doses of 10 - 400 mg or multiple doses between 50 and 400 mg TID (Figure 4.2.1: 1).

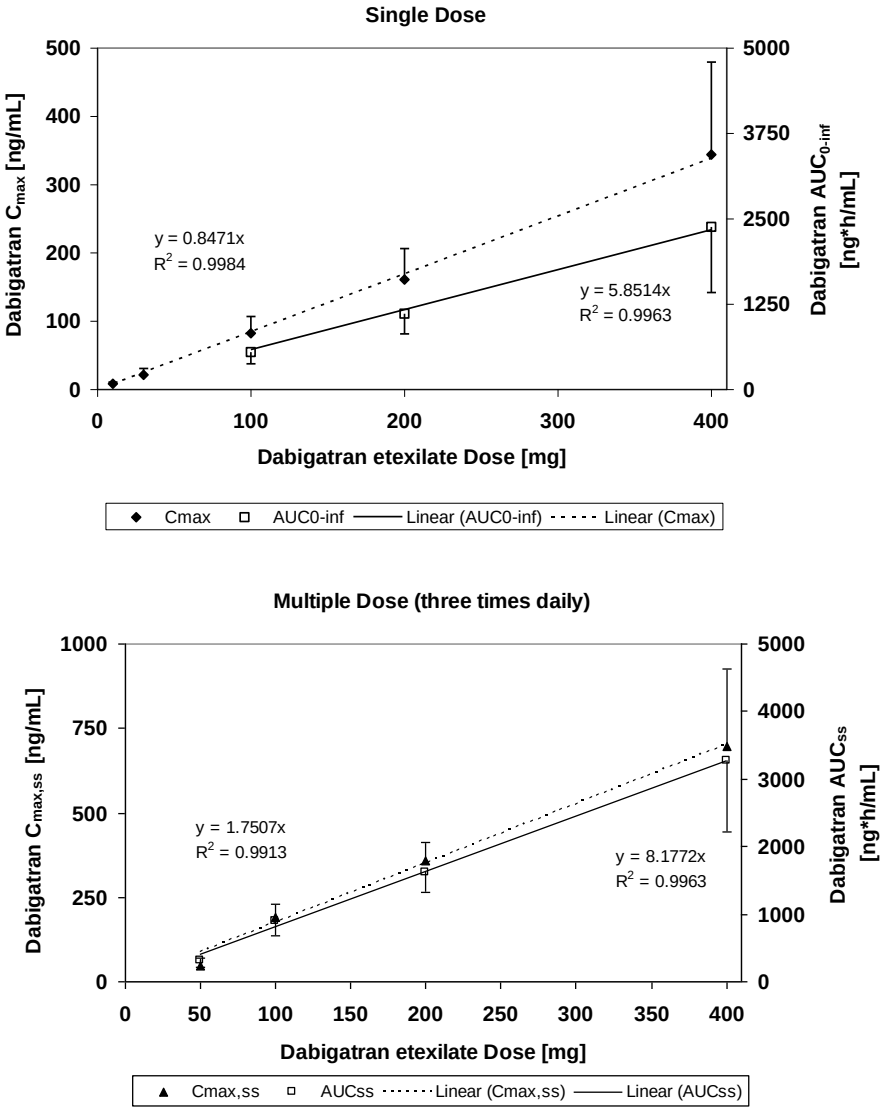


Figure 4.2.1: 1 Dose-Proportionality of Dabigatran Plasma Concentration Mean (SD) Increases of C_{max} and $AUC_{0-\infty}$, for Single Dose and $C_{max,ss}$ and AUC_{ss} for Multiple Doses

Source: U99-1502, Figure 9.4.1: 2; U00-1856, Figure 16.3.2: 60

Following intravenous administration of [^{14}C]-labeled dabigatran to healthy male volunteers, total radioactivity was primarily excreted via urine (range: 83.3%-87.2%) while following oral administration of [^{14}C]-labeled DE, total radioactivity was primarily recovered in feces (range: 82.6% - 88.6%) due to an incomplete absorption of DE. The current HPMC capsule formulation has an average absolute bioavailability of 6.5%. Despite the low bioavailability, reproducible and therapeutically sufficient exposure was observed in a long-term,

uncontrolled Phase II extension study in which plasma samples were collected periodically up to 51 months from AF subjects treated with DE 150 BID (Figure 4.2.1: 2).

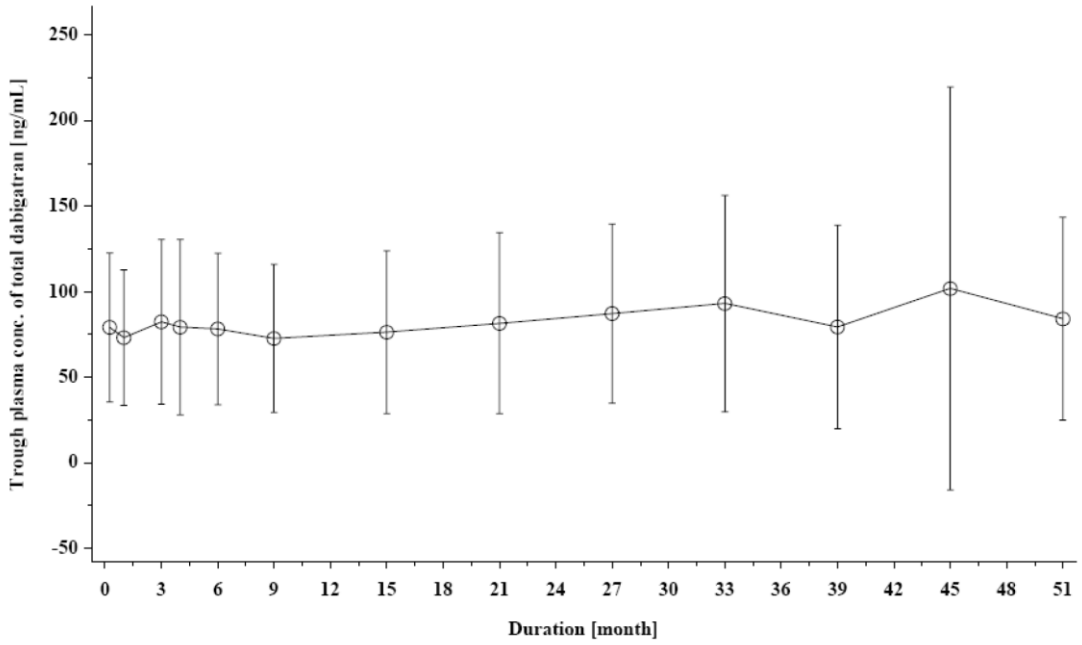


Figure 4.2.1: 2 Arithmetic Mean (SD) Trough Plasma Concentrations of Total Dabigatran Treatment Duration Exceeding 3 Years with DE 150 BID

Source: U09-3247; Figure 11.5.2: 1

Low (~ 30%) concentration independent binding of dabigatran to human plasma proteins has been observed. The volume of distribution of dabigatran is 60-70L, which indicates no extensive extravascular distribution into tissue.

4.2.2 Metabolism and Elimination

Dabigatran was by far the dominant compound in plasma, urine and feces following both oral administration of DE and intravenous administration of dabigatran. After oral administration, the pro-drug DE was not detected in urine. The predominant metabolic reaction was the cleavage of the pro-drug by esterase-catalyzed hydrolysis. Conversion of the pro-drug DE occurs via two intermediates, BIBR951 (an active thrombin inhibitor) and BIBR1087 (a pharmacologically inactive intermediate). After oral administration of DE, the vast majority is excreted in the feces. After DE administration, the pro-drug and the two intermediates are generally observed at trace concentrations compared with dabigatran and for very short periods of time (<6 h), indicating very rapid and complete conversion of DE to the active entity dabigatran. The exposure in humans to the pro-drug and each of the two intermediates was less than 1% of the exposure of dabigatran in human volunteers.

Dabigatran is subject to conjugation with activated glucuronic acid to yield a pharmacologically equipotent 1-O-acyl glucuronide which further undergoes non-enzymatic isomerization (Figure 4.2.2: 1).

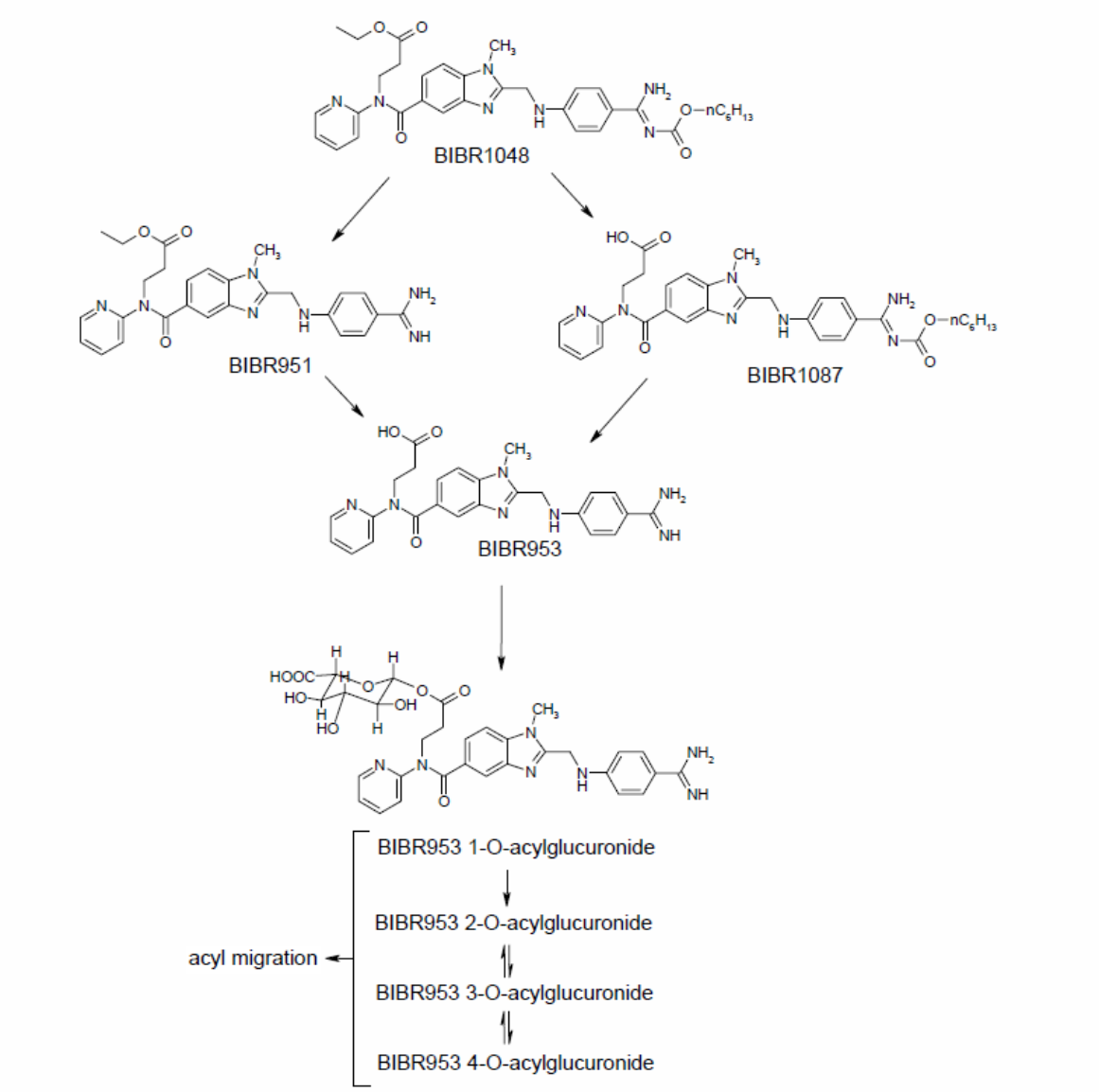


Figure 4.2.2: 1 Dabigatran Metabolism

Source: U06-1104-01, Figure 1: 1

The dabigatran glucuronide isomers generally amounted to approximately 20% of the total dabigatran AUC after oral dosing, independent of dose, duration of treatment or intrinsic (gender, age, race, renal or hepatic impairment) or extrinsic factors (co-medication). As the glucuronide is fully active, all analyses are in general referring to total dabigatran (sum of free and conjugated dabigatran in plasma).

After infusion of dabigatran, total and renal clearance ranged from 92-141 mL/min and 81-106 mL/min, respectively. Hence, dabigatran is almost exclusively excreted via glomerular filtration without net secretion or re-absorption.

The terminal half-lives of dabigatran after single oral dose are on average 9.41 h and 10.1 h in young male and female volunteers, respectively, and 10.7 h and 11.2 h in healthy, elderly (≥ 65 years) male and female volunteers, respectively. The half-life is prolonged to 15.3 h and 18.4 h in volunteers with mild or moderate renal impairment, respectively. The excretion of dabigatran into human breast milk or other excreta, such as sweat, semen or saliva was not investigated. Animal experiments in lactating rats demonstrated that between 0.08% and 0.125% of the oral dose of DE was recovered in milk (based on total radioactivity). This indicated slow transfer into milk and no accumulation of dabigatran in breast milk.

4.3 PHARMACOKINETICS IN SPECIAL POPULATIONS

The impact of creatinine clearance, age or sex on clearance, the impact of proton-pump inhibitors (PPI), amiodarone, or verapamil comedication on bioavaialbility and the impact of weight on volume of distribution, was incorporated into a combined view. Renal function was by far the most important factor compared to others including demographic factors such as gender, weight, age or ethnicity or extrinsic factors such as PPI or P-gp inhibitor co-medication.

4.3.1 Effect of Renal Insufficiency

In a dedicated Phase I study investigating the PK of dabigatran after a single oral dose of DE 150 QD in subjects with different degrees of renal impairment (none up to end stage renal disease), exposure and $t_{1/2}$ increased with decreasing CrCl. In the healthy control group, the gMean terminal half-life was 13.4 h. With moderate and severe renal insufficiency, the gMean half-lives increased to 18.4 h and 27.2 h, respectively. The gMean $AUC_{0-\infty}$ increased approximately 1.5-, 3.2- and 6.3-fold in individuals with mild, moderate and severe renal impairment, respectively, when compared to subjects with normal renal function. Dabigatran was shown to be removable from the systemic circulation by hemodialysis. After 4 hrs of dialysis, 68% of total dabigatran plasma concentrations were cleared by hemodialysis. Hemodialysis may be, thus, also applied in case of dabigatran overdosing.

Renal function was found to be a significant and clinically relevant covariate. In RE-LY, this was highly confounded with age. The magnitude of the impact of renal function on dabigatran PK was consistently observed in a PopPK analysis on Phase II data from orthopedic surgery and AF subjects and on Phase III data from in total >10,000 AF subjects. In comparison to the median CrCl of 68.64 mL/min in the RE-LY study, subjects with a CrCl of 50 mL/min and 30 mL/min have an 18% and 46% lower CL/F (apparent clearance). For a male subject, this would result in an about 1.2 and 1.8 fold increased $AUC_{\tau,ss}$ compared to a male subject with CrCL of 68.64 mL/min. The dependence of resulting trough concentrations on creatinine clearance is shown in Figure 4.3.1: 1.

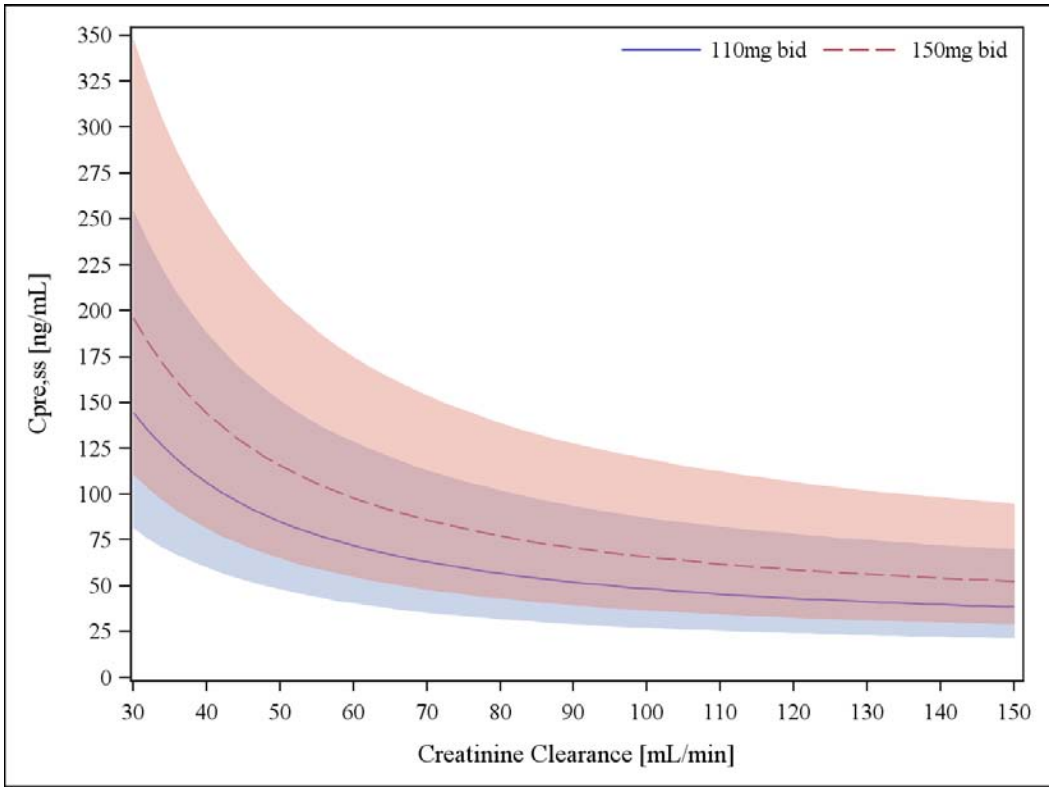


Figure 4.3.1: 1 Model Predicting Dabigatran Trough Steady State Concentration (Cpre,ss) Based on Creatinine Clearance with 80% Prediction Intervals

Source: U10-2017; Figure 11.3.2: 3

4.3.2 Effect of Liver Insufficiency

The influence of hepatic impairment on the absorption and bioconversion of DE was assessed in subjects with moderate hepatic impairment. The mean AUCs were similar to healthy controls (695 ng·h/mL in healthy volunteers and 656 ng·h/mL in subjects with chronic liver disease) and mean terminal half-life was approximately 11 hours in both the control group and in volunteers with hepatic impairment. The bioconversion of the prodrug to dabigatran was slightly slower in subjects with moderate hepatic impairment. Accordingly, the AUCs of DE and the two intermediates, BIBR 1087 and BIBR 951, were increased several fold. Relative to the AUC of total dabigatran in plasma, the AUC of BIBR 1087 represented 8.5%, followed by dabigatran etexilate with 2.6%, and 0.44% for BIBR 951. The AUCs of the pro-drug and its intermediates in the healthy control group were below 1 % of the AUC of total dabigatran. Protein binding and the extent of glucuronidation were not affected in subjects with moderate hepatic impairment.

The observed modest effect on the conversion of the prodrug to dabigatran does not require any dose adjustment in subjects with moderate hepatic impairment.

4.3.3 Effect of Gender, Age, Weight and Race

A meta-analysis on data from Phase I and Phase II studies revealed a gender effect with female subjects having an approximately 31-46% higher exposure than males after the same DE dose. The effect is most likely caused by the on average 29.5% lower CL_{CR} in female subjects. From the RE-LY PopPK analysis, after adjustment for other factors such as CrCl, age and weight, female AF subjects were found to have an 8.3% decreased CL/F compared to male subjects i.e. the steady state exposure ($AUC_{\tau,ss}$) of female subjects would be higher by 9.1% compared to male subjects (but percentiles overlap widely.) The slight effect on exposure was not associated with any increase in bleeding rates. Patients' age was found to affect dabigatran CL/F independently to the effects of CrCl. An increase of 1 year from the median age of 72 years reduced CL/F by 0.41%, A 97 year-old male subject (oldest subject in the RE-LY PopPK dataset) with a median CrCl (68.64 mL/min) and median weight (80.3 kg) had an approximately 11.5% higher steady state exposure ($AUC_{\tau,ss}$) compared to a 72-year-old subject. If not adjusted for renal function, subjects ≥ 75 years had a ~31% higher trough concentration and subjects < 65 years had a ~22% lower trough level compared with subjects aged between 65 and 75 years. These observations indicate that age-related differences in exposure are largely related to renal function, though there is a small additional effect of age itself. The combined effect of age and renal function has been shown.

Body weight was found in the RE-LY PopPK analysis to affect dabigatran volume of distribution (V2/F). An increase of 1 kg from the median body weight in RE-LY of 80.3 kg increased V2/F by 0.77% (The pure effect of weight on exposure is, however, negligible).

Not adjusted for other factors, the dabigatran trough concentrations in RE-LY were about 20% lower in subjects with a body weight > 100 kg compared with 50 - 100 kg. The majority (80.8%) of the subjects were in the ≥ 50 kg and < 100 kg category with no clear difference detected. Limited data in subjects ≤ 50 kg are available. As observed for gender effects, it is likely that any detectable difference in low versus high body weight subjects is largely attributed to body-weight-related differences in renal function.

Several Phase I and Phase II studies were performed in Caucasian and Japanese subjects, which allowed the comparison between these two ethnic groups. PK and resulting exposure were not meaningfully different in healthy subjects of Caucasian or Japanese origin. The RE-LY subgroup analyses in subjects with AF confirmed the lack of any meaningful differences in the PK of dabigatran between Asian, Caucasian and the limited number of Black (n=63) subjects.

4.4 DRUG-DRUG AND DRUG-FOOD INTERACTIONS

4.4.1 Drug-drug Interactions

In total, 13 pharmacokinetic or pharmacodynamic drug interaction studies were conducted, of which 2 were mainly targeted to elucidate the effect of DE on the PK of 2 probe substrates of the most abundant cytochrome P450 (CYP) isoenzymes: atorvastatin (CYP 3A4) and diclofenac (CYP 2C9). Two further studies addressed the effect of drugs that increased the gastrointestinal pH.

One study assessed potential PK/PD interactions with clopidogrel. Eight studies assessed potential interactions with various P-gp inhibitors, substrates or inducers.There was no significant influence of DE on the pharmacokinetics of either atorvastatin or diclofenac, and the exposure of dabigatran was not significantly altered by these drugs.

The bioavailability of dabigatran was modestly reduced (about 30%) in a dedicated Phase I study by the concomitant administration of the proton pump inhibitor (PPI) pantoprazole while the H_2-receptor antagonist ranitidine did not reduce the bioavailability of DE. In the clinical setting of RE-LY, about 14% of all observations were recorded under proton pump inhibitor (PPI) comedication. In this large Phase III dataset, covariate analysis revealed that PPIs decreased the bioavailability/steady-state exposure by 12.5%. In the RE-LY study, the H_2-receptor antagonist ranitidine did not reduce the bioavailability of DE.

In a Phase 1 study, steady state coadministration of dabigatran and clopidogrel had no effects on the PK or PD of either compound. In this Phase 1 study, when a loading dose of clopidogrel (300 or 600 mg) was given dabigatran $AUC_{\tau,ss}$ and $C_{max,ss}$ increased by about 30 to 40%. As clopidogrel is a substrate of P-glycoprotein (P-gp) a high loading dose may have competitively inhibited intestinal P-gp.

The steady state pharmacokinetics of digoxin (P-gp substrate) and dabigatran were not altered upon co-administration. $AUC_{\tau,ss}$ after DE 150 BID was compared with or without co-administration of pantoprazole, digoxin, atorvastatin, diclofenac or clopidogrel (Figure 4.4.1: 1, dashed reference lines are the lower and upper customarily used bioequivalence (BE) limits of 0.8 and 1.25).

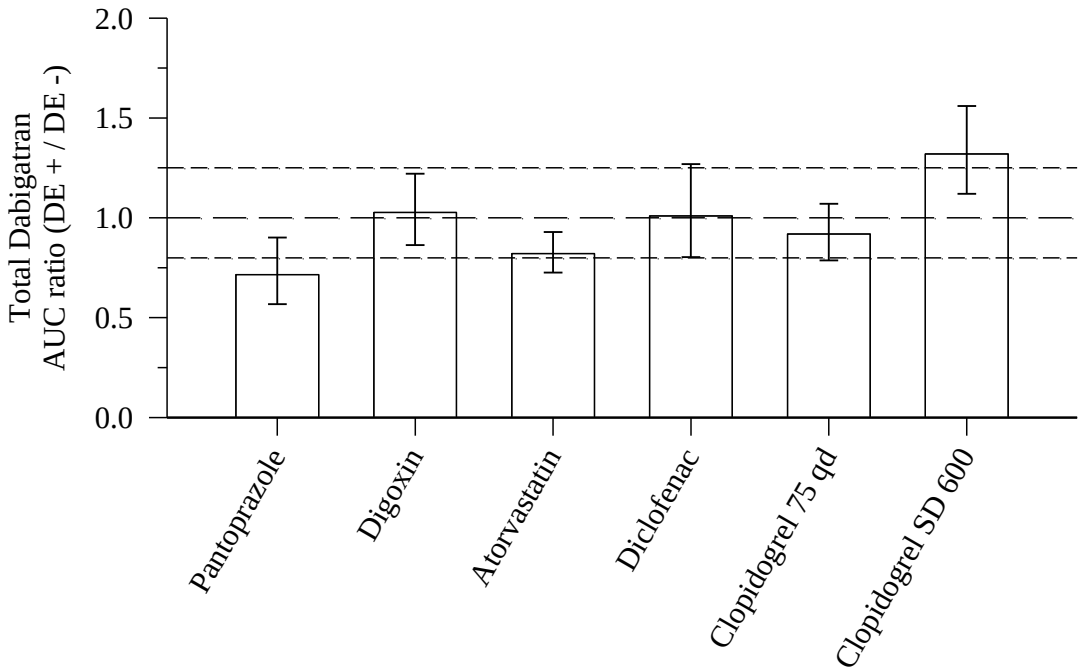


Figure 4.4.1: 1 Total Dabigatran AUC Ratio and 90% CI with BE Limits (0.80-1.25)

Source: U03-1353; U06-1608; U06-1611; U06-1612; U09-1547

The *in vitro* results imply that the efflux transporter P-gp is involved in the intestinal absorption of DE, whereas P-gp is not involved in determining the distribution and elimination of dabigatran. In total, seven *in vivo* drug interaction studies were performed in healthy volunteers to investigate the effects of concomitant use of:

- P-gp inhibitors: verapamil, quinidine, clarithromycin, ketoconazole and amiodarone or
- P-gp inducer: rifampicin.

The maximum increase in dabigatran bioavailability of about 150% (relates to an $AUC_{+ketoconazole}$ / $AUC_{-ketoconazole}$ gMean ratio of 2.5) was observed for ketoconazole, a potent inhibitor of P-gp. A similar effect was observed when a single dose of instant-release verapamil was co-administered.

A smaller increase was observed after single-dose administration of twice the dose of an extended release formulation of verapamil. After multiple dosing of verapamil (120 mg BID or QID), there was a 50-60% increase in dabigatran bioavailability. Amiodarone and quinidine exerted similar effects (50-60% increased bioavailability of dabigatran) as steady state verapamil.

Clarithromycin did not meaningfully influence the pharmacokinetics of dabigatran. (Figure 4.4.1: 2).

Consistent with all P-gp interactions between DE and P-gp inhibitors, which should only occur in the gut, when verapamil was administered 2 hours before DE intake, there was a marginal (<20%) impact on dabigatran bioavailability (Figure 4.4.1: 2).

After 7 days pre-treatment with rifampicin (600 mg QD), dabigatran AUC and C_{max} were reduced by 66% and 67%, respectively. Seven days after cessation of rifampicin treatment, dabigatran exposure was similar to when dabigatran etexilate was administered alone.

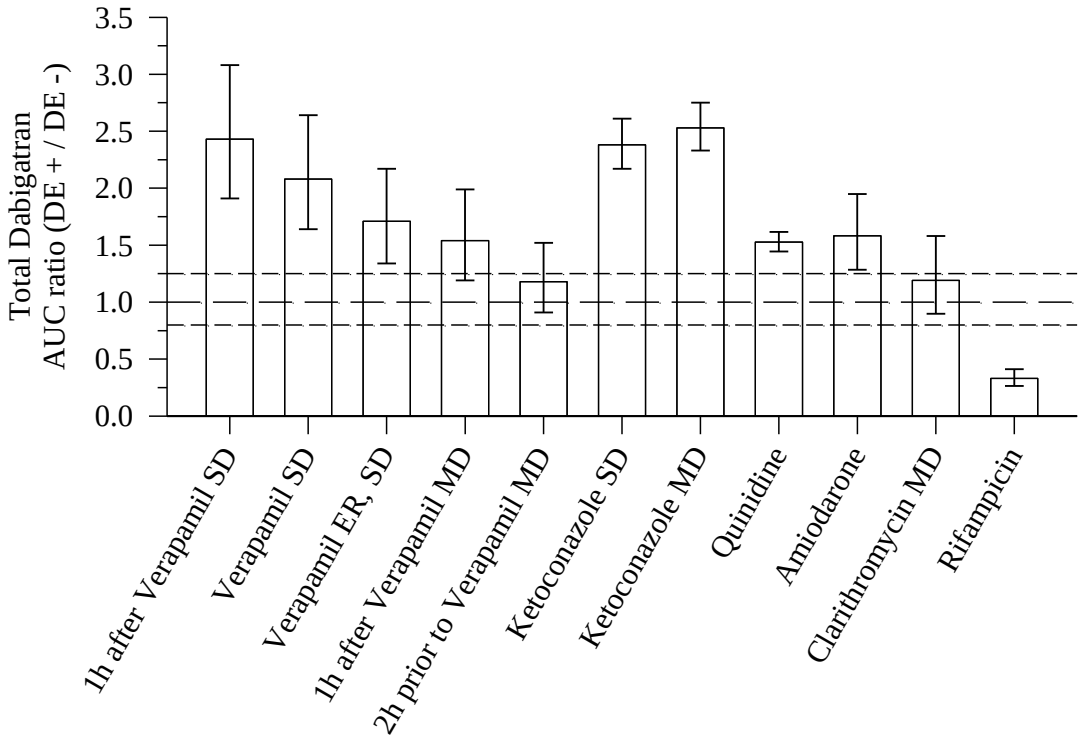


Figure 4.4.1: 2 Total Dabigatran AUC ratio and 90% CI after a Single Dose of DE 150 With- or Without Co-Administration of P-gp Inhibitors and Inducers

SD: Single Dose; ER: Extended Release; MR: Multiple Dose
Source: U06-1610, Table 11.1: 1; U08-2188; U09-1052; U09-3246; U09-1349; U09-1350

In RE-LY, the effect of concomitant use of verapamil, amiodarone or combined potent P-gp inhibitors (eg, verapamil and amiodarone) on trough and 2-hour dabigatran plasma concentrations was assessed. A maximum increase of dabigatran plasma levels of 20% was observed when amiodarone, verapamil or any strong P-gp inhibitor was co-administered during RE-LY (Table 4.4.1: 2). Patients co-administered with amiodarone were found to have a 13% increased bioavailability/steady-state exposure. Patients who received verapamil co-administration had a 20% increased bioavailability/steady-state exposure.

The larger effects seen in Phase 1 studies compared to the RE-LY study may be partially related to:

- continuous use of the P-gp inhibitors
- administration of the inhibitor not exactly 1 hour before DE intake
- use of P-gp inhibitors below their maximum labelled dose.

The theoretical risk of major bleeding in an average RE-LY subject of male gender, 72 years of age and with a CrCl of 68 mL/min with or without co-medication of chronic verapamil, amiodarone or quinidine, based on the maximum Phase I effect (+ 63%) is shown in Table 4.4.1: 1. The risk of major bleeding is compared to the observed occurrence of major bleeding in warfarin-treated subjects in RE-LY. Even the maximum effect observed during the Phase I studies would not increase the risk of major bleeding beyond the levels observed in subjects treated with warfarin in RE-LY.

Table 4.4.1: 1 Effect of P-gp Inhibitor Co-Medication on the Theoretical Risk of Major Bleeding (MBE) Compared to MBE Under Warfarin Treatment in RE-LY

	- P-gp inhibitor (control)	**+ P-gp inhibitor (+63%)**	**Warfarin**
Theoretical risk of MBE (%)	3.31	4.57	5.1

Source: NDA Amendment; Section 8.5, Table 3.2: 1

Furthermore, the difference in the observed event rates (i.e., major bleeding) in subjects receiving- or not receiving verapamil, amiodarone or diltiazem for certain times of treatment in RE-LY were not different from warfarin (NDA Amendment, Table 15.3.2.2.3: 6).

Table 4.4.1: 2 Effect of P-gp Inhibitor Co-Medication on Dose-normalized Dabigatran Trough and 2-Hour Post-Dose Concentrations in RE-LY

	Without co-medication			With co-medication			**gMean Ratio (+)/(-)**
Trough	N	gMean [ng/mL/mg]	gCV [%]	N	gMean [ng/mL/mg]	gCV [%]	
P-gp inhibitors	9726	0.773	80.9	2820	0.866	83.4	**1.12**
Amiodarone	11245	0.783	80.5	1310	0.885	90.1	**1.13**
Verapamil	11926	0.787	81.6	633	0.913	80.6	**1.16**
Diltiazem	11546	0.792	82.2	1012	0.807	75.4	**1.02**
Quinidine	12513	0.793	81.7	46	0.913	73.1	**1.15**
2-hour post-dose							
P-gp inhibitors	10574	1.48	73.5	3128	1.66	76.5	**1.12**
Amiodarone	12283	1.50	73.6	1428	1.65	80.4	**1.10**
Verapamil	13019	1.50	74.3	700	1.80	74.0	**1.20**
Diltiazem	12568	1.51	74.8	1150	1.58	70.5	**1.05**
Quinidine	13665	1.52	74.4	54	1.46	81.2	**0.96**

Source: NDA Amendment; Tables 15.6.1.1: 23-27

4.4.1.1 Pharmacodynamic Interaction

Antiplatelet agents (aspirin or clopidogrel) are known to increase bleeding. In the RE-LY study, the yearly major bleeding events were about twice as high in subjects receiving additional ASA or clopidogrel, but this effect was equivalent to the effect of ASA or clopidogrel on warfarin medication.

4.4.2 Drug-food Interactions

The effect of co-administration of high fat and high caloric meals on the bioavailability of DE has been investigated in 3 different studies. A total of 36 subjects participated in the 3 clinical studies.

Results from the 3 food-interaction studies with different DE tablet and capsule formulations yielded consistent results. None of the studies suggested a remarkable alteration of the DE bioavailability upon co-administration with high fat, high-caloric meals that would require either dose adjustments or respective recommendations for intake. For the to-be-marketed HPMC capsule formulation, bioavailability was increased on average by 27% and median

time to peak concentration was delayed from 2.0h to 4.0h (Figure 4.4.2: 1). Based on these findings, DE HPMC capsules can be taken with or without food.

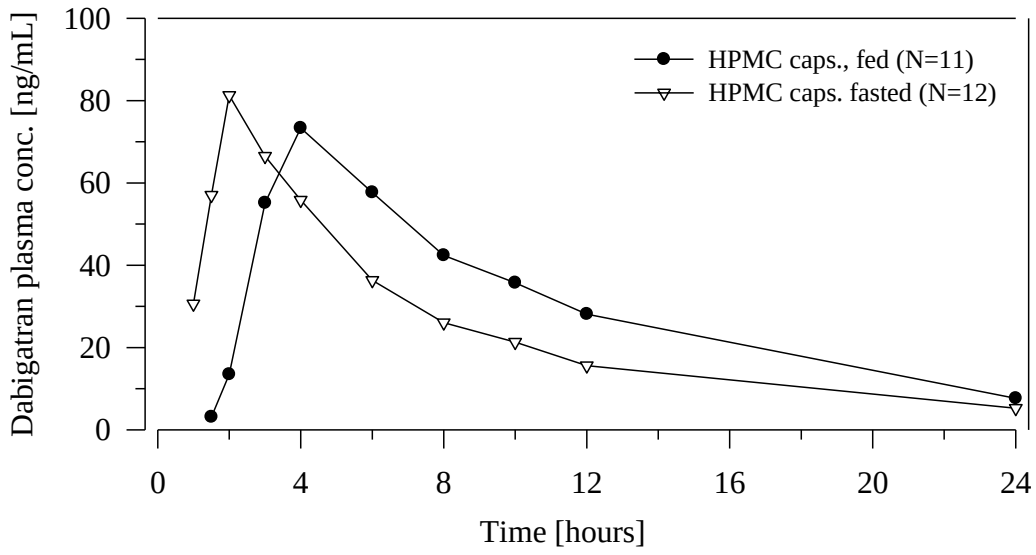


Figure 4.4.2: 1 gMean Total Dabigatran Plasma Concentration - Single Oral Dose of DE 150 in Fasted vs Fed Subjects

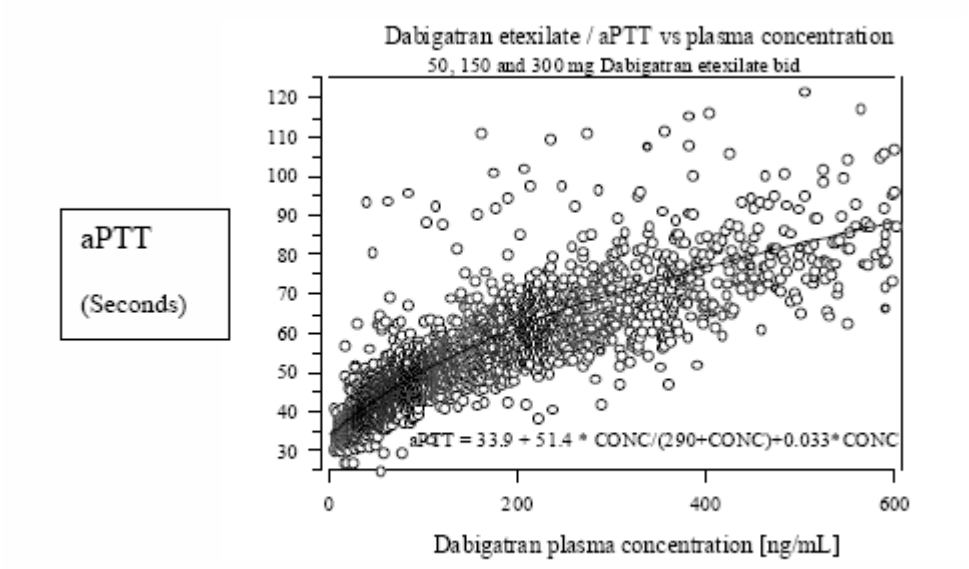
Source: U04-1459, Figure 15.5.5: 2

4.5 PHARMACOKINETICS/PHARMACODYNAMICS

4.5.1 Coagulation Time Assays

The prolongation of blood coagulation was assessed using conventional coagulation time assays. These assays comprised activated partial thromboplastin time (aPTT), prothrombin time (PT), expressed as International Normalized Ratio (INR), thrombin time (TT), and ecarin clotting time (ECT). The time curves for aPTT, INR, TT and ECT paralleled plasma concentration-time curves, with the maximum effect (E_{max}) of dabigatran on clotting parameters occurring at the same time as dabigatran C_{max}. This is indicative of a direct inhibitory effect by dabigatran on thrombin. At the highest DE dose tested (DE400 TID), 2- and 3-fold prolongations were observed at steady state for aPTT trough and peak levels. The pharmacodynamic effects of dabigatran declined in parallel with plasma concentrations, with residual effects still present 24 hours after the last administration.

While ECT and TT were linearly related to the dabigatran plasma concentrations, aPTT and dabigatran plasma level were related by a non-linear function as depicted by the respective regression curves (Figure 4.5.1: 1).



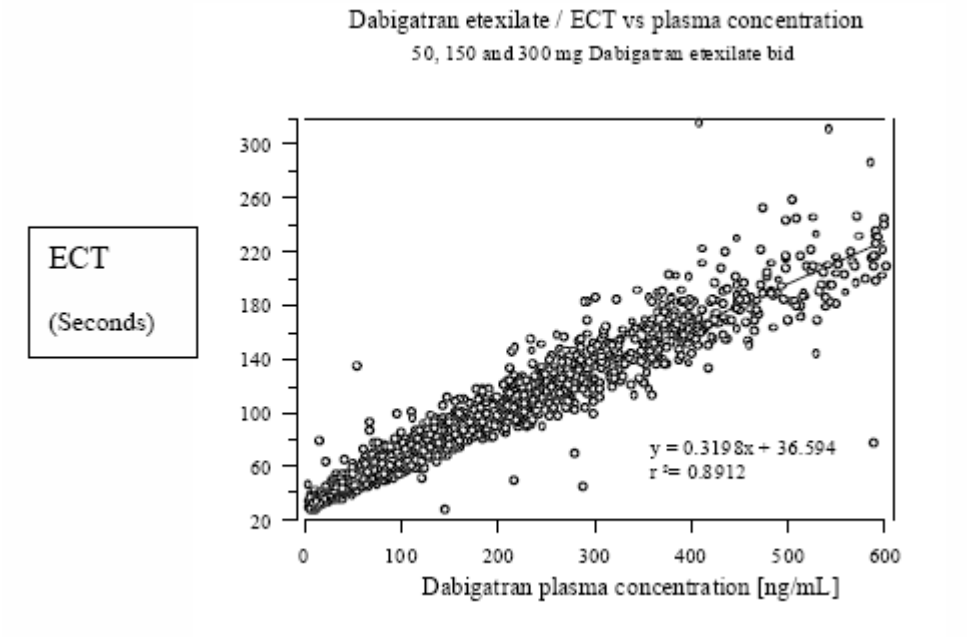


Figure 4.5.1: 1 Dabigatran Plasma Concentration Effects on Coagulation of aPTT and ECT at Steady State

Source: U06-1615, Figure 15.6.5.1: 5 and Figure 15.6.5.2: 8

INR does not correlate well with dabigatran levels and is not appropriate to assess the anticoagulant effects of dabigatran.

The PK/PD relationship was not different between males and females and not affected by mild or moderate renal or liver insufficiency. No apparent difference in the relationship between dabigatran exposure and pharmacological effect was observed between Japanese and

Caucasian subjects. The effect of ASA, gender, CL_{CR} and age on aPTT/concentration relationship was further tested for AF subjects in a population PK/PD model but nothing was found to significantly affect the PK/PD relationship. Further, no difference became obvious when comparing the pharmacological response of dabigatran in subjects with AF or healthy volunteers. In AF subjects of the RE-LY study, the gMean trough and 2-hour post-dose aPTT levels with DE 110 BID and DE 150 BID were 50.5 s and 54.9 s and 59.8 s and 65.4 s, respectively. In addition, ratios of post dose aPTT to pre-dose aPTT were 1.18 in the DE 110 BID group and 1.19 in the DE 150 BID group. The 90^{th} percentile at trough after 150 mg BID in RE-LY was 76.4 s.

Human QT study

In healthy subjects administered a single oral dose of either DE 150 or DE600, the upper limit of the 95% confidence interval of the individually corrected QT interval (QTcI) prolongation was well below 10 ms at both dose levels around t_{max} (1.5 to 3 h post dose), indicating no clinically relevant increase in the QTcI, compared with placebo. There was also no QTcI prolongation of greater 4 ms at any later or earlier time point between 1 and 6 h post dose. The heart rate changes were minimal for all treatments and for all time intervals, all in the range of +/- 2.0 beats per minute. In summary, there was no evidence that dabigatran, its pro-drug or intermediate metabolites had an adverse impact on cardiac electrophysiology, especially on cardiac repolarization as assessed by mean changes or outliers in the QT interval.

4.6 EXPOSURE-RESPONSE IN ATRIAL FIBRILLATION SUBJECTS

In all age groups, there was an association between dabigatran trough plasma concentrations and the probability of stroke/SEE (Figure 4.6: 1). The risk of stroke/SEE increased substantially with increasing age.

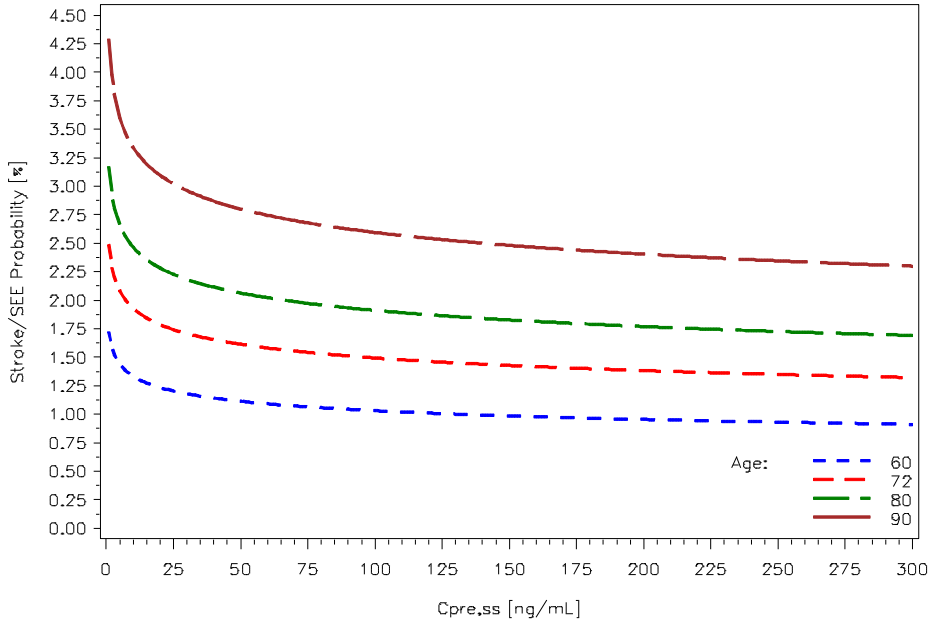


Figure 4.6: 1 Model Predicted Probability Stroke and Systemic Embolic Event vs. Trough Plasma Concentration of Total Dabigatran by Age in AF Subjects Receiving Either DE 110 BID or DE 150 BID (RE-LY)

Source: U10-3483-01

The relationship between the risk of stroke and dabigatran trough plasma concentrations is more pronounced when considering ischemic strokes/SEE rather than all strokes (Figure 4.6: 2). Note that the slope of the curves decreases with increasing dabigatran plasma concentrations. There is relatively little difference in stroke risk across a wide range of higher dabigatran trough concentrations, but age continues to influence stroke risk substantially. Twice as many subjects in RE-LY receiving DE 110 mg BID had trough plasma concentrations <50 ng/mL compared to subjects treated with DE 150 mg BID (33.5% vs. 16.8%). This could explain the fact that DE 150 BID was consistently found to be more efficacious than DE 110 BID. On the other hand, DE doses greater than 150 mg BID (median trough concentration of 150 mg BID 93 ng/mL) would be expected to result in only modest reductions in stroke risk/SEE.

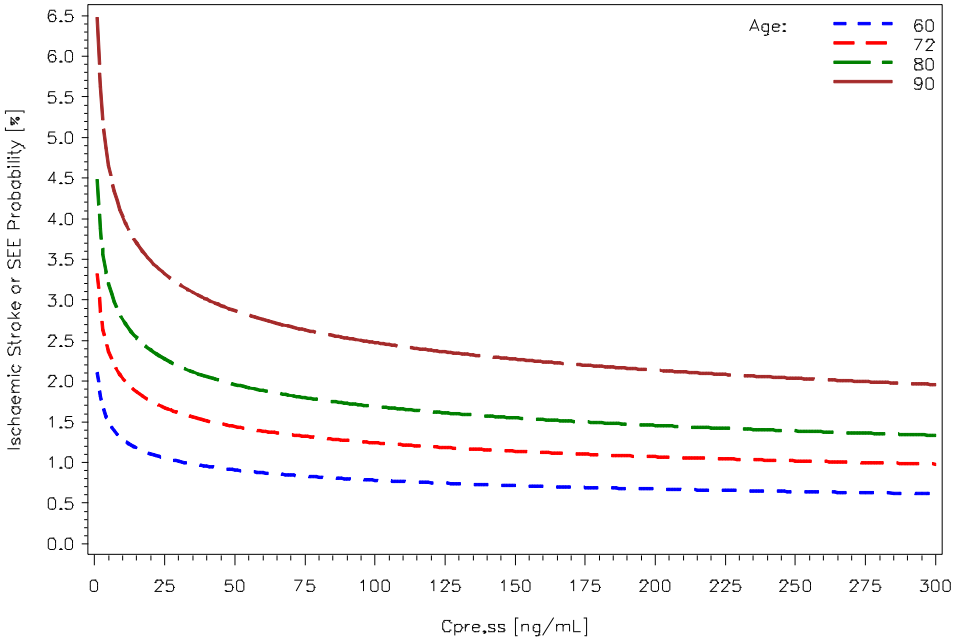


Figure 4.6: 2 Model Predicted Probability of Ischemic Stroke and Systemic Embolic Event vs. Trough Plasma Concentration of Total Dabigatran by age in AF Subjects Receiving Either DE 110 BID or DE 150 BID (RE-LY)

Source: U10-3483-01

There was a strong relationship between trough dabigatran concentration and an increased probability of having a major bleed (Figure 4.6: 3) consistent with the dabigatran dose-response relationship for bleeding in RE-LY. Since the slope of this curve is increasing rapidly, DE doses above those used in RE-LY (DE 150 BID) would be expected to substantially increase major bleeding rates.

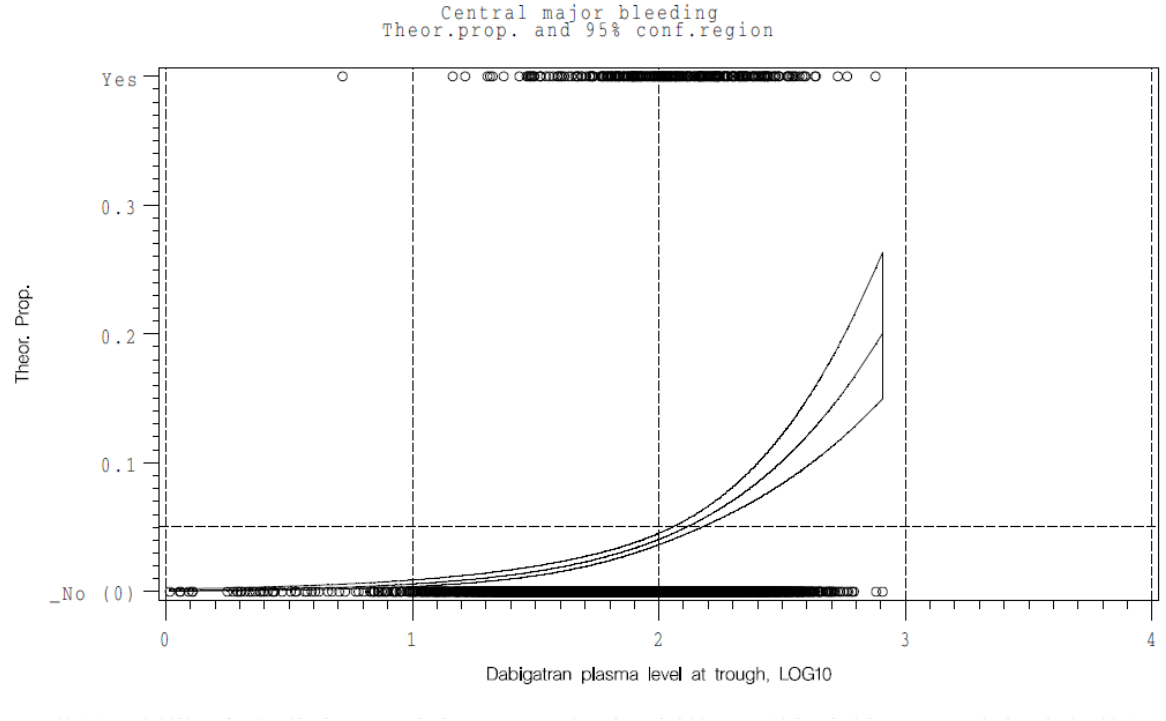


Figure 4.6: 3 Probability of Major Bleeding Events vs. Log Trough Plasma Concentration of Total Dabigatran in AF Subjects in RE-LY Receiving Either DE 110 BID or DE 150 BID. The Horizontal Line at 5.1% Depicts the Percent of Major Bleedings in the Warfarin-Treated Subjects of RE-LY

Source: NDA Amendment, Table 15.3.2.1: 5 and Section 8.5 Statdoc 18.3.1

As shown in Table 4.6: 1, the mean dabigatran plasma concentration in subjects with major or any bleeding (minor+major) were about 50% and 20% higher (with a large overlap between groups) than in subjects without a major or minor bleeding.

Beside exposure the risk of major bleeding is also dependent on other additional factors, especially age, renal impairment and concomitant administration of ASA.

Table 4.6: 1 Trough Plasma Concentration of Total Dabigatran Grouped by Bleeding Event Occurrence and Overall Trough Concentration in AF Subjects of RE-LY after DE 110 BID or DE 150 BID.

Trough total dabigatran plasma concentration [ng/mL]					
	Major bleed	Any bleed	No bleed	DE 110 BID	DE 150 BID
N	323	2319	5899	4227	4222
Mean	141	111	92.4	81.3	114
SD	97.7	83.0	67.9	58.9	81.9
Median	116	88.2	75.3	65.9	93.0
gMean	113	86.9	72.8	64.7	91.0
gCV [%]	79.8	81.4	84.0	79.9	81.9

Source: NDA Amendment, Table 15.6.1.1: 16 and Table 15.6.1.1: 17

The exposure-bleeding relationship is in complete agreement with the RE-LY results of significantly less bleeding events reported with the DE 110 BID dose compared with DE 150 BID and warfarin.

The balance between bleeding and ischemic stroke/SEE risk supports the use of the DE 150 BID dose in general. Some factors increase bleeding risk, especially older age which is frequently confounded with decreased renal function in subjects age 80 and above. DE 110 may provide the best risk/benefit ratio for those patients.

5. CLINICAL DEVELOPMENT OVERVIEW

The focus of this section is the SPAF indication. Following this discussion is a brief overview of clinical development for the non-SPAF indications (Section 5.2).

5.1 SPAF CLINICAL DEVELOPMENT

The clinical development program for dabigatran etexilate in the SPAF indication was designed to establish that fixed doses of DE without monitoring could be an alternative to warfarin in the entire group of patients with atrial fibrillation (AF) for whom warfarin therapy can be considered.

Three Phase II trials and a single Phase III trial randomized a total of 18,789 subjects, of whom 12,635 were randomized to dabigatran etexilate. Table 5.1: 1 presents the details for these studies.

Table 5.1: 1 Phase II/III Clinical Trials in SPAF Indication

Study ID (Phase)	Study Design	Treatment Groups	Duration	Number Randomized N
1160.20 (Phase II)	Randomized, parallel, open-label warfarin, ASA, double-blind dabigatran doses	DE 50 BID – DE 300 BID DE 50 BID – DE 300 BID + ASA 81-325 mg QD Warfarin, adjusted dose	12 Weeks	502
1160.42 (Phase II) Extension of 1160.20	Open-label, Long-term, Follow-up	DE 150 BID – DE 300 QD DE 150 BID – DE 300 BID	5 Years	(entered from 1160.20) 361
1160.49 (Phase II in Japan)	Randomized, parallel group, open-label for warfarin and dabigatran doses, 12 weeks treatment	DE 110 BID DE 150 BID Warfarin, adjusted dose	12 Weeks	174
1160.26 (Phase III) RE-LY	Randomized, parallel group, open-label for warfarin, double-blind for dabigatran doses, median 2 years treatment	DE 110 BID DE 150 BID Warfarin, adjusted dose	3 Years	18,113

Source: NDA 22-512, Section 5.2, Listing of Clinical Studies

A 12-week Phase II trial in 502 atrial fibrillation subjects at moderate- to high risk of stroke explored the safety and efficacy of DE 50, 150 or 300 mg twice daily, with or without aspirin, compared to warfarin alone (INR of 2-3; **P**revention of **E**mbolic and **T**h**RO**mbotic Events in Patients with Persistent Atrial Fibrillation (**PETRO**), (U06-1615-02). This study established that bleeding rates of warfarin alone and DE 150 mg BID were similar over 12 weeks of treatment. In addition, the suppression of D-dimer with the DE 150 mg BID dose was similar to warfarin, while that of the DE 50 mg BID dose was not. There were too few strokes to reach meaningful conclusions about the potential of any of the studied DE doses to prevent strokes, although during the extension study doses at- or lower than DE 150 mg/day subsequently appeared to be less effective at stroke prevention. The DE 300 mg BID dose

had excessive bleeding in the presence of aspirin (Figure 5.1: 1). Long-term follow-up of the subjects on DE 300 mg BID also identified excess bleeding in subjects not on ASA and that dose regimen was subsequently terminated for safety reasons with all subjects converted to a DE 300 mg total daily dose or removed from the trial (PETRO extension, U09-3247-01).

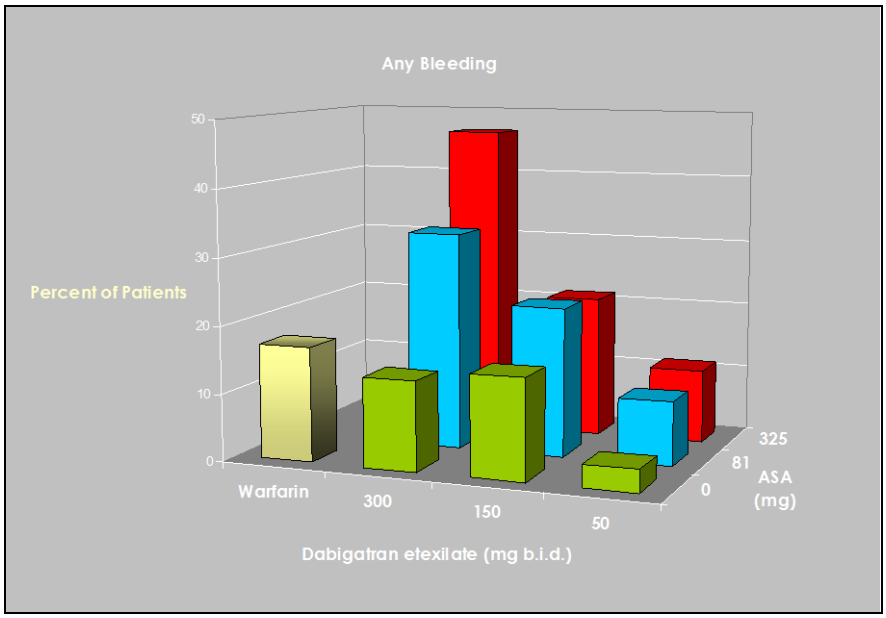


Figure 5.1: 1 Any bleeding rates by dabigatran dose and by ASA dose compared to warfarin in the PETRO trial (1160.20)

Source: U06-1615-02

Section 5.3 discusses dose selection for the SPAF development.

5.2 NON-SPAF CLINICAL DEVELOPMENT

Dabigatran has been evaluated for the prevention of VTE in subjects undergoing orthopedic surgery, treatment for VTE, secondary VTE prevention for subjects with prior VTE events, for prevention of coronary events in subjects with ACS, and for pediatric VTE treatment.

There are four completed Phase II and four completed Phase III studies in the indication "primary VTE prevention following major orthopedic surgery". The completed Phase III studies include 2 studies in subjects following total knee replacement (TKR), and two studies in subjects following total hip replacement (THR). In this program over 12,500 subjects have been exposed to multiple doses of dabigatran etexilate (>8000 subjects) or enoxaparin (>4000 subjects) after undergoing total hip or knee joint replacement surgery. These subjects were randomized to treatment with one of two dose regimens of dabigatran etexilate (either DE 150 QD or DE 220 QD with first dose DE 75 QD or DE 110 QD) or to the locally approved regimen of enoxaparin (40 mg QD following total hip replacement THR world wide, and following TKR outside of North America; 30 mg bid following TKR in North America). All Phase III studies for the prevention of VTE following orthopedic surgery (OS;

OS defined as total hip or knee replacement) were conducted as randomized, double-blind clinical trials. Based upon data from the VTE clinical program, DE gained regulatory approval in over 70 countries, including Europe and Canada, for the prevention of VTE in subjects undergoing hip or knee replacement. Additional registration submissions are planned in other countries including the United States.

The acute VTE treatment program consists of 2 studies. Both of these studies were randomized, double-blind, active-controlled trials comparing DE 150 BID to warfarin for duration of 6 months. RECOVER II is ongoing. RECOVER has been completed (U09-1400-01). In the RECOVER study, DE 150 BID was non-inferior to warfarin for the primary endpoint recurrent symptomatic VTE ([2.4%] vs 2.1%); risk difference 0.4% (95% confidence interval [CI], -0.8 to 1.5; P<0.001 for non-inferiority). Major bleeding occurred in 1.6% dabigatran vs (1.9%) warfarin (hazard ratio 0.82; 95% CI, 0.45 to 1.48), and any bleeding was observed in 205 compared with 277 subjects (hazard ratio 0.71, 95% CI, 0.59 to 0.85). Deaths, acute coronary syndromes and abnormal liver function tests were similar in the two groups. Adverse events leading to discontinuation of the study drug occurred in 9.0% of subjects randomized to dabigatran and 6.8% of subjects randomized to warfarin (P=0.05).

The Phase II RE-DEEM study compared 4 dabigatran etexilate arms (DE 50 BID, DE 75 BID, DE 110 BID and DE 150 BID) to placebo throughout a 6 month treatment period on major and clinically relevant minor bleeding events; subjects with a recent ACS episode and additional risk factors for cardiovascular events who were receiving dual antiplatelet therapy were included (U10-1294-02). Additionally, biomarkers of hypercoagulable state (D-dimer) and two composite ischemic endpoints (composite endpoint of cardiovascular (CV) death, non fatal myocardial infarction (MI) and stroke and composite endpoint of all-cause death, non fatal MI, stroke and severe recurrent ischemia (SRI)) were evaluated in this study.

A dose-dependent increase in the incidences of MBEs/CRBEs (primary endpoint) was observed among the dabigatran etexilate groups. Patients receiving DE 50 BID or DE 75 BID had a bleeding risk similar to placebo whereas subjects treated with DE 110 BID or DE 150 BID had a bleeding risk higher than placebo. The overall increase in major bleeding events was modest. There was no increase in fatal bleeding events with dabigatran. D-dimer and F1.2 concentrations were reduced in all treatment groups at 1 and 4 weeks of treatment; the reductions were greater in all dabigatran etexilate groups than in the placebo group. The incidences of the 2 composite endpoints of adjudicated major cardiovascular events did not reveal clinically significant differences between treatment groups. Overall, treatment with dabigatran etexilate up to DE 150 BID was well tolerated in this population. Further trials in this indication are under consideration.

5.3 SPAF PHASE III DOSE SELECTION

Based on the bleeding and efficacy data and anticoagulant effects from the SPAF Phase II trials, a dose of DE 300 mg/day was chosen as the target dose for stroke prevention. However, the precision of this dose selection was limited by the wide distance between the tested doses in Phase II, the use of minor bleed rates in AF subjects, and the extrapolation of efficacy data from short-term exposure in a surgical subject population. A second target dose of 220 mg/day was therefore selected based upon the effectiveness of this dose in Phase II

trials of VTE prevention in orthopedic surgery, and its anticoagulant effect as determined by changes in aPTT. The aPTT changes seen with the DE 150 BID dose were greater than those for ximelagatran 36 mg BID, a dose that appeared effective in stroke prevention (SPORTIF III and SPORTIF V), while the modelled effect of DE 110 BID on aPTT was similar to that of ximelagatran 36 mg BID.

The decision to dose dabigatran etexilate twice daily was based on its pharmacological profile. The half-life of dabigatran is 10-18 hours in the target population, which would normally support once daily dosing. However, it was considered important to minimize the daily fluctuations in plasma concentrations of dabigatran. The peak-trough ratio of dabigatran after twice daily dosing was approximately 2:1, while once daily dosing had a 6:1 peak trough ratio (see Table 5.3: 1).

Table 5.3: 1 Peak and Trough Concentrations of Dabigatran Dose Regimens

	DE150 mg qd	DE 220 mg qd [est]	DE 300 mg qd	**DE 150 mg BID**
PEAK (ng/mL)	89	130	185	**126**
TROUGH (ng/mL)	14	22	29	**68**

Source: U04-1195-01, U06-1615-02

An additional important consideration was to ensure that there was still some anticoagulant effect in most subjects at the end of the dosing interval. Figure 5.3: 1 shows the distribution of aPTT values hours after a dose of DE 150 mg BID. Less than 2% of subjects had no detectable effect, i.e., similar to the control value of 33 seconds.

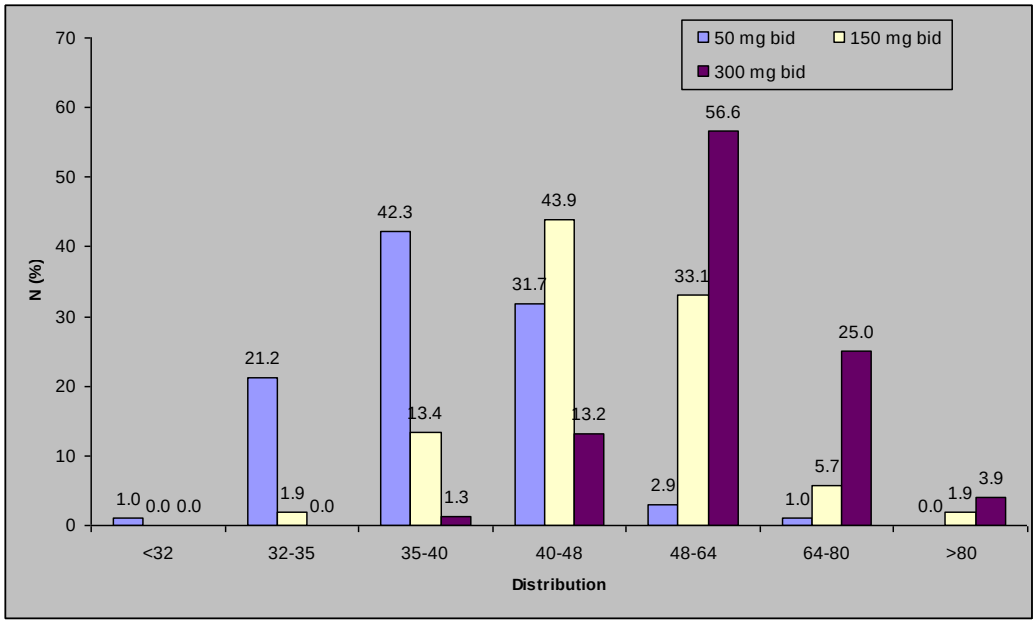


Figure 5.3: 1 Distribution of aPTT Values at Trough from PETRO (Study 1160.20). X-axis is aPTT in seconds. Control value of aPTT in absence of anticoagulant is ~33 seconds

Source: U06-1615-02, U06-3419-01

These data identified 2 doses for further testing in Phase III. Longer-term data from the follow-up study of dabigatran-treated subjects with AF (U06-3419-01) substantiated the elimination of high doses (DE 300 BID) without ASA due to excessive bleeding and low doses (<DE 150 QD) based on the occurrence of an increased number of strokes.

5.4 SPAF PHASE III RESULTS

Design

The RE-LY study was a randomized, parallel group, active-controlled, non-inferiority trial of 2 blinded doses of DE (DE 110 BID and DE 150 BID) compared with open-label warfarin in subjects with non-valvular AF (U09-3249-01). The trial had a PROBE (**P**rospective, **R**andomized, **O**pen trial with **B**linded adjudication of **E**vents) design. The trial was designed to evaluate whether DE 110 BID and DE 150 BID were non-inferior to adjusted-dose guideline recommended warfarin (target INR of 2.0 to 3.0) in the prevention of stroke and systemic embolism in AF subjects with at least 1 additional risk factor for stroke. The study was designed so that half of the subjects were warfarin-naïve; the other half were warfarin-treatment experienced. The results of this study are the primary basis for the proposed marketing application of DE for SPAF.

A single, large open-label trial to substantiate efficacy, with appropriate measures to minimize bias, required a rigorous non-inferiority margin, internal consistency across a wide range of subgroups, and convincing results, i.e., a p-value for the test of non-inferiority much

smaller than p<0.05. An event rate of 1.5-2.5% per year, a rigorous non-inferiority margin (NIM), and sufficient power, required a trial size of at least 5,000 subjects per group for a comparison of a single DE dose with warfarin. The RE-LY study enrolled more subjects than any previous single trial ever completed in subjects with AF.

Inclusion/Exclusion Criteria

The subject population in Phase III was recruited primarily from cardiology practices who managed subjects with atrial fibrillation. Qualifying subjects had a moderate to high risk of stroke (in addition to AF, presence of at least one risk factor: left ventricular ejection <=40%; symptomatic heart failure - NYHA>=2; age >=75 years; age >=65 years and also having diabetes mellitus or having CAD or having hypertension), and were to be eligible for warfarin prophylaxis. Subjects with documented paroxysmal, persistent, or permanent AF were included. Equal numbers of anticoagulant-naïve and anticoagulant-experienced subjects were randomized. Due to observations of hepatotoxicity with ximelagatran, another direct thrombin inhibitor, subjects with active liver disease were excluded and regular laboratory monitoring of hepatic function was done.

Study Organization

The execution of RE-LY required close collaboration between academic leaders managing the trial and the Sponsor (Boehringer-Ingelheim) who formed the various groups/committees that supported the conduct of the trial. The group responsible for developing and managing the clinical trial database was the Population Health Research Institute (PHRI). PHRI also coordinated the development of study policy, event adjudication, safety monitoring by the DSMB, and data management. The following committees were in place during the conduct of RE-LY.

- RE-LY Operations Committee
- RE-LY Steering Committee
- Data Safety and Monitoring Board
- Central Adjudication Committee

The Operations Committee was comprised of academic leaders and representatives of the Sponsor, PHRI, Uppsala Clinical Research (UCR), and Lankenau Medical Research (LIMR). Executive membership of the Operations Committee consisted of the co-chairs, the co-principal investigators, and Sponsor representatives. The remainder of the membership was comprised of key study operational team members from the Sponsor, PHRI, LIMR and UCR. This group was primarily responsible for overseeing, managing, and reporting on the day to day global operations in the various areas of study execution (e.g., site management/performance, drug logistics, data management, site performance, regulatory/protocol issues etc.).

The Operations Committee convened regularly by teleconference, every 2-4 weeks, with frequency adjusted at the discretion of the executive leadership based on the phase of the trial, and what issues were being addressed regarding trial conduct. In addition to routine teleconference calls, the Operations Committee also met at face to face meetings. As needed, clinical experts would be invited to participate to discuss trial conduct issues which required input to the group in support of the development of a communication at the trial level, the development of an amendment, or an assessment of trial conduct. The standard meeting agendas were amended jointly by the group with opportunity to include relevant items. No aggregated, by treatment data from the study were reviewed by this committee during the conduct of the trial.

A Steering Committee provided scientific support for the conduct of the study. The Steering Committee was composed of the National Coordinators, and the Operations Committee. The National Coordinators (NC) represented the countries and regions participating in the trial. The members were largely cardiologists, since subjects with AF are most often cared for by cardiologists and individuals with significant experience in the conduct and execution of clinical trials. The NC membership and invitation was defined jointly with the study co-chairs and co-principal investigators and the Sponsor. The committee had the responsibility for supporting the Operations Committee and ratifying proposals concerning, design, conduct and reporting of the study. In that capacity, the Steering Committee met on average twice a year, to review the progress of the study and discuss scientific issues encountered during the study as required. No aggregated, by treatment data from the study were reviewed by this committee during the conduct of the trial.

The Population Health Research Institute (PHRI) is an affiliate of the Hamilton Health Sciences Corporation and McMaster University. The PHRI is located at the Hamilton General Hospital/McMaster Clinic, in Hamilton, Ontario, Canada. PHRI operated independently from the sponsor with the primary functions related to study and data management with all aspects of the handling of the clinical database (e.g., development, maintenance, data collection and monitoring, quality control etc). PHRI also developed and maintained the study's central automated randomization system (AReS) designed to support subject randomization and the medication re-supply activities during study follow-up. No aggregated, by treatment data from the study were reviewed by PHRI during the conduct of the trial.

The Data Safety Monitoring Board (DSMB) had the responsibility to monitor the safety of subjects in RE-LY by conducting formal reviews of accumulated safety and efficacy data. The DSMB membership included cardiologists, a neurologist, a hematologist, statisticians, and a hepatologist. The DSMB was operated under the governance of a charter and operated independently of the Sponsor, Operations Committee, PHRI, Steering Committee and all other study related personnel. The study unblinded trial statistician supported the DSMB with trial data analyses as per protocol and at their request. The unblinded statistician was located at PHRI and remained independent of all committees, decisions, and operations related to the conduct of the trial. Meetings of the DSMB were conducted via teleconference and face-to-face. The structure of the DSMB meetings allowed for a brief open session for attendance by the academic leadership (Co-Chairs and Co-PIs) and a sponsor representative to review the current progress of the study and any critical issues emerging with the members of the

DSMB. As specified by the charter, the chair on behalf of the committee, issued a statement after each meeting to the study Co-Chairmen reporting the results of the committee's review.

The Central Adjudication Committee was charged with the responsibility of overseeing the blinded adjudication of specific study outcome events to provide consistency and validity in the assessment of outcomes. The Central Adjudication Committee operated under the governance of an Adjudication Manual which included the charter. The Central Adjudication Committee comprised of a core group, a stroke subcommittee, and a host of international individual adjudicators. Membership included neurologists and cardiologists who reviewed specially compiled outcome event dossiers blinded to treatment allocation.

The adjudication process was coordinated at PHRI by a dedicated Adjudication Coordinator whose main function was to receive, prepare (assure completeness, accuracy, and blinding of all source documents), issue and track the event dossiers issued to the adjudicators and/or stroke subcommittee through to a final resolution with updates to the database.

During the course of the trial, all non-English source documents received by PHRI for reported outcome events were translated in preparation for inclusion in registration dossiers. To increase the efficiency of adjudication of events with non-English records where a backlog occurred, these translations were sent to English-speaking adjudicators after being checked for blinding by the Adjudication Coordinator.

Sponsor representatives provided regulatory support, monitored all clinical sites and provided local site support in each participating country.

Additional support for site coordination was provided by Uppsala Clinical Research Center in Uppsala, Sweden, and Lankenau Institute for Medical Research, Wynnewood Pennsylvania

5.4.1 DE Blinded Doses vs Open-Label Warfarin Study Design – Real World Approach

Of the 6 historical trials that establish the efficacy of warfarin compared to placebo, most were not double-blind, double-dummy trials. However, the results of these studies were similar whether truly double-blind or not (P99-02978). The decision to conduct an open-label or a blinded trial against dose-adjusted warfarin was discussed with the FDA. It was clear that a double-blind trial was preferred and that an open-label trial would be subject to greater scrutiny and would require a higher level of evidence for registration. It was also agreed that documented and pervasive measures to remove or minimize bias, including methods to remove ascertainment bias, would be required.

At the time of the design of RE-LY, the feasibility of conducting a double-blind multicenter trial versus dose-adjusted warfarin in approximately 1,000 sites worldwide was uncertain. The largest double-blind trial versus warfarin ever conducted up to that time was SPORTIF V (N=3,922), with sites only in the USA and Canada.

Treatment with DE is fundamentally different from treatment with warfarin. Warfarin and other VKAs require regular monitoring and dose adjustments. Proper use of warfarin also requires careful attention to diet and concomitant medication use because of their drug-food

and drug-drug interactions. DE, on the other hand, required no monitoring, no dose adjustments, and no dietary restrictions and had a limited list of potential drug interactions. In addition, because of the different pharmacokinetics of the two drugs, interruption of treatment for surgery or procedures is also different. In most subjects, DE can be stopped 24-48 hours before a procedure and re-started without bridging, whereas warfarin requires 3-5 days interruption before a procedure, often with bridging therapy to deal with the additional 3-5 days to get back to therapeutic levels. These differences in the management of treatments could be obscured by a double-blind design and it would not be possible to ascertain their relevance in the event dabigatran etexilate was used to treat subjects with AF.

Because of these considerations, and since all key endpoints (stroke, death, major bleed) could be independently adjudicated without knowledge of any treatment assignments and were objective and clinically relevant, the sponsor elected to conduct an DE double-blind doses vs open-label warfarin study but introduced multiple additional measures to minimize bias including a review of these approaches with the FDA Division of Cardio-Renal Drug Products. This design allowed making 3 separate comparisons among the treatment groups. Both doses of dabigatran were compared to warfarin and a double-blind comparison could be made between the 2 blinded dabigatran groups. The double-blind comparison between the 2 dabigatran groups could establish a dose-response relationship for both safety and efficacy endpoints. The design also allowed identification of subject subgroups that might have a different benefit/risk ratio from the overall population and, as such, could receive a different dosing recommendation.

5.4.2 Strategies to Ensure Data Integrity

The PROBE design (Prospective, Randomized, Open trial with Blinded adjudication of Events) was selected as the design for RE-LY. The PROBE design has the advantages of being able to compare therapies which may be quite different, but cannot remove all the bias of an open-label design, especially in the areas of treatment discontinuation and adverse event reporting, where the biases of the investigator and the subject may come into play. Multiple additional measures to protect against bias were therefore incorporated into the trial.

Measures used to decrease open-label bias:

- Blinded adjudication of events by at least 2 adjudicators. In an open-label study, the primary safety and efficacy endpoints need to be clinically relevant, objective, and not subject to bias. Stroke/SEE and major bleeding are clinically relevant and objective endpoints. In addition, all deaths, myocardial infarctions, and pulmonary emboli were blindly adjudicated.
- Database and data handling was done by a totally independent academic group
- Blinding of sponsor and trial management personnel to “by treatment” analyses during the trial
- Interactive Voice Response System (IVRS) randomization
- Case report form construction to elicit events based on investigations and other assessments to be routinely performed by personnel at each site
- Study design included measures to keep direct contact with study site personnel at the same frequency for 3 treatment groups

Other measures to minimize ascertainment or reporting bias:

- Blinded DE doses
- Use of subject stroke and bleeding questionnaires at each visit to preserve constancy of data collection and limit reporting bias
- Blinded review of TIAs for possible under-reporting of strokes and forwarding for adjudication
- Review of AEs for terms that suggest unreported stroke or bleed and forwarding for adjudication
- Screening of hemoglobin changes in lab data for possible under-reporting of major bleeds and forwarding for adjudication
- Evaluating reports of anemia for possible events and forwarding for adjudication
- Review of free text fields on CRFs to identify potential outcomes events for further evaluation and possible adjudication

In conclusion, the organizational structure of the RE-LY study and its overall conduct was designed to ensure that neither the sponsor nor anyone else involved in the conduct of the study except the DSMB and its associated statistician had access to aggregated, "by treatment" data, unblinded safety data (other than expedited safety reports forwarded to regulators and investigators) or any "by treatment" data analyses until after database lock. The study database was independently managed and analyzed by PHRI. Processes within PHRI ensured blinding of all participants to "by treatment" analyses were reviewed by an independent auditor at the end of the trial.

5.4.3 SPAF Pivotal Trial

RE-LY was designed to enrol 15,000 subjects, the largest trial in AF subjects ever undertaken when it was planned. With the size of this trial, these methods and assumptions were made: 1) specific measures were implemented to minimize bias and 2) with a predetermined non-inferiority margin of 1.46, the RE-LY trial would provide sufficient power to determine DE efficacy and safety in the AF population to support a marketing application in the United States.

The Operations Committee of RE-LY decided in mid-2007 (because of rapid enrolment and uncertainties of overall event rate and the duration of follow-up required) to continue recruitment until the middle of December 2007 with a minimum 1 year follow-up of the last subject, as originally planned in the protocol. It was estimated that 3,000 additional subjects could be recruited in this time in addition to the original planned 15,000 subjects. This approach protected against the possibility that the actual annual event rate would decrease as the trial progressed as observed in other studies (R08-5518, ACTIVE-W). The anticipated increase of subject numbers would either increase the number of primary events over the original target, thus increasing power, or compensate for a decrease in event rate, should it have occurred toward the end of the trial.

5.4.4 Use of Two Dabigatran Doses

The rationale for dose selection was provided in Section 5.3.

In addition to the increased chance of identifying an optimal dose, including two doses in RE-LY had other advantages:

Inclusion of two blinded DE doses likely would increase the strength of evidence developed by a single trial by providing two independent comparisons of the test treatment against warfarin and the ability to demonstrate a dose response relationship between the 2 blinded DE doses. The ability to provide replication and/or consistency of results also could have provided additional supportive evidence of robustness.

Phase II data provided limited information on dose-response for safety and efficacy due to observed and expected low annual occurrence rate of the key safety (major bleeding) and efficacy (stroke/SEE) outcomes. Data on different DE doses are necessary to fully explore the risks and benefits. Comparing two different DE doses to warfarin in Phase III would yield more information to assess dosing recommendations. The inclusion of 2 DE doses doubled the amount of safety data available on dabigatran compared to use of a single dose, since the randomization ratio was 1:1.

Blinded DE doses were a potential counterbalance to some of the possible bias in reporting adverse events introduced by subjects and their physicians knowing they were receiving DE or open-label warfarin. Observations between the two doses of dabigatran of relative efficacy or safety (e.g., dose-response) are independent of investigator or subject bias. These dose comparisons can provide additional assurance of the reliability of the results.

5.4.5 Non-Inferiority Study Design

As stated earlier, the inclusion of 2 blinded DE doses and 3 between-group comparisons strengthened the non-inferiority design of RE-LY compared to a simpler 2-group comparison. The evidence for efficacy in a non-inferiority trial depends on the similarity of outcomes between a test treatment and a standard treatment, not the differences between, e.g., test treatment and placebo. The specification of this similarity is done by establishing that the test treatment (DE) is not worse (non-inferior) than standard treatment (warfarin) by a prespecified amount. Inherent in this calculation is that the test treatment is superior to placebo. To do this, important assumptions should be considered:

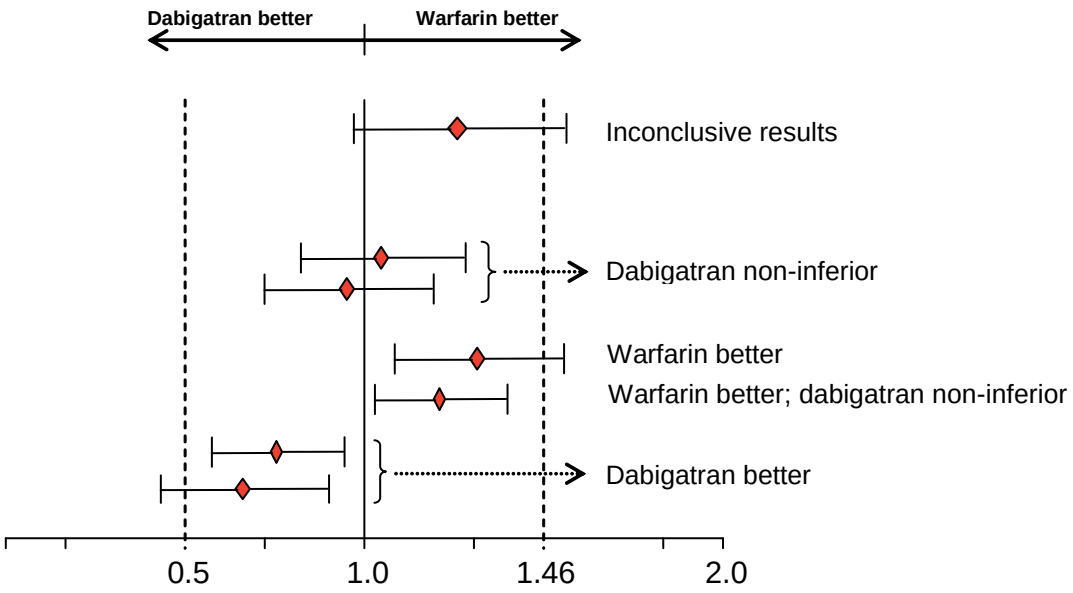
1. *The standard treatment has clinical efficacy of substantial magnitude that is precisely estimated, ideally using data from multiple adequate and well-controlled trials, with such estimates being relevant to the setting of the non-inferiority trial.*

2. *The non-inferiority design must be implemented in a rigorous manner to ensure that reliable and interpretable evidence is provided.*

The non-inferiority margin 1.46 was derived using data from the 6 historical placebo controlled warfarin trials in subjects with AF conducted between 1989 and 1992

(P99-02978). A meta-analysis of these 6 historical trials, using a fixed effects model, showed that the risk ratio of warfarin against placebo was 0.38, with the 95% CI of the risk ratio being (0.28, 0.52). No heterogeneity of warfarin's treatment effect across the 6 trials was observed. To preserve 50% of warfarin's beneficial effect using the upper bound of the 95% CI risk ratio, the margin was calculated to be 1.46 using a linear (non-logarithmic scale). Therefore, the non-inferiority of DE to warfarin is concluded if the upper bound of the confidence limit of the hazard ratio of DE vs. warfarin is <1.46 (Figure 5.4.5: 1).

As scientific discourse regarding non-inferiority and the best methods to use in clinical trials using this approach have been continuing, FDA has included newer thinking in its evaluation of non-inferiority studies. One consideration has been to utilize a logarithmic scale, rather than a linear one to calculate a non-inferiority margin. If this is done, the appropriate non-inferiority margin to use based upon the warfarin placebo controlled trials would be 1.38, rather than 1.46. Consequently, although the RE-LY protocol pre-specified a non-inferiority margin of 1.46, comparisons to a non-inferiority margin of 1.38 was also met and is discussed in this document and submitted in the NDA.



Relation of hazard ratio ranges to determine non-inferiority of dabigatran vs. warfarin

Figure 5.4.5: 1 Hazard Ratios for Meeting the Non-Inferiority Margin

The RE-LY protocol specified comparing both doses of dabigatran to warfarin. The Hochberg procedure was used to adjust for the prespecified multiple comparisons for the primary endpoint in RE-LY. The comparisons followed the steps below:

Step 1: Compare the upper bound of the 95% CI (one-sided $\alpha = 0.025$) of the HR of DE 110 BID vs. warfarin and the HR of DE 150 BID vs. warfarin to the non-inferiority margin 1.46. If the upper bounds for both DE doses are < 1.46, then claim non-inferiority to warfarin for both doses. Note if the upper bounds of the 95% CIs for both DE doses were above 1.46, then both doses fail to meet non-inferiority.

Step 2: If the upper bound for only one of the two DE doses was greater than or equal to 1.46, reject the non-inferiority claim for this dose, and compare the upper bound of the more stringent 97.5% CI (one sided α=0.0125) of the HR of the other dose to the non-inferiority margin 1.46; claim non-inferiority for this dose if the upper bound of the 97.5% CI was <1.46.

Superiority testing was pre-specified in the trial statistical analysis plan providing that non-inferiority if at keast 1 dose of DE was established. The test of superiority was to follow the Hochberg procedure as described above.

5.5 SUBJECT DEMOGRAPHICS AND DISPOSITION

5.5.1 Demographics

RE-LY included 18,113 subjects randomized (1:1:1; 2 blinded doses of DE, DE 110 BID or DE 150 BID; or open-label warfarin) with target INR for warfarin at 2.0-3.0. The study was conducted in 44 countries. RE-LY included 36.1% of subjects from either the United States or Canada. The average age was 71.5 years, 70.0% were white and 63.6% were males. Approximately one quarter had diabetes mellitus (23%) and just over a quarter had a history or coronary artery disease (28%) with about one third (32%) having a history of heart failure (NDA Amendment, Table 15.1.4: 11). Nearly half the subjects were prior smokers (43%) and 7.4% were current smokers. Mean BP at study entry was 131/77 mmHg, a value lower than other recent trials. The overall mean $CHADS_2$score was 2.1 with a median score of 2.0 in all treatment groups (NDA Amendment, Table 15.1.4: 17). Study entry criteria required the presence of at least one additional risk factor, however, some of the protocol specific risk factors for stroke were not in total concordance with the $CHADS_2$scoring system, therefore there were a small number of subjects enrolled that had $CHADS_2$scores of zero. The median creatinine clearance was 68.4 mL/min. At baseline, subjects had paroxysmal (32.8%), persistent (32.0%), or permanent (35.2%) AF.

Patients had similar baseline characteristics across the treatment groups with respect to cardiovascular risk factors (hypertension, diabetes, prior coronary artery disease, prior MI, prior stroke) (Table 5.5.1: 1, NDA Amendment, Table 15.1.4: 11) .

Table 5.5.1: 1 Baseline Demographics

	DE 110 BID	DE 150 BID	Warfarin	Total
Randomized	6015 (100.0%)	6076 (100.0%)	6022 (100.0%)	18,113 (100.0%)
Age (mean in years)	71.4	71.5	71.6	71.5
Male	64.3%	63.2%	63.3%	63.6%
Race: white	70.0%	70.2%	69.8%	70.0%
Weight (mean in kg)	82.9	82.4	82.6	82.6
VKA naïve	50.0%	49.8%	51.4%	50.4%
Never on VKA	31.1%	31.4%	32.7%	31.7%
CrCL (median in mL/min)	68.7	67.9	68.5	68.4
Systolic BP (mean in mmHg)	130.8	130.9	131.2	131.0
Diastolic BP (mean in mmHg)	77.0	77.0	77.1	77.0
AF type				
Persistent	1950 (32.4%)	1909 (31.4%)	1930 (32.0%)	5789 (32.0%)
Paroxysmal	1929 (32.1%)	1978 (32.6%)	2036 (33.8%)	5943 (32.8%)
Permanent	2132 (35.4%)	2188 (36.0%)	2055 (34.1%)	6375 (35.2%)
Previous cardioversion	1658 (27.6%)	1683 (27.7%)	1651 (27.4%)	4992 (27.6%)
Previous AV nodal ablation	119 (2.0%)	136 (2.2%)	132 (2.2%)	387 (2.1%)
Pacemaker	613 (10.2%)	679 (11.2%)	646 (10.7%)	1938 (10.7%)
Implantable defibrillator	136 (2.3%)	138 (2.3%)	125 (2.1%)	399 (2.2%)
Regions				
USA, Canada	2166 (36.0%)	2200 (36.2%)	2167 (36.0%)	6533 (36.1%)
Central Europe	707 (11.8%)	706 (11.6%)	706 (11.7%)	2119 (11.7%)
Western Europe	1544 (25.7%)	1555 (25.6%)	1552 (25.8%)	4651 (25.7%)
Latin America	320 (5.3%)	320 (5.3%)	316 (5.2%)	956 (5.3%)
Asia	923 (15.3%)	933 (15.4%)	926 (15.4%)	2782 (15.4%)
$CHADS_2$				
0	151 (2.5%)	146 (2.4%)	155 (2.6%)	452 (2.5%)
1	1809 (30.1%)	1815 (29.9%)	1707 (28.3%)	5331 (29.4%)
2	2088 (34.7%)	2136 (35.2%)	2229 (37.0%)	6453 (35.6%)
≥3	1966 (32.7%)	1979 (32.6%)	1931 (32.1%)	5876 (32.4%)

CrCL is creatinine clearance.
VKA-Naive: received two months or less of oral anticoagulant in subject's life time up to the time of randomization.
Source data: NDA Amendment; Table 15.1.4: 1, Table 15.1.4: 3, Table 15.1.4: 5, Table 15.1.4: 7, Table 15.1.4: 9 and Table 15.1.4: 17

Baseline Medications

Baseline medication use prior to randomization was balanced across the treatment groups (Table 5.5.1: 2). Approximately 88% of the subjects were receiving antithrombotic therapy at baseline: 62.3% were on an oral anticoagulant, 39.5% were on ASA, 5.6% were on clopidogrel, and 3.6% were receiving ASA and clopidogrel. Most subjects (80.1%) were receiving anti-hypertensive medications at baseline, including diuretics, angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs). Beta blockers, calcium channel blockers and other drugs commonly used in AF subjects were administered in almost 90% of subjects at baseline, with 62.9% receiving beta-blockers and 29.2% receiving digoxin. Calcium channel blockers and other drugs were taken by 10.9%, 5.9% and 0.5% and included amiodarone, verapamil and quinidine, respectively. Statins were taken with a frequency of 44.5%; proton pump inhibitors were taken with a frequency of

14.2%, and 6.4% subjects received other non-steroidal anti-inflammatory drugs/COX_2 inhibitors.

Table 5.5.1: 2 Commonly Used Baseline Medications

	DE 110 BID N (%)	DE 150 BID N (%)	Warfarin N (%)	Total N (%)
Randomized	6015 (100.0)	6076 (100.0)	6022 (100.0)	18113 (100.0)
Antithrombotic Therapy	5285 (87.9)	5356 (88.2)	5354 (88.9)	15995 (88.3)
Oral Anticoagulant	3782 (62.9)	3789 (62.4)	3707 (61.6)	11278 (62.3)
ASA	2384 (39.6)	2338 (38.5)	2431 (40.4)	7153 (39.5)
Clopidogrel	338 (5.6)	337 (5.5)	345 (5.7)	1020 (5.6)
ASA+Clopidogrel	214 (3.6)	211 (3.5)	228 (3.8)	653 (3.6)
Antihypertensive	4830 (80.3)	4895 (80.6)	4784 (79.4)	14509 (80.1)
Diuretic	3049 (50.7)	3116 (51.3)	3073 (51.0)	9238 (51.0)
ACE inhibitors	2699 (44.9)	2754 (45.3)	2670 (44.3)	8123 (44.8)
ARB	1448 (24.1)	1470 (24.2)	1418 (23.5)	4336 (23.9)
Beta-blocker, Ca channel blocker and rate and rhythm control drugs used in AF	5406 (89.9)	5472 (90.1)	5368 (89.1)	16246 (89.7)
Beta-blocker	3789 (63.0)	3887 (64.0)	3722 (61.8)	11398 (62.9)
Digoxin	1781 (29.6)	1742 (28.7)	1767 (29.3)	5290 (29.2)
Amiodarone	647 (10.8)	672 (11.1)	657 (10.9)	1976 (10.9)
Verapamil	352 (5.9)	350 (5.8)	369 (6.1)	1071 (5.9)
Quinidine	28 (0.5)	25 (0.4)	31 (0.5)	84 (0.5)
Metabolic, anti-inflammatory and other				
Statin	2702 (44.9)	2682 (44.1)	2673 (44.4)	8057 (44.5)
Proton pump inhibitors	847 (14.1)	878 (14.5)	842 (14.0)	2567 (14.2)
Other NSAID	311 (5.2)	294 (4.8)	319 (5.3)	924 (5.1)
COX2 inhibitor	79 (1.3)	86 (1.4)	79 (1.3)	244 (1.3)

Source: NDA Amendment; Table 15.1.4: 19

5.5.2 Disposition

This study was conducted in 44 countries. A total of 20,377 subjects were screened (enrolled), and 18,113 were randomized (entered).

The 18,113 randomized subjects were equally distributed across the 3 treatment groups with 6,015 randomized to DE 110 BID, 6,076 to DE 150 BID and 6,022 to warfarin (Table 5.5.2: 1). Overall, 36.1% of subjects were from either the United States or Canada, 25.7% from Western Europe, 15.4% from Asia, 11.7% from Central Europe, 5.9% from

Australia, Israel, and South Africa and 5.3% from Latin America. The number of subjects randomized to the 3 treatment groups was equally distributed across each geographic region.

All except 73 randomized subjects received study medication (99.6%).

Overall, 17,321 (96.0%) of the 18,040 treated subjects completed the study; 78.1% completed on study medication and 18.1% completed follow-up but stopped study medication prematurely in RE-LY. A higher frequency of subjects completed the study on medication in the warfarin group compared to the DE 110 BID and DE 150 BID groups (77.1%, 76.4%, and 80.8% for DE 110 BID, DE 150 BID, and warfarin, respectively).

A total of 680 (3.8%) of the 18,040 treated subjects were prematurely discontinued from the study and did not complete the regular trial follow-up visits through the final study period.

Only 24 (0.1%) treated subjects had an unknown final vital status. None of these subjects had a primary outcome event reported, none had contact with their study site and there was no documentation of their vital status or death during study close out. Subjects that withdrew consent or were at sites closed prematurely in RE-LY for cause and were unable to be followed at other sites were not considered to have an unknown vital status.

Table 5.5.2: 1 Disposition of Subjects - Overall Population

	DE 110 N (%)	DE 150 N (%)	Warfarin N (%)	Total N (%)
Enrolled (screened)				20377
Not entered				2264
Entered (randomized)	6015	6076	6022	18113
Not Treated (randomized)	32	17	24	73
Completed follow-up	14	7	5	26
Withdrew consent or lost to follow-up or other	18	10	19	47
Treated (randomized)	5983 (100.0)	6059 (100.0)	5998 (100.0)	18040 (100.0)
Completed study	5780 (96.6)	5824 (96.1)	5756 (96.0)	17360 (96.2)
Completed on study medication	4610 (77.1)	4627 (76.4)	4849 (80.8)	14086 (78.1)
Completed follow-up but stopped study medication prematurely	1170 (19.6)	1197 (19.8)	907 (15.1)	3274 (18.1)
Outcome events	421 (7.0)	431 (7.1)	333 (5.6)	1185 (6.6)
Serious AEs not related to outcome events	194 (3.2)	196 (3.2)	148 (2.5)	538 (3.0)
Subject preference	393 (6.6)	408 (6.7)	331 (5.5)	1132 (6.3)
Elevated liver function test result	25 (0.4)	16 (0.3)	11 (0.2)	52 (0.3)
Hospitalization	139 (2.3)	148 (2.4)	154 (2.6)	441 (2.4)
Adverse Event	296 (4.9)	325 (5.4)	192 (3.2)	813 (4.5)
Other	444 (7.4)	492 (8.1)	371 (6.2)	1307 (7.2)
Premature discontinuation from study	203 (3.4)	235 (3.9)	242 (4.0)	680 (3.8)
Sites closed for cause	25 (0.4)	27 (0.4)	27 (0.4)	79 (0.4)
Withdrew consent	126 (2.1)	144 (2.4)	136 (2.3)	406 (2.3)
Lost to follow-up	17 (0.3)	31 (0.5)	40 (0.7)	88 (0.5)
Other	35 (0.6)	33 (0.5)	39 (0.7)	107 (0.6)
Final vital status unknown	5 (0.1)	8 (0.1)	11 (0.2)	24 (0.1)

Subjects may be counted in more than one of the subclasses.
Outcome events include: stroke, systemic emboli, myocardial infarction, pulmonary emboli, transient ischemic attack (TIA), bleeding and death (U09-3249-01, Section 9.5.1.4)
Hospitalization could have been for elective procedures or those not otherwise specified.
The subjects identified above as "lost to follow-up" are those with this status in their CRF, although additional information on their vital status may have been available.
Source data: NDA Sequence 0155; Tables 2.21.3.7

5.5.3 Permanent Discontinuation of Study Medication

RE-LY had a PROBE design; therefore, all subjects and their physicians were aware of whether they were receiving warfarin or dabigatran, although the dabigatran dose was not known to them. Furthermore, half of the subjects were warfarin-treatment experienced and, as such, familiar with the nuisance and other troublesome issues associated with taking a VKA. Subjects experiencing adverse events and/or bleeding episodes after taking DE may have been biased to discontinue the new drug and to return to taking an agent with which they were familiar and knowledgeable if they had previously tolerated warfarin or another

VKA. Warfarin-experienced subjects randomized to either DE group discontinued their study medications due to AEs much more frequently than warfarin subjects (DE 110 BID [4.9%], DE 150 BID [5.3%], and warfarin [2.8%]). However, in the VKA-naïve cohort, differences between the DE and warfarin groups were smaller (DE 110 BID [5.3%], DE 150 BID [5.5%], and warfarin [3.8%]). The discontinuation rate for subjects randomized to warfarin was clearly higher for subjects that were previously VKA-naïve. This bias cannot be eliminated with a PROBE design study and likely influenced the observed discontinuation rates in RE-LY.

Overall, 3,773 (20.9%) RE-LY subjects permanently discontinued study medication; more subjects discontinued in the DE groups (22.0%-22.8%) than in the warfarin group (17.9%) (Table 5.5.3: 1). The most frequent reason for permanent discontinuation of any study medication was "Subject didn't want to take study drug" (7.1%).

The frequency of permanent discontinuation of study medication due to outcome events was 4.4% and 4.1% vs. 3.0%, for DE 110 BID, DE 150 BID and warfarin, respectively. The frequency of major bleeding events (MBEs) leading to permanent discontinuation of study medication was similar across all treatment groups (range 0.9% to 1.1%). For most categories of permanent treatment discontinuation, other than death, MI or procedure/hospitalization/surgery, there were more discontinuations on both DE doses than warfarin. For MI there were similar numbers of subjects permanently discontinuing study medication in all treatment groups. For the procedure/hospitalization/surgery category, there were more subjects discontinued from the warfarin group than either DE group.

Patients discontinuing either DE blinded dose always had the option to take non-study warfarin or another VKA. Patients discontinuing warfarin only had the option to take ASA or nothing. These facts likely had an impact on the trial and this should be considered when interpreting the data on permanent treatment discontinuations.

Table 5.5.3: 1 Permanent Discontinuation of Study Medication

	DE 110 BID N (%)	DE 150 BID N (%)	Warfarin N (%)	Total N (%)
Subjects treated	5983 (100.0)	6059 (100.0)	5998 (100.0)	18040 (100.0)
Subjects with permanent discontinuation	1318 (22.0)	1382 (22.8)	1073 (17.9)	3773 (20.9)
Serious AE not related to outcome event	162 (2.7)	170 (2.8)	119 (2.0)	451 (2.5)
Subject didn't want to take study drug	424 (7.1)	459 (7.6)	405 (6.8)	1288 (7.1)
Outcome event	261 (4.4)	246 (4.1)	177 (3.0)	684 (3.8)
Stroke	53 (0.9)	42 (0.7)	26 (0.4)	121 (0.7)
SEE	10 (0.2)	1 (0.0)	2 (0.0)	13 (0.1)
PE	5 (0.1)	5 (0.1)	1 (0.0)	11 (0.1)
MI	9 (0.2)	8 (0.1)	8 (0.1)	25 (0.1)
Major Bleed	53 (0.9)	61 (1.0)	66 (1.1)	180 (1.0)
Minor bleed	67 (1.1)	76 (1.3)	37 (0.6)	180 (1.0)
TIA	20 (0.3)	15 (0.2)	0 (0.0)	35 (0.2)
Death	18 (0.3)	17 (0.3)	18 (0.3)	53 (0.3)
Not identified	42 (0.7)	37 (0.6)	33 (0.6)	112 (0.6)
Other	471 (7.9)	507 (8.4)	372 (6.2)	1350 (7.5)
Adverse event	157 (2.6)	164 (2.7)	72 (1.2)	393 (2.2)
Lab changes	44 (0.7)	57 (0.9)	17 (0.3)	118 (0.7)
Procedure/hospitalization/surgery	30 (0.5)	35 (0.6)	46 (0.8)	111 (0.6)
Other	240 (4.0)	251 (4.1)	237 (4.0)	728 (4.0)

Note: A subject was counted in multiple categories when multiple reasons were given. When an outcome event was given as the reason for discontinuation, the exact event was identified using specific rules.
Source: NDA Amendment; Table 15.1.1: 3

5.6 INR CONTROL AND CONCOMITANT MEDICATIONS

5.6.1 INR Control

Compliance to warfarin was determined by INR control as assessed by the percent of time the INR was in the specified target range of 2-3 (time in therapeutic range, TTR). A linear interpolation using the Rosendaal method was performed. When calculating TTR, INRs during the first week after randomization and while study warfarin was temporarily or permanently stopped were excluded. A warfarin dosing algorithm was provided to all sites.

The overall mean percent of time INR was in the range of 2-3 was 64.4%, and the median was 67.3%. The percentage of TTR (INR 2-3) monotonically increased throughout the study, while the percentage of time INR was below 2.0 monotonically decreased throughout the study. However, the mean percentage of time INR was above 3.0 remained constant between 13.0% and 13.5% from 6 months after randomization until the end of the study (Table 5.6.1: 1).

Table 5.6.1: 1 Mean (SD) and Median Percentage of Time of INR Categories Warfarin−Treated Subjects

Months since randomization	Number of subjects N	% of time INR<2 Mean	(SD)	median	2<=INR<=3 Mean	(SD)	median	INR>3 Mean	(SD)	median
1	4897	31.6	(38.7)	9.5	49.2	(38.5)	47.8	19.2	(31.4)	0.0
3	5667	29.0	(30.7)	19.2	56.3	(30.4)	58.6	14.6	(21.3)	3.6
6	5564	26.2	(25.4)	19.2	60.3	(25.3)	63.4	13.5	(16.2)	8.1
9	5399	24.3	(22.2)	18.4	62.5	(22.4)	65.4	13.3	(14.0)	9.9
12	5235	22.8	(19.9)	17.9	64.0	(20.4)	66.6	13.2	(12.7)	10.5
16	5079	21.6	(18.1)	17.4	65.3	(18.7)	67.4	13.1	(11.6)	10.9
20	4405	21.1	(17.2)	16.7	66.0	(17.9)	68.1	12.9	(10.9)	11.0
24	3542	20.2	(16.2)	16.4	66.7	(17.0)	68.7	13.0	(10.4)	11.0
28	2551	19.4	(15.2)	15.8	67.4	(16.2)	68.9	13.2	(9.9)	11.4
32	1640	18.7	(14.5)	15.4	67.9	(15.4)	69.2	13.4	(9.6)	12.0
36+	714	17.7	(13.3)	14.5	69.2	(14.2)	70.3	13.2	(8.6)	12.0
Overall	5789	22.2	(19.1)	17.2	64.4	(19.8)	67.3	13.4	(12.6)	11.0

Source: NDA Amendment, Table 15.1.5: 10

INR control is often evaluated using clinical cut points for TTR. The following table presents cut points at 65% and 68%. The mean TTR for subjects in these categories were ~78 and ~80%, respectively (Table 5.6.1: 2).

Table 5.6.1: 2 Summary of INR for Well-Controlled Warfarin Subjects

TTR threshold	Subjects with mean TTR ≥ threshold	Mean TTR of subjects in the specific threshold category (SD)	Median TTR
≥65%	**3194**	**78.35 (8.72)**	**77.33**
≥68%	**2807**	**79.98 (8.02)**	**78.84**

Source: NDA Sequence 0148, Tables 2.13.2.3.1 and 2.13.2.3.2

INR Control by VKA Status

The VKA-experienced group had a higher TTR compared to the VKA-naïve group throughout the study. For both the VKA-experienced and VKA-naive subject groups, the TTR increased throughout the entire study, while the percentage of time below an INR of 2.0 decreased throughout the study (Table 5.6.1: 3).

Table 5.6.1: 3 Mean (SD) and Median Percentage of Time of INR in Categories by VKA Use (Naïve or Experienced) Warfarin−treated Subjects

Months since rand.	VKA_naive Number of subj N	VKA_naive % of time INR<2 Mean (SD) median	VKA_naive % of time 2<=INR<=3 Mean (SD) median	VKA_naive % of time INR>3 Mean (SD) median	VKA_experienced Number of subj N	VKA_experienced % of time INR<2 Mean (SD) median	VKA_experienced % of time 2<=INR<=3 Mean (SD) median	VKA_experienced % of time INR>3 Mean (SD) median
1	2579	36.4 (39.6) 20.0	43.4 (36.8) 39.1	20.2 (31.4) 0.0	2318	26.2 (36.9) 0.0	55.7 (39.2) 60.0	18.1 (31.3) 0.0
3	2878	35.0 (32.4) 27.2	51.0 (30.3) 53.1	14.0 (20.7) 3.6	2799	22.9 (27.6) 11.5	61.9 (29.5) 64.5	15.3 (22.0) 3.7
6	2813	31.0 (27.5) 23.5	56.2 (26.2) 59.3	12.8 (15.8) 7.5	2751	21.3 (22.1) 15.6	64.6 (23.6) 67.1	14.2 (16.5) 9.1
9	2707	28.4 (24.1) 22.1	58.9 (23.3) 61.9	12.7 (13.7) 9.3	2692	20.1 (19.2) 15.2	66.0 (20.8) 68.3	13.8 (14.2) 10.7
12	2609	26.2 (21.6) 20.8	61.1 (21.3) 63.9	12.6 (12.3) 9.8	2626	19.3 (17.3) 15.2	66.9 (19.0) 69.0	13.8 (13.1) 11.1
16	2515	24.5 (19.4) 19.6	62.9 (19.4) 65.1	12.6 (11.3) 10.5	2564	18.8 (16.3) 15.1	67.6 (17.7) 69.9	13.6 (11.8) 11.3
20	2144	23.8 (18.4) 19.4	63.8 (18.6) 66.0	12.4 (10.7) 10.6	2261	18.4 (15.5) 14.9	68.2 (17.0) 69.8	13.4 (11.1) 11.5
24	1634	22.8 (17.3) 18.7	64.7 (17.8) 66.8	12.5 (10.4) 10.6	1908	18.0 (14.8) 14.7	68.5 (16.2) 70.1	13.5 (10.5) 11.5
28	1075	22.1 (16.5) 18.0	65.3 (17.3) 67.1	12.7 (9.9) 10.9	1476	17.4 (13.9) 14.4	69.0 (15.1) 70.1	13.6 (10.0) 11.8
32	560	21.7 (15.7) 17.7	65.3 (16.8) 67.0	13.0 (9.7) 11.6	1080	17.2 (13.5) 14.1	69.2 (14.5) 70.3	13.6 (9.5) 12.3
36+	177	21.2 (15.1) 17.6	66.2 (15.7) 67.9	12.6 (9.5) 11.2	537	16.5 (12.5) 13.8	70.1 (13.5) 71.3	13.4 (8.7) 12.3
Overall	2955	24.9 (20.7) 19.5	61.8 (21.1) 64.7	13.3 (13.5) 10.6	2834	19.3 (16.8) 15.3	67.2 (18.0) 69.5	13.6 (11.6) 11.3

Source: NDA Amendment, Table 15.1.5: 11

INR Control by Region and Country

INR control was evaluated by region and country. In general, subjects from US/Canada and Western Europe had relatively better INR control than subjects from Asia and other regions. The mean and median TTR was 66.7% and 68.4%, respectively, in US/Canada and 68.7% and 71.8%, respectively, in Western Europe.

5.6.2 Concomitant Medications

No large differences were observed across treatment groups for medication use during the study period (Table 5.6.2: 1).

Approximately 40% of the subjects used ASA at least once during the study (similar to baseline use), while 20% of the subjects received ASA throughout the study (100% of the time).

PPIs were used at least once in 24% of subjects, almost 10% more than at baseline. There was a slight increase in use of PPIs in the DE groups compared to warfarin (24.6%, 24.7%, and 21.1% of subjects in the DE 110 BID, DE 150 BID, and warfarin groups, respectively, used PPIs at least once during the study). Approximately one-third of subjects used antibiotics during the trial (NDA Amendment, Table 15.1.4: 22).

P-gp inhibitors, including amiodarone, verapamil, digoxin, and quinidine, were used by 14.9%, 7.2%, 34.1% and 0.7% of all subjects, respectively, at anytime during the study.

Table 5.6.2: 1 Medication Use During the Study

	DE 110 BID N (%)	DE 150 BID N (%)	Warfarin N (%)	Total N (%)
Total randomized	6015 (100.0)	6076 (100.0)	6022 (100.0)	18113 (100.0)
Antithrombotic therapy				
ASA				
Used any time	2400 (39.9)	2389 (39.3)	2406 (40.0)	7195 (39.7)
100% (always)	1274 (21.2)	1190 (19.6)	1247 (20.7)	3711 (20.5)
Clopidogrel				
Used any time	443 (7.4)	452 (7.4)	441 (7.3)	1336 (7.4)
100% (always)	143 (2.4)	133 (2.2)	152 (2.5)	428 (2.4)
ASA+ Clopidogrel				
Used any time	306 (5.1)	297 (4.9)	305 (5.1)	908 (5.0)
100% (always)	76 (1.3)	63 (1.1)	84 (1.4)	223 (1.2)
Antihypertensives				
ARB				
Used any time	1745 (29.0)	1790 (29.5)	1752 (29.1)	5287 (29.2)
100% (always)	1273 (21.2)	1286 (21.2)	1280 (21.3)	3839 (21.2)
ACE inhibitors				
Used any time	3018 (50.2)	3043 (50.1)	2990 (49.7)	9051 (50.0)
100% (always)	2346 (39.0)	2369 (39.0)	2366 (39.3)	7081 (39.1)
Beta-blocker, Ca channel blocker and rate and rhythm control drugs used in AF				
Digoxin				
Used any time	2069 (34.4)	2049 (33.7)	2055 (34.1)	6173 (34.1)
100% (always)	1503 (25.0)	1442 (23.7)	1507 (25.0)	4452 (24.6)
Beta blocker				
Used any time	4146 (68.9)	4211 (69.3)	4044 (67.2)	12401 (68.5)
100% (always)	3448 (57.3)	3516 (57.9)	3369 (55.9)	10333 (57.0)
Amiodarone				
Used any time	881 (14.6)	899 (14.8)	922 (15.3)	2702 (14.9)
100% (always)	464 (7.7)	497 (8.2)	482 (8.0)	1443 (8.0)
Quinidine				
Used any time	41 (0.7)	40 (0.7)	43 (0.7)	124 (0.7)
100% (always)	22 (0.4)	22 (0.4)	24 (0.4)	68 (0.4)
Verapamil				
Used any time	426 (7.1)	422 (6.9)	457 (7.6)	1305 (7.2)
100% (always)	269 (4.5)	253 (4.2)	281 (4.7)	803 (4.4)
Metabolic, anti-inflammatory and other				
Statin				
Used any time	3015 (50.1)	2998 (49.3)	3071 (51.0)	9084 (50.2)
100% (always)	2486 (41.3)	2480 (40.8)	2450 (40.7)	7416 (40.9)
Cox_2 Inhibitors				
Used any time	158 (2.6)	164 (2.7)	164 (2.7)	486 (2.7)
100% (always)	64 (1.1)	62 (1.0)	66 (1.1)	192 (1.1)
Other NSAIDs				
Used any time	784 (13.0)	726 (11.9)	769 (12.8)	2279 (12.6)
100% (always)	225 (3.7)	211 (3.5)	238 (4.0)	674 (3.7)
Proton pump inhibitors				
Used any time	1480 (24.6)	1501 (24.7)	1270 (21.1)	4251 (23.5)
100% (always)	739 (12.3)	771 (12.7)	746 (12.4)	2256 (12.5)

Source data: NDA Amendment; Table 15.1.4: 22

6. CLINICAL EFFICACY – RE-LY

Efficacy results of RE-LY present yearly event rates (counting the first event in each subject), hazard ratios (DE/warfarin) and relative risk reductions (DE/warfarin). For clarification, if the hazard ratio is <1, e.g., 0.80 (corresponds to a 20% relative risk reduction), than the result demonstrates a benefit favouring DE-treated subjects, and vice versa, if the hazard ratio is >1, the result demonstrates a benefit favouring warfarin. Hazard ratios also are presented comparing both DE doses.

6.1 OVERVIEW

RE-LY was a Phase III, prospective, randomized comparison of 2 blinded DE doses vs open-label warfarin with a PROBE design having a primary efficacy endpoint of stroke/SEE. The study enrolled subjects with nonvalvular AF and at least one risk factor for stroke. A total of 18,113 subjects were randomized to one of 2 blinded doses of dabigatran etexilate (DE 110 BID and DE 150 BID) or to open-label warfarin, titrated to a target INR of 2 to 3. The subject population included balanced proportions of VKA-naïve and VKA-experienced subjects.

DE 150 BID significantly reduced the risk of stroke and systemic embolism compared to warfarin with a comparable major bleeding rate while significantly decreasing the occurrence of intracranial hemorrhage and the incidence of life-threatening and all bleeding events and was better than warfarin in reducing ischemic strokes and vascular mortality;

DE 110 BID was non-inferior to warfarin for reducing the risk of stroke and systemic embolism, while major bleeding, life-threatening bleeding, intracranial bleeding and any bleeding were all significantly reduced by this lower dose compared to warfarin mean.

6.2 ANALYSIS POPULATIONS

Two data sets were used for most analyses:

1) Randomized set (All randomized subjects), and
2) Safety dataset (every randomized subject that was administered at least one dose of study medication) and events occurred within 6 days of permanent discontinuation.

The analyses using randomized set included outcome events that occurred between the date of randomization to the date of study termination. The analyses using safety set included outcome events that occurred between the date of first study medication to the date of last study medication plus six days.

6.3 PRIMARY EFFICACY ENDPOINT - STROKE/SYSTEMIC EMBOLISM

The primary efficacy measure was the time to the first occurrence of stroke/SEE. Comparisons between treatment groups were performed using a Cox regression analysis with treatment in the model. Descriptive statistics, such as yearly event rate and Kaplan-Meier plots, are also presented.

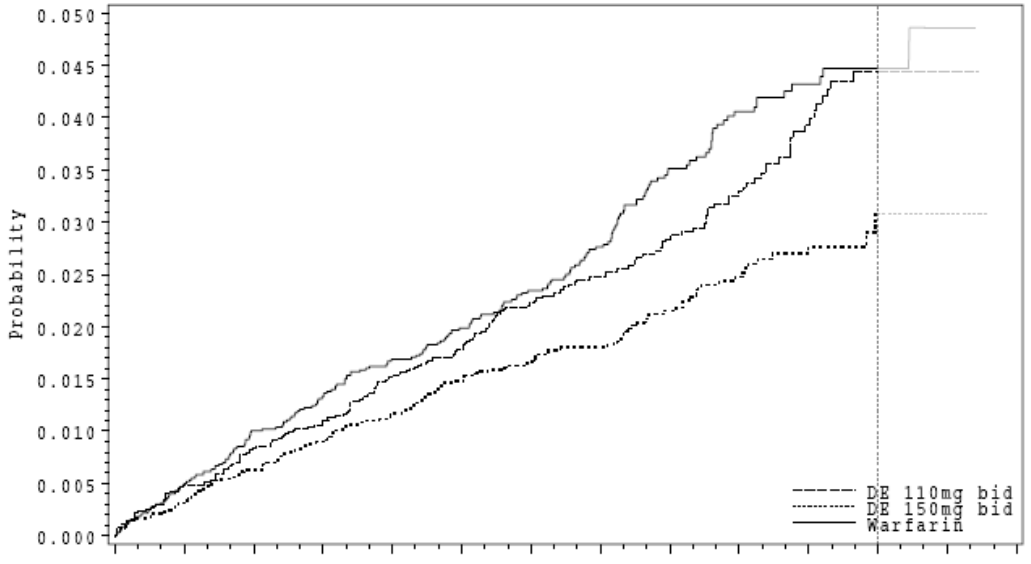
The yearly event rate for stroke/SEE was numerically lower for both DE groups than in the warfarin group (Table 6.3: 1). A total of 519 subjects with adjudicated stroke/SEEs were documented during the trial. The yearly rate for stroke/SEE was 1.54%, 1.11% and 1.71% in the DE 110 BID, DE 150 BID and warfarin groups, respectively.

Table 6.3: 1 Yearly Event Rate (%) for Composite Endpoint of Stroke/SEE

	DE 110 BID N (%)	**DE 150 BID N (%)**	**Warfarin N (%)**
Subjects randomized	6015	6076	6022
Subject-years	11899	12033	11794
Subjects with stroke/SEE	183 (1.54)	134 (1.11)	202 (1.71)
Stroke	171 (1.44)	122 (1.01)	186 (1.58)
Ischemic stroke	152 (1.28)	103 (0.86)	134 (1.14)
Hemorrhagic stroke	14 (0.12)	12 (0.10)	45 (0.38)
Stroke of uncertain classifications	7 (0.06)	9 (0.07)	10 (0.08)
SEE	15 (0.13)	13 (0.11)	21 (0.18)

Each subject with an event was counted once for the composite endpoint and once for each component of the composite endpoint. In case of recurrent events, only the first event was considered.
Subject-years = sum (date of study termination – date of randomization +1) of all randomized subjects / 365.25.
Yearly event rate (%) = No. of subjects with event/subject-years * 100
Source: NDA Amendment; Table 15.2.1.1: 1

As can be seen in the Kaplan-Meier (KM) curve below, the DE 150 BID group started separating from both the DE 110 BID and warfarin groups as early as 2 months into the study and this separation continued to increase throughout the entire study, (Figure 6.3: 1). At the end of the study, the cumulative rate of stroke/SEE for the DE 150 BID group was approximately 3%, while the rates were above 4% for the DE 110 BID and warfarin groups. For almost all of the study duration, the KM curve for DE 110 BID was below that of warfarin, the KM curve for DE 150 BID was widely separated from that of warfarin.



Subjects at risk

DE 110mg bid	6015	5927	5862	5797	5713	5481	4615	3778	3132	2386	1446	495	87
DE 150mg bid	6076	6010	5940	5861	5782	5555	4700	3847	3238	2428	1481	494	90
Warfarin	6022	5937	5862	5782	5719	5438	4615	3702	3092	2338	1364	383	76

Figure 6.3: 1 Kaplan-Meier Estimate of Time to First Stroke/SEE

Source: NDA Amendment; Figure 15.2.1.1: 1

Non-inferiority of both DE doses compared to warfarin was demonstrated using the protocol-specified Hochberg procedure since the upper bound of the 95% CIs for both DE doses were well below the pre-specified non-inferiority margin 1.46 (Table 6.3: 2). The relative risk reductions compared to warfarin for stroke/SEE by DE 110 BID and DE 150 BID were 10% and 35%, respectively.

The non-inferiority of both DE doses compared to warfarin was also demonstrated using a 1.38 NIM, as currently preferred by FDA (Table 6.3: 2).

After establishing noninferiority of both DE does, DE 110 BID and DE 150 BID were further tested for superiority. DE 110 BID was not superior to warfarin (p=0.2943). Therefore, DE 150 BID was compared to warfarin for superiority at the α=0.025 level (rather than α=0.05) using the Hochberg procedure to adjust for multiple comparisons. DE 150 BID was further tested and found to be superior to warfarin for the primary endpoint of stroke/SEE (p=0.0001) (Table 6.3: 2).

Table 6.3: 2 Hazard Ratios and CIs for Composite Endpoint of Stroke/SEE

	DE 110 BID vs Warfarin	**DE 150 BID vs Warfarin**
Hazard ratio (SE)	0.90 (0.09)	0.65 (0.07)
95% CI	0.74, 1.10	0.52, 0.81
97.5% CI	0.71, 1.13	0.51, 0.83
P-value for non-inferiority using 1.46	<0.0001	<0.0001
P-value for non-inferiority using 1.38	<0.0001	<0.0001
P-value for superiority	0.2943	0.0001

Source: NDA Amendment; Table 15.2.1.1: 3, Table 15.2.1.1: 4, Table 15.3.5.4: 4

DE 150 BID significantly reduced the risk of the primary efficacy endpoint, stroke/SEE compared to DE 110 BID in this blinded comparison (hazard ratio: DE 110 BID/DE 150 BID: 1.39; 95% CI: 1.11 – 1.73; p = 0.0041, NDA Amendment; Table 15.2.1.1: 3).

6.3.1 Sensitivity Analyses

Several sensitivity analyses were performed for the primary endpoint. Three different sensitivity analyses are presented in this section including, stroke/SEE analysis of the first 450 adjudicated events, stroke/SEE analysis using the safety set and analyses of the investigator reported stroke/SEE.

6.3.1.1 Analysis of the First 450 Adjudicated Events

The originally planned number of subjects with stroke/SEE in this study was 450 prior to a protocol amendment to increase enrollment. At the end of the study, 519 subjects were reported to have at least one adjudicated stroke/SEEs. The analysis including the first 450 subjects who had the primary endpoint event stroke/SEE was performed as a sensitivity analysis. The last of these 450 adjudicated stroke/SEEs occurred on October 24, 2008. Subjects without a stroke/SEE prior to October 24, 2008 were considered censored on this date or on their study termination date (for those subjects who terminated earlier), for purposes of this analysis.

Frequency and yearly event rates, KM estimates and hazard ratios were similar to the primary analysis when considering only the first 450 adjudicated stroke/SEEs. Both DE doses were non-inferior to warfarin using either 1.46 or 1.38 as the NIM (p<0.0001). DE 150 BID remained superior to warfarin (p=0.0031).

6.3.1.2 Sensitivity Analyses Using the Safety Set

The analyses based on the safety set (18,040 subjects receiving at least one dose of any study medication with censoring 6 days after termination of study medication) were consistent with the randomized set, with lower hazard ratios of DE compared to warfarin (Table 6.3.1.2: 1). This analysis included stroke/SEE that occurred between date of the first study medication to the date of the last study medication plus six days. Both DE 110 BID and DE 150 BID were non-inferior to warfarin using the margin of 1.46. DE 150 BID remained superior to warfarin as well (p<0.0001).

Table 6.3.1.2: 1 Hazard Ratio for Composite Endpoint of Stroke/SEE (safety set)

	DE 110 BID vs Warfarin	DE 150 BID vs Warfarin
Hazard ratio (SE)	0.85 (0.10)	0.56 (0.07)
95% CI	0.67, 1.06	0.43, 0.72
97.5% CI	0.65, 1.10	0.41, 0.75
P-value for non-inferiority at 1.46	<0.0001	<0.0001

Safety Set
Source: NDA Amendment; Table 15.2.1.2: 6

Analyses of investigator-reported events

A total 567 strokes were reported by investigators and 490 cases were confirmed after adjudication (86%) (Table 6.3.1.2: 2). Approximately half of investigator-reported SEEs were positively adjudicated. The difference in the number of strokes between the DE 150 BID and the warfarin group as reported by the investigators was larger than the difference following adjudication. This analysis again provides support for the robustness of the superiority of DE 150 BID compared to warfarin for the prevention of stroke/SEE.

Table 6.3.1.2: 2 Number of Investigator Reported and Adjudicated Events

	DE 110 BID		DE 150 BID		Warfarin	
	No. of events adjudicated N	No. events agreed N (%)	No. of events adjudicated N	No. events agreed N (%)	No. of events adjudicated N	No. events agreed N (%)
Stroke	199	173 (86.9)	155	130 (83.9)	213	187 (87.8)
Ischemic	156	137 (87.8)	110	92 (83.6)	128	112 (87.5)
Hemorrhagic	15	13 (86.7)	18	13 (72.2)	59	44 (74.6)
Uncertain	26	6 (23.1)	27	6 (22.2)	25	6 (24.0)
Missing type*	2	0	0	0	1	0
SEE	35	16 (45.7)	37	14 (37.8)	32	21 (65.6)

No. of events adjudicated: outcome events that were sent to the Adjudication Committee for adjudication.
No. of events agreed: events confirmed by the Adjudication Committee.
* Three investigator-reported strokes were not categorized.
Source: NDA Amendment; Table 15.2.2.3: 5

6.3.1.3 INR Control as Related to Primary Efficacy - Stroke/SEE for warfarin Control

For the primary endpoint, a comparison was made between both double-blind DE doses and well-controlled warfarin at the cutoffs the mean TTR values for the cutoffs of 65% and 68% were 78% and 80%, respectively (Table 6.3.1.3: 1).

Table 6.3.1.3: 1 Yearly Event Rates of Stroke/SEE Related to Warfarin Control

	DE 110 BID	DE 150 BID	Warfarin
TTR threshold ≥ 65%			
Subjects	5983	6059	3194
Subject-years	10242	10261	6175
Stroke/SEE: N(%)	133 (1.30)	88 (0.86)	76 (1.23)
TTR threshold ≥ 68%			
Subjects	5983	6059	2807
Subject-years	10242	10261	5414
Stroke/SEE: N(%)	133 (1.30)	88 (0.86)	65 (1.2)

Note that in the placebo controlled SPORTIF V trial, the TTR was 68%, warfarin rate was 1.2%
Source: NDA Sequence 0148, Table 2.13.2.1.1 and NDA Amendment Table 15.2.1.2: 13

The hazard ratios, CI and p–values for the comparisons of both DE doses and well-controlled warfarin (the mean TTR values for the cutoffs of 65% and 68% were 78% and 80%, respectively) are presented below (Table 6.3.1.3: 2). The results are similar to the primary efficacy analysis including all warfarin-treated subjects; DE 110 BID remains non-inferior to well-controlled warfarin. The hazard ratios were DE 150 BID vs well-controlled warfarin (the mean TTR values for the cutoffs of 65% and 68% were 78% and 80%, respectively) are both well below 1.00 and the upper bound of both CI are <1.00. These results are consistent with those of the primary efficacy endpoint. DE 150 BID remains superior to warfarin even when only well controlled warfarin patients are selected (the mean TTR values for the cutoffs of 65% and 68% were 78% and 80%, respectively).

Table 6.3.1.3: 2 Efficacy Analysis of Stroke/SEE Related to Warfarin Control

	DE 110 vs Warfarin	DE 150 vs Warfarin
Subjects with mean TTR ≥ 65%		
Hazard Ratio	1.03	0.68
95% CI	0.78, 1.36	0.50, 0.92
P-value	0.8487	0.0140
Subjects with mean TTR ≥ 68%		
Hazard Ratio	1.05	0.70
95% CI	0.78, 1.42	0.51, 0.96
P-value	0.7400	0.0268

Note that in the placebo controlled SPORTIF trial, the TTR was 68%, warfarin rate was 1.2%
Source: NDA Amendment Table 15.2.1.2:14; NDA Sequence 0148, Tables 2.13.2.1.2
The Cox regression model for these analyses included baseline $CHADS_2$ as a covariate

6.4 SECONDARY EFFICACY ENDPOINTS

Death is a competing risk factor for the stroke/SEE endpoint. For the analysis of stroke/SEE, subjects who died without an occurrence of stroke/SEE were censored at the time of death. The inclusion of death in a composite endpoint is one way of addressing competing risks.

6.4.1 Stroke/SEE/All-Cause Death

The results for the secondary composite endpoint of stroke/SEE and all-cause death showed the same pattern as for the primary endpoint; namely, the yearly event rate of the 3-component composite endpoint was numerically lower than warfarin for both DE doses. Additionally, each component of this composite endpoint was numerically lower for both DE doses compared to warfarin (Table 6.4.1: 1).

Table 6.4.1: 1 Yearly Event Rate (%) for composite endpoint of stroke/SEE/all-cause death – overall population

	DE 110 BID N (%)	DE 150 BID N (%)	Warfarin N (%)
Randomized	6015	6076	6022
Subject-years	11899	12033	11794
Subjects with Stroke/SEE/death (%/year)	577 (4.85)	520 (4.32)	613 (5.20)
Stroke	171 (1.44)	122 (1.01)	186 (1.56)
SEE	15 (0.13)	13 (0.11)	21(0.18)
Death	446 (3.75)	438 (3.64)	487 (4.13)

Each subject with an event was counted once for the composite endpoint and once for each component of the composite endpoint.
In case of recurring events in the same subject, only the first event was counted.
Subject-years = sum (date of study termination – date of randomization +1) of all randomized subjects / 365.25.
Yearly event rate (%) = No. of subjects with event/subject-years * 100.
Source: NDA Amendment; Table 15.2.2.1: 1

The Kaplan-Meier estimates for stroke/SEE/death shows that the 3 curves appear to diverge with the DE 150 BID curve appearing to be lower than the warfarin curve at approximately 15 month into the study. The DE 110 BID curve is consistently below the warfarin curve after about 1 year and this continues through the end of the study (Figure 6.4.1: 1).

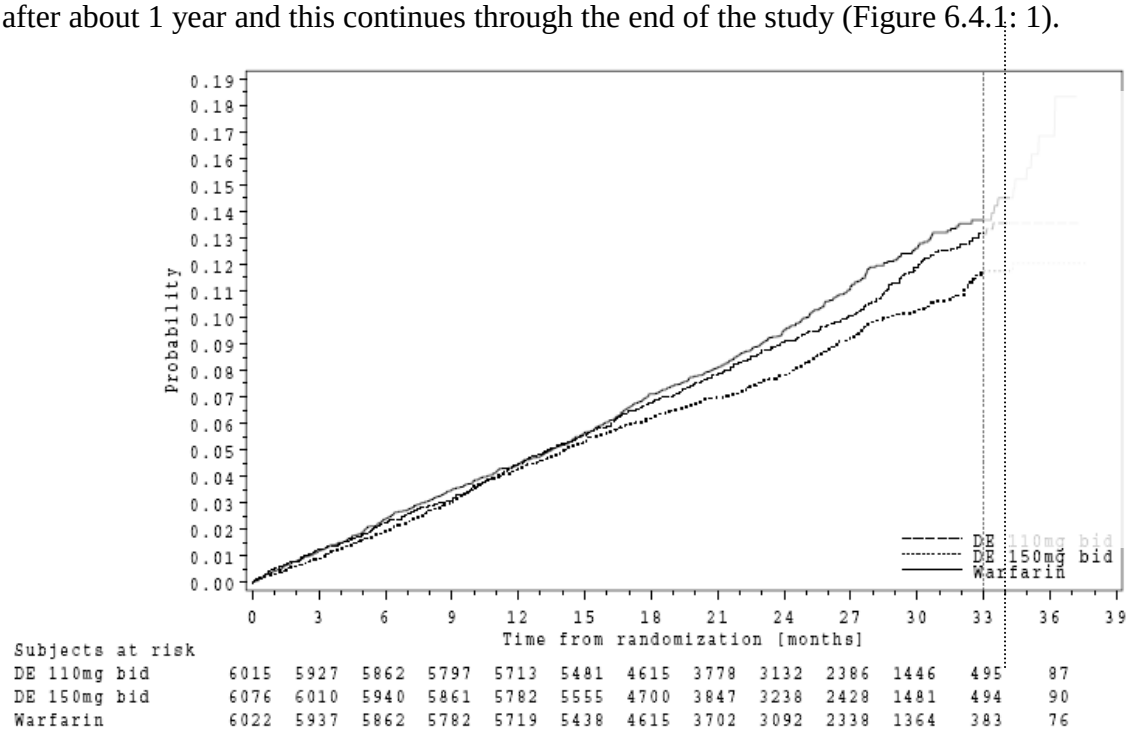


Figure 6.4.1: 1 Kaplan-Meier Estimates of Time to First Stroke/SEE/Death

Source: NDA Amendment; Figure 15.2.2.1: 1

Hazard ratios, CIs and p values are presented in the following table (Table 6.4.1: 2). The hazard ratio for DE 150 BID over warfarin was 0.83 (a relative risk reduction of 17%) and was statistically significant (p=0.0015).

Table 6.4.1: 2 Hazard Ratios and 95% CIs for Composite Endpoint of Stroke/SEE/Death

	DE 110 BID vs Warfarin	DE 150 BID vs Warfarin
Hazard ratio (SE)	0.93 (0.05)	0.83 (0.05)
95% CI	0.83, 1.04	0.74, 0.93
P-value	0.2206	0.0015

Source: NDA Amendment; Table 15.2.2.1: 2

6.4.2 Stroke, SEE, PE, MI and Vascular Death

The composite endpoint of stroke/SEE/PE/MI and vascular death was another secondary endpoint (Table 6.4.2: 1). Results for the analysis of this composite endpoint were similar to those of the stroke/SEE/death endpoint. Numerically fewer events were observed for both DE doses compared to warfarin. Vascular death and stroke contributed most to this endpoint and again there were numerically fewer events on both DE doses compared to warfarin. Slightly higher rates were observed for both DE groups compared to the warfarin group with the less common MIs and PEs, but without any apparent dose response relationship.

Table 6.4.2: 1 Yearly Event Rate (%) for composite endpoint of stroke/SEE/PE/MI and vascular death

	DE 110 BID N (%)	DE 150 BID N (%)	Warfarin N (%)
Subjects randomized	6015	6076	6022
Subject-years	11899	12033	11794
Subjects with composite endpoint (%/year)	496 (4.17)	435 (3.61)	504 (4.27)
Stroke	171 (1.44)	122 (1.01)	186 (1.58)
SEE	15 (0.13)	13 (0.11)	21 (0.18)
PE	14 (0.12)	18 (0.15)	12 (0.10)
MI	87 (0.73)	89 (0.74)	66 (0.56)
Vascular death	289 (2.43)	274 (2.28)	317 (2.69)

Each subject with an event was counted once for the composite endpoint and once for each component of the composite endpoint.
Subject-years = sum (date of study termination – date of randomization +1) of all randomized subjects / 365.25.
Yearly event rate (%) = No. of subjects with event/subject-years * 100
Source data: NDA Amendment; Table 15.2.2.2: 1

Hazard ratios, CIs and p values are presented in the following table (Table 6.4.2: 2). As with the other secondary endpoint, both hazard ratios were below 1.00, with the DE 150 BID group demonstrating a significantly lower relative risk (16% reduction) compared to warfarin ($p < 0.01$).

Table 6.4.2: 2 Hazard Ratios and 95% CIs for Composite Endpoint of Stroke/SEE/PE/MI and Vascular Death

	DE 110 BID vs Warfarin	DE 150 BID vs Warfarin
Hazard ratio (SE)	0.98 (0.06)	0.84 (0.06)
95% CI	0.86, 1.10	0.74, 0.96
P-value	0.6972	0.0096

Source: NDA Amendment; Table 15.2.2.2: 2

6.4.3 Other Efficacy Endpoints

Each component of a composite endpoint was analyzed separately. Incidences of the following components of composite endpoints are included in this section: stroke (ischemic and hemorrhagic), death (all-cause and vascular death), MI, PE, and TIA.

6.4.3.1 Stroke

All strokes were adjudicated and classified into one of three categories; ischemic stroke, hemorrhagic stroke and stroke with uncertain classification (Table 6.4.3.1: 1). The latter category consisted mainly of events with no available imaging. For the 3 categories of stroke, both DE doses had numerically fewer events than the warfarin group except for ischemic strokes when comparing DE 110 BID to warfarin.

Table 6.4.3.1: 1 Yearly Event Rate (%) for Stroke

	DE 110 BID N (%)	DE 150 BID N (%)	Warfarin N (%)
Subjects randomized	6015	6076	6022
Subject-years	11899	12033	11797
Stroke	171 (1.44)	122 (1.01)	186 (1.58)
Ischemic stroke	152 (1.28)	103 (0.86)	134 (1.14)
Hemorrhagic stroke	14 (0.12)	12 (0.10)	45 (0.38)
Stroke with uncertain classifications	7 (0.06)	9 (0.07)	10 (0.08)

Each subject with an event was counted once for the composite endpoint and once for each component of the composite endpoint.
Subject-years = sum (date of study termination – date of randomization +1) of all randomized subjects / 365.25.
Yearly event rate (%) = No. of subjects with event/subject-years * 100
Source: NDA Amendment; Table 15.2.1.1: 1

6.4.3.2 Hemorrhagic stroke

The frequency of hemorrhagic strokes in the DE groups was less than one third of the hemorrhagic strokes observed in the warfarin group (Table 6.4.3.1: 1). Hazard ratios were well below 1.00 for both DE groups, with the DE 110 BID group demonstrating a 69% relative risk reduction (p=0.0001) and DE 150 BID group demonstrating a 74% relative risk reduction compared to warfarin (p<0.0001) (Table 6.4.3.2: 1).

Table 6.4.3.2: 1 Hazard ratios and 95% CIs for hemorrhagic stroke

	DE 110 BID vs Warfarin	DE 150 BID vs Warfarin
Hazard ratio (SE)	0.31 (0.09)	0.26 (0.08)
95% CI	0.17, 0.56	0.14, 0.49
P-value	0.0001	<0.0001

Source data: NDA Amendment; Table 15.3.2.1: 9

As seen in the Kaplan-Meier estimates for hemorrhagic stroke (Figure 6.4.3.2: 1), both DE doses reduced hemorrhagic stroke throughout the trial. Kaplan-Meier curves appeared to diverge very early in the study and continued to diverge until the end of the study.

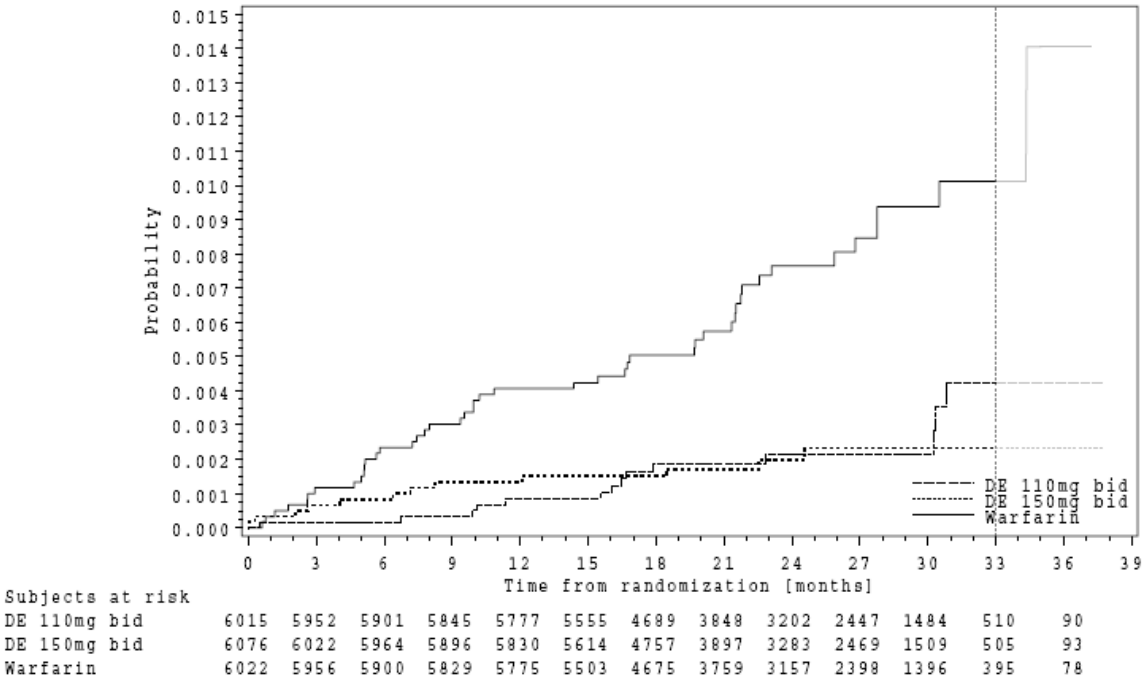


Figure 6.4.3.2: 1 Kaplan-Meier Estimates of Time to First Hemorrhagic Stroke

Source: NDA Amendment; Table 15.3.2.1: 7

6.4.3.3 Ischemic stroke

DE 150 BID reduced the risk of ischemic stroke by a 25%; p=0.0296), while DE 110 BID was not statistically different from warfarin (Table 6.4.3.3: 1). The impact of the higher dose of dabigatran on ischemic stroke is important because it indicates that the advantage of dabigatran compared to warfarin is not limited to effects on bleeding.

Table 6.4.3.3: 1 Hazard Ratios and 95% CIs for Ischemic Stroke

	DE 110 BID vs Warfarin	DE 150 BID vs Warfarin
Hazard ratio (SE)	1.13 (0.13)	0.75 (0.10)
95% CI	0.89, 1.42	0.58, 0.97
p-value	0.3139	0.0296

Source: NDA Amendment; Table 15.2.1.1: 8

The Kaplan-Meier estimates show that DE 150 BID separated early in the study from the other treatment groups and remained below both warfarin and DE 110 BID throughout the study (Figure 6.4.3.3: 1).

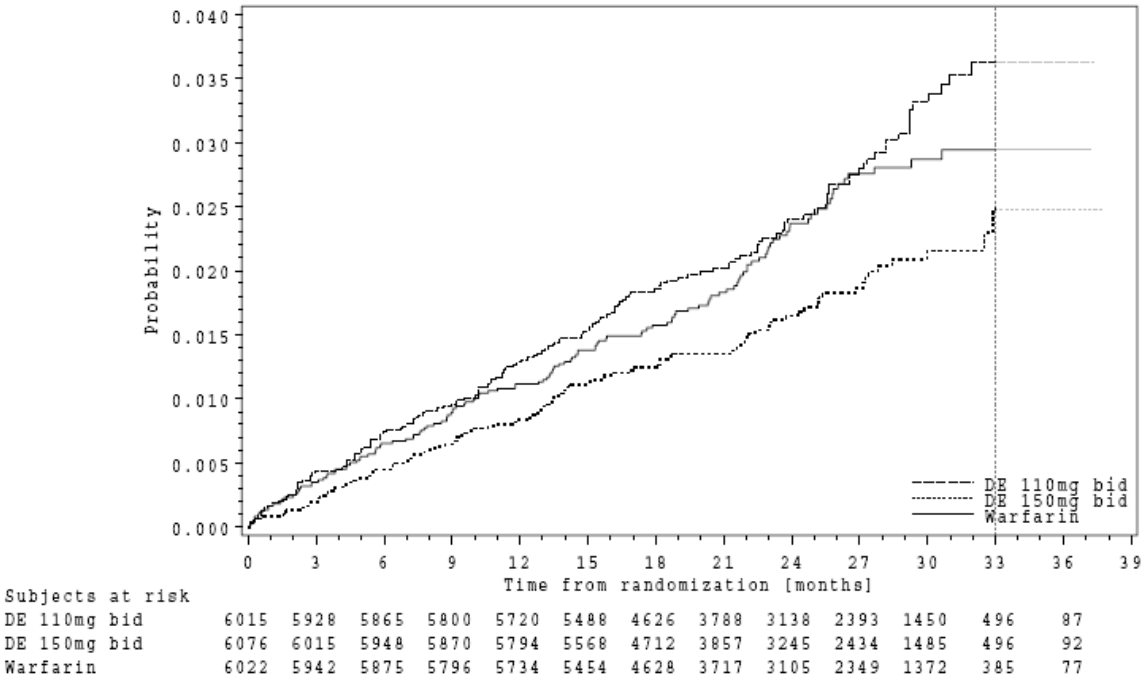


Figure 6.4.3.3: 1 Kaplan-Meier Estimates for Time to Ischemic Stroke

Source: NDA Amendment, Figure 15.2.1.1: 2

6.4.3.4 Myocardial Infarction

The frequency of adjudicated MIs (clinical and silent) was greater in DE-treated subjects than in those treated with warfarin in both the randomized and safety sets (Table 6.4.3.4: 1). The hazard ratios, for all MI events, for DE 110 BID and DE 150 BID vs. warfarin were 1.29 (p=0.0929) and 1.27 (p=0.1240), respectively (Table 6.4.3.4: 2).

Table 6.4.3.4: 1 MI (Clinical and/or Silent) - Subject Number and Yearly Event Rate

	DE 110 BID N (Annual rate)	**DE 150 BID N (Annual rate)**	**Warfarin N (Annual rate)**
Subjects randomized	6015	6076	6022
MI (clinical and silent)	98 (0.82)	97 (0.81)	75 (0.64)
MI (clinical)	87 (0.73)	89 (0.74)	66 (0.56)
MI (silent)	11 (0.09)	8 (0.07)	9 (0.08)

Subject-years = sum (date of study termination – date of randomization +1) of all randomized subjects / 365.25.
Yearly event rate (%) = No. of subjects with event/subject-years * 100.
Source: NDA Amendment, Table 15.2.6.2: 5

Table 6.4.3.4: 2 Hazard Ratios and 95% CI for MI

	DE 110 BID vs Warfarin	**DE 150 BID vs Warfarin**
Randomized Set (all MI)		
Hazard ratio (SE)	1.29 (0.20)	1.27 (0.19)
95% CI	0.96, 1.75	0.94, 1.71
p-value	0.0929	0.1240
Randomized Set (clinical MI only)		
Hazard ratio (SE)	1.30 (0.21)	1.32 (0.21)
95% CI	0.95, 1.80	0.96, 1.81
p-value	0.1037	0.0877

In case of recurrent event, the first event was considered.
Source: NDA Amendment, Table 15.2.5: 2 and Table 15.2.6.1: 1

The Kaplan-Meier estimates for clinical MIs over time are shown in Figure 6.4.3.4: 1.

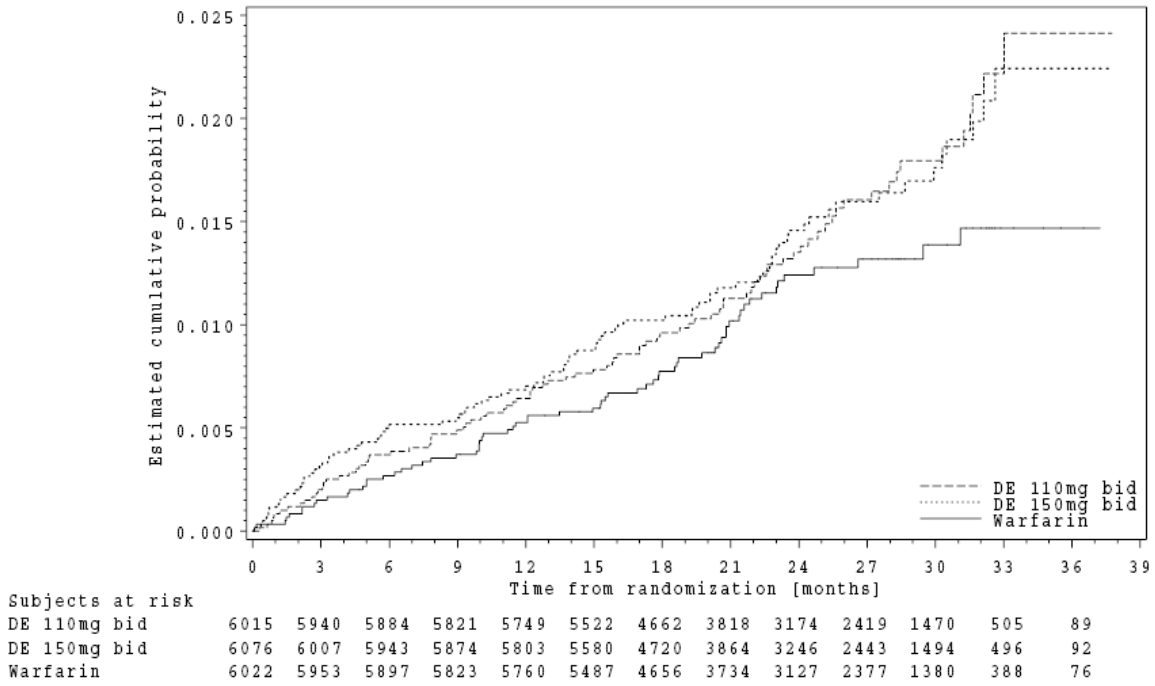


Figure 6.4.3.4: 1 Kaplan-Meier Estimate of the Time to First MI, randomized set

Source data: NDA Amendment, Figure 15.2.5: 1

Characteristics of subjects sustaining MI

The reasons for the imbalance in MIs between the DE and warfarin groups are unclear. Subjects had similar baseline characteristics across the treatment groups, with respect to cardiovascular risk factors (hypertension, diabetes, prior coronary artery disease, prior MI, prior stroke), except for current smokers, which had more than twice the frequency in DE 110 BID subjects who sustained an MI, than those who did not (NDA Sequence 0132, Table 7.6)

Concomitant antithrombotic therapies

A review of concomitant therapies during the treatment period for anti-thrombotic therapies showed a somewhat greater use of anti-platelet agents prior to the onset of MI, in the DE treatment groups, than in the warfarin treatment group. There was also a nearly two-fold greater use of non-study oral anticoagulant and parenteral anticoagulant therapy reported for subjects in the DE treatment groups compared to those randomized to warfarin, prior to the first MI (see Table 6.4.3.4: 3). This higher use of non-study oral anticoagulant use in the DE treatment groups prior to MI, may have resulted from (1) the fact that subjects with symptoms consistent with acute coronary syndrome, were required to have DE treatment discontinued (Study 1160.26 Protocol, U09-3249-01, Appendix 16.1.1.1, Section 4.2.1), or (2) subjects who had permanent discontinuation of study drug, would have been put on non-study drug oral anticoagulant because of their underlying condition of atrial fibrillation and risk for stroke.

Table 6.4.3.4: 3 Anti-thrombotic concomitant medication use at the visit prior to index MI (randomized set, subjects with clinical MI)

	Medication taken at visit prior to MI						Medication not taken at visit prior to MI					
	DE 110 BID		DE 150 BID		Warfarin		DE 110 BID		DE 150 BID		Warfarin	
	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)
Total MIs	87	(100)	89	(100)	66	(100)	87	(100)	89	(100)	66	(100)
ASA	46	(52.9)	44	(49.4)	28	(42.4)	41	(47.1)	45	(50.6)	38	(57.6)
Clopidogrel (C)	23	(26.4)	21	(23.6)	9	(13.6)	64	(73.6)	68	(76.4)	57	86.4)
ASA +C	17	(19.5)	17	(19.1)	7	(10.6)	70	(80.5)	72	(80.9)	59	(89.4)
Non study OAC	19	(21.8)	17	(19.1)	6	(9.1)	68	(78.2)	72	(80.9)	60	(90.9)
PAC	25	(28.7)	28	(31.5)	10	(15.2)	62	(71.3)	61	(68.5)	56	(84.8)

ASA = Aspirin, OAC = oral anticoagulant, PAC = parenteral anticoagulant
Source: NDA Sequence 0132, Table 7.27

MI event occurrence with respect to study drug treatment or discontinuation

If one evaluates the frequency of MI occurrence by time off study drug, approximately 20% of MI events occurred in subjects not receiving study drug (see Table 6.4.3.4: 4). There is no evidence that these off treatment MI events resulted from a rebound, hypercoagulable state. If one reviews the incidence of first MI, on and off treatment, one sees that the imbalance in incidence of first MI is the same, on treatment, off treatment > 6 days, and off treatment > 90 days. It does not seem that the imbalance in MI can be attributed to a pharmacodynamic effect of dabigatran, since the imbalance persists, even after >90 days. Furthermore, approximately 20% of subjects with an index MI were taking non-study drug oral anticoagulants at the visit prior to the index MI event, with a greater number on both DE doses compared to warfarin.

These data need to be reviewed with the following understanding: (1) the protocol for the U09-3249-01 (Appendix 16.1.1.1, Section 4.2.1, named "Rescue medication and additional treatments") specified that for DE treatment groups, Acute Coronary Syndrome, "In patients with documented or suspected acute coronary syndrome, study drug should be temporarily discontinued," (2) research subjects who are hospitalized for symptoms of acute coronary syndrome do not typically take their study medication to the hospital, and (3) the method for the determination of MI onset date, was not specified, ie, review of the source documentation indicated that in some instances the MI date was the date of hospitalization, in other instances the date of MI determination occurred after diagnostic data reports were completed (e.g., cardiac enzymes).

Table 6.4.3.4: 4 Number of subjects with first clinical MI by time of occurrence from study drug discontinuation, randomized set

	DE 110 BID		DE 150 BID		Warfarin	
	N	**(%)**	**N**	**(%)**	**N**	**(%)**
Total Randomized	6015	(100)	6076	(100)	6022	(100)
Total number of first MI cases	87	(1.4)	89	(1.5)	66	(1.1)
MI on or ≤ 6 days off study drug	69	(1.1)	69	(1.1)	54	(0.9)
On study drug	56	(0.9)	59	(1.0)	46	(0.8)
Off study drug						
≤ 6 days off study drug	13	(0.2)	10	(0.2)	8	(0.1)
> 6 days off study drug	17	(0.3)	20	(0.3)	12	(0.2)
> 90 days off study drug	13	(0.2)	14	(0.2)	6	(0.1)
Randomized not treated	1		0		0	

Source: NDA Amendment, Table 15.2.5: 15

Characterization of MI severity

The diagnosis of acute myocardial infarction for the purposes of event adjudication in this study, was based on the presence of two of three criteria, including symptoms consistent with chest pain (85.3% of cases), ECG changes (61.7% of cases), and enzyme elevations (93.2% of cases) (Table 6.4.3.4: 5). ECG changes that were captured in the case report forms were described only as "new Q waves" or ST-T changes. Myocardial infarctions were not characterized as ST segment elevation or non-ST segment elevation MIs. Consequently, information about MI severity was not systematically captured and was limited to whatever data was clinically available.

The incidence of cardiovascular death with recent MI was low, with 15, 7 and 8 fatal MIs in the DE 110 BID, DE 150 BID and warfarin groups, respectively (NDA Sequence 0132, Table 7.29). If one looks at the distribution of biomarkers most indicative of- and specific for irreversible myocardial injury, new Q waves, CK-MB >5X the upper limit of normal (ULN) or troponin >5X the ULN the incidence is balanced, without a dose (DE 110 BID vs. DE 150 BID) or treatment-related relationship (DE vs. warfarin). No measurements of left ventricular systolic function were systematically collected during the conduct of the study. There was no evidence of a treatment or dose related impact on the prevalence of ECG or enzyme changes between treatment groups (Table 6.4.3.4: 5).

Table 6.4.3.4: 5 MI Severity after adjudication

	DE 110 BID		DE 150 BID		Warfarin	
	N	(%)	N	(%)	N	(%)
Total number of adjudicated MIs	90	(100)	102	(100)	74	(100)
MI Symptoms	74	(82.2)	92	(90.2)	61	(82.1)
ECG changes	56	(62.2)	59	(57.8)	49	(66.2)
New Q wave	10	(11.1)	7	(6.9)	12	(16.2)
ST-T changes	52	(57.8)	56	(54.9)	47	(63.5)
Cardiac enzymes	83	(92.2)	95	(93.1)	70	(94.6)
Peak CK-MB	52	(57.8)	54	(52.9)	44	(59.5)
Within normal range	9	(10.0)	5	(4.9)	7	(9.5)
>ULN and ≤ 2 X ULN	11	(12.2)	11	(10.8)	6	(8.1)
> 2 X ULN and ≤ 5 X ULN	13	(14.4)	12	(11.8)	12	(16.2)
> 5 X ULN	19	(21.1)	26	(25.5)	19	(25.7)
Troponin	80	(88.9)	91	(89.2)	68	(91.9)
Within normal range	0		2	(2.0)	2	(2.7)
>ULN and ≤ 2 X ULN	15	(16.7)	13	(12.7)	10	(13.5)
> 2 X ULN and ≤ 5 X ULN	11	(12.2)	11	(10.8)	11	(14.9)
> 5 X ULN	54	(60.0)	65	(63.7)	45	(60.8)

Source: NDA Sequence 0132, Table 7.25

In conclusion, MIs were found with a greater frequency (0.2% per year) in both DE treatment groups compared to the warfarin treatment group. There was no apparent dose relationship as there were similar numbers of events in both DE groups. The observed imbalance could not be explained by differences in baseline risk factors or concomitant treatments. Approximately 20% of first MIs in the DE treatment groups in RE-LY occurred when subjects were off study drug. Approximately 20% of subjects randomized to DE were receiving non-study drug oral anticoagulants at the visit prior to their first MI in RE-LY.

6.4.3.5 Pulmonary Embolism

The DE 110 BID and DE 150 BID groups had a few more PEs than the warfarin group, although the yearly event rates were low in all groups (Table 6.4.3.5: 1). The difference between DE and warfarin in PE was not significant.

Table 6.4.3.5: 1 Yearly Event Rate for Pulmonary Embolism

	DE 110 BID N (%)	DE 150 BID N (%)	Warfarin N (%)
Subjects randomized	6015	6076	6022
Subject-year	11899	12033	11794
PE	14 (0.12)	18 (0.15)	12 (0.09)

Subject-years = sum (date of study termination – date of randomization +1) of all randomized subjects / 365.25.
Yearly event rate (%) = No. of subjects with event/subject-years * 100
Source: NDA Amendment; Table 15.2.2.3: 3

6.4.3.6 Transient Ischemic Attack

The DE 110 BID and DE 150 BID groups had relatively lower event rates for TIA than warfarin (Table 6.4.3.6: 1).

Table 6.4.3.6: 1 Yearly Event Rate (%) for TIA

	DE 110 BID N (%)	DE 150 BID N (%)	Warfarin N (%)
Subjects randomized	6015	6076	6022
Subject-year	11899	12033	11794
TIA	74 (0.62)	87 (0.72)	99 (0.84)

Subject-years = sum (date of study termination – date of randomization +1) of all randomized subjects / 365.25.
Yearly event rate (%) = No. of subjects with event/subject-years * 100
Source: NDA Amendment; Table 15.2.2.3: 1

6.4.3.7 Death

The 1,371 reported deaths were adjudicated into vascular and non-vascular deaths (Table 6.4.3.7: 1). Fewer vascular deaths and overall deaths were observed in both DE groups compared to the warfarin group. The difference in overall death did not reach significance (p=0.0517). DE 150 BID was associated with lower rates of vascular death compared to warfarin (p=0.0430).

Table 6.4.3.7: 1 Yearly Event Rate (%) for Death

	DE 110 BID N (%)	DE 150 BID N (%)	Warfarin N (%)
Randomized	6015	6076	6022
Total Death	446 (4.4)	438 (4.1)	487 (4.7)
Vascular	289 (2.43)	274 (2.28)	317 (2.69)
Cardiovascular death	160 (2.7)	151 (2.5)	156 (2.6)
Sudden/arrhythmic	89 (1.5)	75 (1.2)	87 (1.4)
Pump failure	71 (1.2)	76 (1.3)	69 (1.1)
Other vascular	105 (1.7)	93 (1.5)	125 (2.1)
Stroke	30 (0.5)	23 (0.4)	44 (0.7)
Pulmonary embolus	2 (0.0)	1 (0.0)	4 (0.1)
Hemorrhagic	11 (0.2)	13 (0.2)	18 (0.3)
Unknown	46 (0.8)	41 (0.7)	46 (0.8)
Non-vascular	163 (2.7)	173 (2.8)	177 (2.9)

Subject-years = sum (date of study termination – date of randomization +1) of all randomized subjects / 365.25.
Yearly event rate (%) = No. of subjects with event/subject-years * 100
Source: NDA Amendment; Table 15.2.2.1: 1

All-cause death

The yearly rate for all-cause death was 3.75%, 3.64% and 4.13% in the DE 110 BID, DE 150 BID and the warfarin groups, respectively (Table 6.4.3.7: 1).

The hazard ratios for DE 110 BID and DE 150 BID vs. warfarin were 0.91 and 0.88, respectively, with corresponding risk reductions relative to warfarin of 9% and 12%, respectively (Table 6.4.3.7: 2). The lower number of deaths in DE groups is mostly due to fewer vascular deaths; DE seems to have little, if any, effect on non-vascular deaths (Table 6.4.3.7: 1).

Table 6.4.3.7: 2 Hazard Ratios and 95% CIs for All-Cause Death

	DE 110 BID vs Warfarin	DE 150 BID vs Warfarin
Hazard ratio (SE)	0.91 (0.06)	0.88 (0.06)
95% CI	0.80, 1.03	0.77, 1.00
P-value	0.1308	0.0517

Source: NDA Amendment; Table 15.3.2.4: 3

Vascular death

As with all-cause death, fewer deaths were reported in both DE groups compared to the warfarin group, with the DE 150 BID group having significantly fewer vascular deaths than the warfarin group (Table 6.4.3.7: 3). More than 60% of all deaths were adjudicated as vascular deaths (Table 6.4.3.7: 1). Deaths for which no other cause was apparent were to be adjudicated as vascular deaths, as is standard in cardiovascular outcome studies.

Table 6.4.3.7: 3 Hazard Ratios and 95% CIs for Vascular Death

	DE 110 BID vs Warfarin	DE 150 BID vs Warfarin
Hazard ratio (SE)	0.90 (0.07)	0.85 (0.07)
95% CI	0.77, 1.06	0.72, 0.99
P-value	0.2081	0.0430

Source: NDA Amendment; Table 15.3.2.4: 4

The Kaplan-Meier estimates for vascular death show that the DE 150 BID group curve diverges from the warfarin curve almost from the start of the trial, with the separation becoming larger throughout the trial (Figure 6.4.3.7: 1). The Kaplan-Meier estimate suggests that DE 150 BID may have a beneficial effect on vascular mortality.

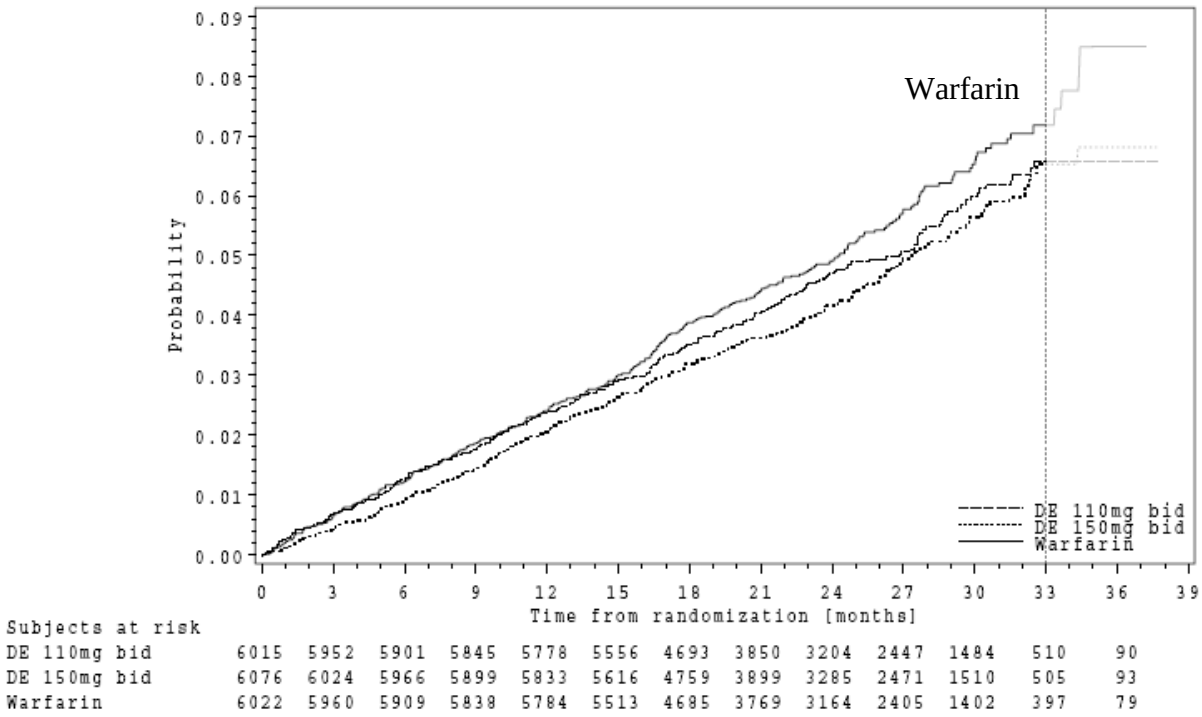


Figure 6.4.3.7: 1 Kaplan-Meier Estimates for Time to Vascular Death

Source: NDA Amendment; Figure 15.3.2.4: 2

6.5 SUBGROUPS

6.5.1 Specific Subject Populations

6.5.1.1 History of VKA use - VKA-Naïve vs. VKA-Experienced

No treatment by VKA-use interaction (p=0. 8691) was determined. DE 150 BID was superior to warfarin for both historical VKA-experienced (p=0. 0068) and also for VKA-naïve subjects (p=0. 0051). DE 110 BID was similar to warfarin in reducing the occurrences of stroke/SEE for both VKA-experienced and VKA-naïve subjects (Table 6.5.1.1: 1).

The same overall pattern of results was observed when testing the interaction and differences for the historical categories of “never used VKA” vs. “used VKA at least once.” No interaction was observed for treatment by VKA use, DE 150 BID was superior to warfarin, and DE 110 BID was similar to warfarin. (Table 6.5.1.1: 1).

Table 6.5.1.1: 1 Hazard Ratio and 95% Confidence Interval for Stroke/SEE by History of VKA use Subgroups

	DE 110 BID vs Warfarin	DE 150 BID vs Warfarin	Interaction p-value
Baseline VKA use			0.8691
Naïve			
Hazard ratio	0.93	0.63	
95% CI	0.70, 1.24	0.46, 0.87	
P-value	0.6359	0.0051	
Experienced			
Hazard ratio	0.87	0.66	
95% CI	0.66, 1.15	0.48, 0.89	
P-value	0.3204	0.0068	
Baseline VKA use			0.2522
Never Used VKA			
Hazard ratio	0.80	0.50	
95% CI	0.57, 1.13	0.34, 0.74	
P-value	0.2058	0.0004	
Used VKA at least once			
Hazard ratio	0.96	0.74	
95% CI	0.75, 1.23	0.57, 0.97	
P-value	0.7574	0.0276	

The hazard ratio and interaction p−values were calculated from Cox regression model with all 3 treatment groups and each specified subgroup variable in the model. In case of recurrent event, the first event was considered.
Subjects were considered to be warfarin treated (experienced) subjects if previously treated with any Vitamin-K antagonist for at least 2 months. Warfarin naïve subjects were treated for <2 months with any Vitamin-K antagonist.
Source: NDA Amendment; Table 15.2.3.1.: 2

6.5.1.2 Renal Impairment

Hazard ratios for stroke/SEE did not differ across degrees of renal function in the DE 110 BID vs. warfarin comparison. For DE 150 BID vs. warfarin, the hazard ratio is the smallest in subjects with baseline CrCl between 30 and 50 mL/min, and increased in the subgroups with higher baseline CrCl (NDA Amendment, Table 15.2.3.2: 2). Stroke/SEE rates generally increased with decreasing renal function, as expected.

6.5.1.3 Additional Subgroup Analyses

For all additional subgroups using baseline demographic information, there was no treatment by subgroup interaction observed for the subgroup analyses for the primary efficacy measure of stroke/SEE (all p-values above 0.45; NDA Amendment Tables 15.2.3.2 and 15.2.4:3-4)). Similar results were noted when assessing subgroups on the secondary efficacy measure stroke/SEE/all-cause death. The DE 150 BID was superior to warfarin for most of the subgroups and for those subgroups with a reasonable numbers of subjects to test for interaction. No treatment effect was observed with DE 110 BID (p-values above 0.5928) in comparison with warfarin and was consistent across all subgroups with a reasonable number of subjects except for ethnic groups (i.e., few blacks and Hispanics enrolled and none with events).

6.6 EFFICACY SUMMARY AND CONCLUSIONS

- For the primary efficacy endpoint, stroke/SEE, non-inferiority for both doses of dabigatran with warfarin was established ($p < 0.0001$ for non-inferiority) and DE 150 BID was superior to warfarin ($p = 0.0001$). The relative risk reductions for DE 110 BID and DE 150 BID were 10% and 35%, respectively.

- DE 150 BID was superior to DE 110 BID for the primary endpoint stroke/SEE (HR DE 110/DE 150: 1.39; $p=0.0041$) in this blinded comparison.

- Both DE doses significantly reduced the occurrence of hemorrhagic stroke compared to warfarin ($p < 0.0001$). The relative risk reductions were 69% and 74% for DE 110 BID and DE 150 BID compared to warfarin.

- Ischemic stroke was reduced by 25% for DE 150 BID compared to warfarin, $p=0.0296$.

- DE 150 BID was associated with 31 fewer ischemic and 33 fewer hemorrhagic strokes than warfarin.

- The risk reductions were 9% and 12% for all-cause deaths, 10% and 15% for vascular deaths by DE 110 BID and DE 150 BID. The 15% reduction for DE 150 BID compared to warfarin had a nominal p-value <0.05.

- Results were similar to the primary endpoint for both secondary endpoints [stroke/SEE/death and stroke/SEE/PE/MI/vascular death] with DE 150 BID superior to warfarin and DE 110 BID found to be comparable to warfarin.

- The frequency of MI was higher in the DE groups compared to the warfarin group (0.2%/year), not achieving statistical significance. The number of MIs was similar in both DE treatment groups. The observed imbalance could not be explained by differences in baseline risk factors or concomitant treatments received during the study. In the DE treatment groups approximately 20% of first MIs in RE-LY occurred off study drug.

- The efficacy of DE was consistent for all subgroups evaluated. No significant subgroup by-treatment interactions were observed.

7. CLINICAL SAFETY

7.1 OVERVIEW

All categories of bleeding occurred less frequently on DE 150 BID compared to warfarin except for non-life-threatening major bleeds. DE 110 BID had lower incidences of all categories of bleeding than DE 150 BID and warfarin. Over twice the number of symptomatic intracranial bleeds occurred with warfarin compared with either DE treatment. DE 150 BID had more major bleeding and any GI bleeding than DE 110 BID or warfarin.

The overall incidence of reported AEs was similar across the 3 treatment groups. No definitive relationship was determined between DE dose and the overall incidence of specific AEs or SAEs other than bleeding-related events. The most frequently reported GI AE (preferred terms) were diarrhea and dyspepsia; incidences were comparable for diarrhea, but approximately 4 times as frequent for both DE groups compared to warfarin for dyspepsia. The incidence of reported SAEs was comparable between the 3 treatment groups. Discontinuations of study drug occurred more frequently on DE 150 BID and DE 110 BID than warfarin. Dyspepsia, nausea and GI bleeding were the most common AEs leading to discontinuation, having higher frequencies for both DE groups compared to warfarin. There were approximately 10 and 15% fewer all-cause deaths and vascular deaths on DE 110 BID and DE 150 BID, respectively, compared to warfarin with only the DE 150 BID vs warfarin comparison having a nominal p-value slightly below 0.05. The hepatic safety profile of dabigatran is comparable to warfarin.

7.2 EXPOSURE

The overall exposure for dabigatran for the SPAF indication was 18,789 subjects of whom 12,635 received dabigatran. The studies contributing to dabigatran exposure were: 1037 subjects were randomized in 2 Phase II studies of 12 weeks duration, while 18,113 subjects were randomized in Phase III study (RE-LY). A Phase II extension study (extension study to PETRO-1160.20, U06-1615-02) had 361 subjects enrolled and there was follow-up for almost 5 years (Table 7.2: 1).

Table 7.2: 1 Summary of overall exposure

Study ID (Phase)	**Study Design**	**Primary Endpoint**	**Treatment Groups***	**Duration**	**No. Subjects Randomized**
1160.26 "RE-LY" (Phase III)	Randomized, parallel group, open-label for warfarin, double-blind for dabigatran	Stroke/SEE	DE 110 mg BID DE 150 mg BID Warfarin, adjusted dose	3 years	N = 6015 N = 6076 N = 6022 Total = 18,113
1160.20 "PETRO" (Phase II)	Randomized, parallel group, open-label for warfarin and ASA, double-blind for dabigatran doses	Safety and dose exploration	DE 50-300mg + ASA 81-325 DE 50 mg BID DE 150 mg BID DE 300 mg BID DE 50 mg BID+ASA 81 mg DE 150 mg BID+ASA 81 mg DE 300 mg BID+ASA 81 mg DE 50 mg BID+ASA 325 mg DE 150 mg BID+ASA 325 mg DE 300 mg BID+ASA 325 mg Warfarin, adjusted dose	12 weeks	N = 58 N = 99 N = 98 N = 20 N = 34 N = 33 N = 27 N = 33 N = 30 N = 70 Total = 502
1160.42 Extension of 1160.20 "PETRO-EX" (Phase II)**	Randomized, Double-blind, Parallel group	Long-term safety	DE 150 mg QD DE 150 mg BID DE 300 mg QD DE 300 mg BID	5 years	(entered from 1160.20) N = 98 N = 88 N = 50 N = 125 Total = 361
1160.49 (Phase II)	Randomized, parallel group, open-label for warfarin, dabigatran doses	Safety and dose exploration	DE 110 mg BID DE 150 mg BID Warfarin, adjusted dose	12 weeks	N = 53 N = 59 N = 62 Total = 174

** For Study 1160.42, treatments are those at enrolment into the study. Most subjects changed regimens at least once during the trial.

In the RE-LY study, a total of 18,113 subjects were randomized and 18,040 received study medication. Exposure to study medication was similar across all treatment groups with median exposure duration of 1.8 years (Table 7.2: 2). The median duration of time in the study was 2.0 years

Table 7.2: 2 Subject Exposure – RE-LY

	DE 110 BID	DE 150 BID	Warfarin	Total
Total treated	5983 (100.0)	6059 (100.0)	5998 (100.0)	18040 (100.0)
Exposure category [N (%)]				
≤14 days	186 (3.1)	198 (3.3)	104 (1.7)	488 (2.7)
>14 days and ≤1 month	130 (2.2)	133 (2.2)	74 (1.2)	337 (1.9)
>1 month and ≤3 months	201 (3.4)	249 (4.1)	156 (2.6)	606 (3.4)
>3 months and ≤6 months	217 (3.6)	228 (3.8)	155 (2.6)	600 (3.3)
>6 months and ≤9 months	166 (2.8)	168 (2.8)	169 (2.8)	503 (2.8)
>9 months and ≤12 months	147 (2.5)	144 (2.4)	147 (2.5)	438 (2.4)
>12 months and ≤16 months	705 (11.8)	717 (11.8)	764 (12.7)	2186 (12.1)
>16 months and ≤20 months	872 (14.6)	869 (14.3)	936 (15.6)	2677 (14.8)
>20 months and ≤24 months	972 (16.2)	948 (15.6)	1023 (17.1)	2943 (16.3)
>24 months and ≤28 months	879 (14.7)	891 (14.7)	947 (15.8)	2717 (15.1)
>28 months and ≤32 months	968 (16.2)	992 (16.4)	1033 (17.2)	2993 (16.6)
>32 months and ≤36 months	515 (8.6)	496 (8.2)	475 (7.9)	1486 (8.2)
>36 months	25 (0.4)	26 (0.4)	15 (0.3)	66 (0.4)
Summary statistics (months)				
Mean	20.54	20.32	21.33	20.73
SD	9.62	9.76	8.80	9.41
Median	21.95	21.39	22.57	22.14
Minimum	0.0	0.0	0.0	0.0
Maximum	36.7	37.0	36.7	37.0
Total subject-years	10242.1	10261.2	10659.3	31162.6

Exposure days are calculated as: the date of last study medication administration - date of first study drug administration +1; the calculated days are converted to months (12*days/365.25).
Total subject-years = sum of exposure days of all subjects / 365.25
Source: NDA Amendment; Table 15.3.1: 1

The number of VKA-experienced and VKA-naïve subjects was similar within treatment groups, as well as across treatment groups. Subjects who were previously treated with VKA remained on treatment longer than subjects who were VKA naïve (Table 7.2: 3).

Table 7.2: 3 Subject Exposure by VKA Status at Study Entry – RE-LY

	VKA naive			VKA Experienced		
	DE 110 BID	**DE 150 BID**	**Warfarin**	**DE 110 BID**	**DE 150 BID**	**Warfarin**
Total treated	2990	3019	3082	2991	3039	2916
Median (months)	20.19	20.07	20.24	23.59	23.46	23.98
Mean	19.38	19.19	19.72	21.71	21.45	23.02

Exposure days are calculated as: the date of last study medication administration - date of first study drug administration +1
Total subject-years = sum of exposure days of all subjects / 365.25
Source: NDA Amendment; Table 15.3.1: 2

7.3 PHASE III SPAF STUDY RE-LY – BLEEDING

7.3.1 Major Bleeds and Other Bleeding

The primary bleeding event analysis used the randomized set, with sensitivity analyses performed on the safety set. All events except for minor bleeds were adjudicated (Central Adjudication Committee). Investigator-reported events, including all bleeding and investigator classified major bleeding, were also analyzed.

Hemorrhagic stroke was part of the pre-specified efficacy endpoint and is discussed in Section 6.4.3.2.

All important prespecified categories of bleeding occurred less frequently on both doses of DE compared to warfarin except for non-life-threatening major bleeds comparing DE 150 BID and warfarin (Table 7.3.1: 1).

Table 7.3.1: 1 Yearly Event Rate of Bleeding - RE-LY Study

	DE 110 BID N (%)	**DE 150 BID N (%)**	**Warfarin N (%)**
Adjudicated Bleeds			
Number of randomized subjects	6015	6076	6022
Subject-years	11899	12033	11794
Major bleeds (%/year)	342 (2.87)	399 (3.32)	421 (3.57)
Life threatening MBEs	147 (1.24)	179 (1.49)	218 (1.85)
Other MBEs	218 (1.83)	248 (2.06)	226 (1.92)
ICH[1]	27 (0.23)	38 (0.32)	90 (0.76)
Minor bleeds[2]	1566 (13.16)	1787 (14.85)	1931 (16.37)
Any bleeds[2]	1754 (14.74)	1993 (16.56)	2166 (18.37)

1 ICH includes intracerebral bleeds, subdural bleeds, and subarachnoid bleeds.
2 Investigator-reported bleeding events. Minor bleeds were not adjudicated.
In case of a recurrent event of the same category, the first event was considered.
Subject-years = sum (date of study termination - date of randomization +1) of all randomized subjects / 365.25.
Yearly event rate (%) = # of subjects with event / subject-years * 100.
Source data: NDA Amendment; Table 15.3.2.1: 1, Table 15.3.2.1: 2

Hazard ratios, confidence intervals and p-values comparing the three treatment groups in RE-LY are presented above in the summary section (Table 7.3.1: 2).

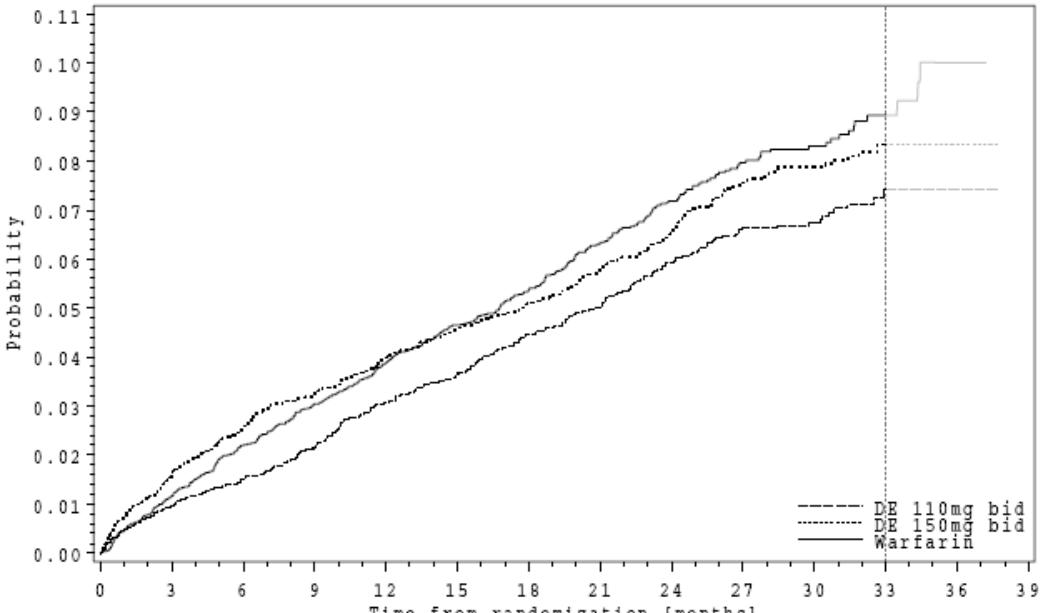
Table 7.3.1: 2 Major Bleeds and Any Bleeds – RE-LY Study

		DE 110 BID vs Warfarin	**DE 150 BID vs Warfarin**	**DE 110 BID vs DE 150 BID**
Adjudicated major bleeds	Hazard ratio (SE)	0.80 (0.06)	0.93 (0.07)	0.86 (0.06)
	95% CI	0.70, 0.93	0.81, 1.07	0.75, 1.00
	P-value	0.0026	0.3146	0.0429
Adjudicated life-threatening bleeds	Hazard ratio (SE)	0.67 (0.07)	0.80 (0.08)	0.83 (0.09)
	95% CI	0.54, 0.82	0.66, 0.98	0.67, 1.03
	P-value	0.0001	0.0305	0.0915
Adjudicated ICH	Hazard ratio (SE)	0.30 (0.06)	0.41 (0.08)	0.72 (0.18)
	95% CI	0.19, 0.45	0.28, 0.60	0.44, 1.18
	P-value	<0.0001	<0.0001	0.1875
Investigator reported any bleeds	Hazard ratio (SE)	0.78 (0.03)	0.91 (0.03)	0.86 (0.03)
	95% CI	0.73, 0.83	0.85, 0.96	0.81, 0.92
	P-value	<0.0001	0.0016	<.0001

In case of recurrent event, the first event was considered.
Source: NDA Amendment; Table 15.3.2.1: 9

The majority (85%) of RE-LY subjects who had a MBE during the study had only 1 bleeding event. Approximately 58% of the RE-LY subjects who had any bleeding event during the study had only one bleeding event. The number of investigator-reported “any bleeding” events were lower for DE 110 BID compared to DE 150 BID and warfarin (Table 7.3.1: 2).

Following are the Kaplan-Meier estimates for time to first major bleeds (Figure 7.3.1: 1).



Subjects at risk													
DE 110mg bid	6015	5905	5826	5739	5626	5386	4515	3686	3043	2309	1405	477	83
DE 150mg bid	6076	5939	5834	5733	5635	5403	4561	3716	3109	2311	1412	473	86
Warfarin	6022	5897	5794	5686	5596	5307	4489	3573	2985	2250	1308	373	73

Figure 7.3.1: 1 Kaplan-Meier Estimates of Time to First Major Bleed

Source: NDA Amendment, Figure 15.3.2.1:1

The DE 150 BID KM estimate is higher than warfarin estimate for the first 12-15 months of RE-LY; thereafter, it remains below the warfarin estimate. The DE 110 BID KM estimate is below the warfarin estimate for the entire study.

Discontinuations of study medication due to major bleeding events

DE 110 BID had more discontinuations than warfarin in the first 6 months of RE-LY, while DE 150 BID had discontinuations than warfarin in the first 18 months of RE-LY. Thereafter, discontinuation rates for major bleeds for the 3 treatment groups were similar (NDA Amendment; Figure 15.3.2.3: 1).

On-treatment analysis of major bleeding events

Since there were more discontinuations on both DE 150 BID and DE 110 BID than warfarin, and such subjects not infrequently were switched to non-study VKA, it is appropriate to evaluate the on-treatment occurrence of major bleeding. The hazard ratio for DE 150 BID compared to warfarin was below 1.0 for the on-treatment analysis of major bleeds. DE 110 BID had significantly fewer major bleeds for the on-treatment analysis than warfarin (Table 7.3.1: 3).

Table 7.3.1: 3 Hazard Ratios and 95% CI for Adjudicated Major Bleeds – Treatment Emergent Events (safety set)

		DE 110mg bid vs Warfarin	DE 150mg bid vs Warfarin
Adjudicated major bleeds	Hazard ratio (SE)	0.83 (0.07)	0.98 (0.07)
	95% CI	0.71, 0.96	0.85, 1.14
	P-value	0.0158	0.8114

Source: NDA Amendment, Table 15.3.2.1: 11

Major bleeding events by criteria and location

There were 1,360 adjudicated MBEs reported by investigators during RE-LY (397, 486, and 477 for DE 110 BID, DE 150 BID, and warfarin, respectively) (Table 7.3.1: 4).

The adjudication committee categorized major bleeds into those considered major and life-threatening. The location and the specific criterion or criteria that were included in the definition of major bleed were not adjudicated. Major bleeds, within a critical area or organ, occurred at twice the frequency after warfarin treatment compared to DE (15.1%, 14.2%, and 30.2% for DE 110 BID, DE 150 BID, and warfarin, respectively) (Table 7.3.1: 4). There was more than twice the number of symptomatic intracranial bleeds on warfarin than on either DE treatment. For all categories of symptomatic bleeding into a critical area/organ, with the exception of intraocular, fewer events occurred for DE compared to warfarin. Additionally, more fatal bleeds were associated with the use of warfarin (Table 7.3.1: 4).

Table 7.3.1: 4 Major Bleeds by Bleeding Criteria as reported by investigators – RE-LY Study

	DE 110mg bid	DE 150mg bid	Warfarin
Total number of major bleeds	397 (100.0)	486 (100.0)	477 (100.0)
Hospitalized for the event	286 (72.0)	368 (75.7)	364 (76.3)
Bleeding criteria			
Drop of Haemoglobin >=20 g/L	266 (67.0)	330 (67.9)	282 (59.1)
Required transfusion >= 2 units	234 (58.9)	315 (64.8)	246 (51.6)
Symptomatic bleeding in critical area/organ	60 (15.1)	69 (14.2)	144 (30.2)
Intraocular	16 (4.0)	10 (2.1)	17 (3.6)
Intraspinal	0	0	0
Intramuscular	8 (2.0)	8 (1.6)	18 (3.8)
Retroperiltoneal	2 (0.5)	9 (1.9)	12 (2.5)
Intra-anticular	4 (1.0)	4 (0.8)	7 (1.5)
Pericardial	2 (0.5)	3 (0.6)	4 (0.8)
Symptomatic intracranial	31 (7.8)	38 (7.8)	88 (18.4)
Subdural	13 (3.3)	23 (4.7)	41 (8.6)
Intracerebral	16 (4.0)	15 (3.1)	45 (9.4)
Gastrointestinal	154 (38.8)	218 (44.9)	139 (29.1)
Other area/organs	41 (10.3)	31 (6.4)	44 (9.2)
Associated with hypotension	18 (4.5)	34 (7.0)	22 (4.6)
Required surgical intervention	36 (9.1)	57 (11.7)	65 (13.6)
Death	25 (6.3)	28 (5.8)	40 (8.4)

1 With compartment syndrome
Source: NDA Amendment; Table 15.3.2.1: 24

Life-threatening Bleeds

Life-threatening bleeds were defined as those that met at least one of the following criteria: fatal, symptomatic intracranial hemorrhage, reduction of hemoglobin level of at least 50 g/L, transfusion of at least 4 units of blood or packed cells, hypotension requiring the use of intravenous ionotropic agents or necessitated surgical intervention. Life-threatening bleeds were categorized by the Adjudication Committee during the adjudication process since life-threatening bleeds are a subset of major bleeds.

Treatment with both blinded DE doses resulted in a significantly lower risk of life-threatening bleeds (hazard ratios 0.67 and 0.80 for DE 110 BID and DE 150 BID vs. warfarin, p=0.0001 and p=0.0305, respectively, Table 7.3.1: 2). DE 110 BID had numerically fewer life-threatening bleeding compared to DE 150 BID (hazard ratio 0.83, p=0.0915).

Intracranial Hemorrhage

Symptomatic intracranial hemorrhage is composed of hemorrhagic stroke plus subdural and subarachnoid hemorrhages. The hazard ratios and CIs were well below 1.00 for both DE groups; hazard ratios for DE 110 BID and DE 150 BID vs. warfarin were 0.30 and 0.41, respectively, with corresponding risk reductions of 70% and 59%, respectively (p<0.0001; Table 7.3.1: 5).

Table 7.3.1: 5 Hazard Ratios and CIs for Adjudicated Intracranial Hemorrhage

	DE 110 BID vs Warfarin	DE 150 BID vs Warfarin
Hazard ratio (SE)	0.30 (0.06)	0.41 (0.08)
95% CI	0.19, 0.45	0.28, 0.60
p-value	<0.0001	<0.0001

Intracranial hemorrhage includes subdural and subarachnoid bleeds in addition to intracerebral bleeds
Source: NDA Amendment; Table 15.3.2.1: 9

As seen in the Kaplan-Meier estimates for intracranial hemorrhage (Figure 7.3.1: 2), both DE doses significantly reduced intracranial hemorrhages compared to warfarin. As with hemorrhagic stroke, the Kaplan-Meier curves appeared to diverge almost from the beginning of the study and continued to diverge until the end of the study.

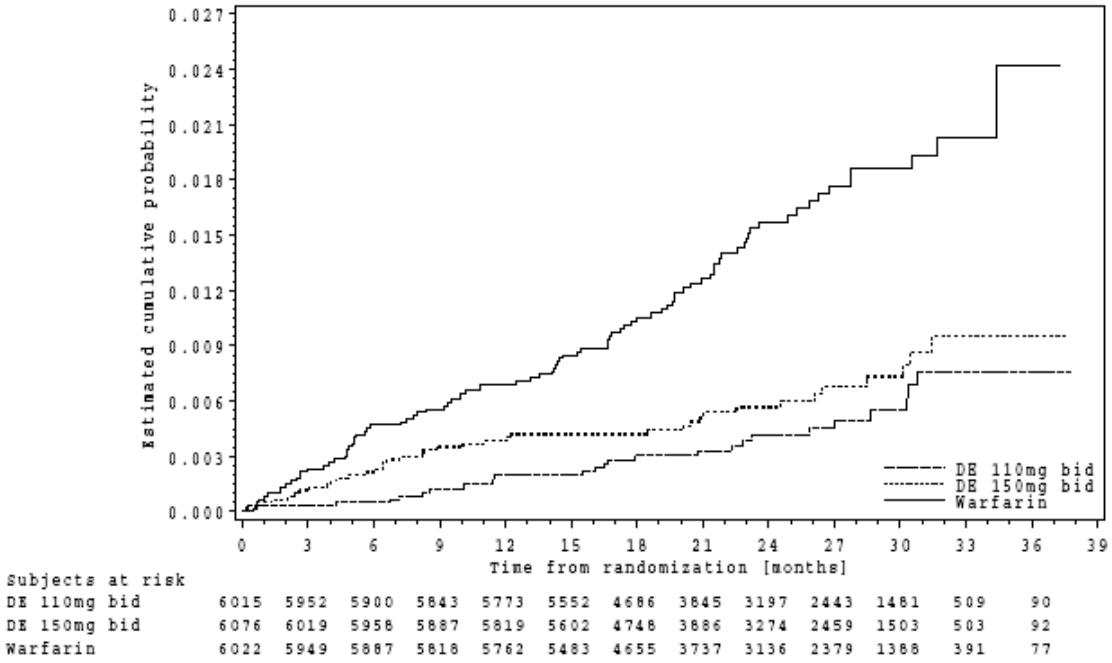


Figure 7.3.1: 2 Kaplan-Meier Estimates of Time to First Intracranial Hemorrhage

Source: NDA Amendment; Figure 15.3.2.1: 8

Gastrointestinal Bleeding

More gastrointestinal (GI) MBEs, life-threatening GI bleeds, and any bleeds were reported for DE 150 BID subjects compared to warfarin ($p<0.004$ for all comparisons; NDA Amendment: Table 15.3.2.2.8: 3), with only a modest increase reported for DE 110 BID subjects compared to warfarin (Table 7.3.1: 6). DE 110 BID had fewer (GI) MBEs and any bleeds than DE 150 BID ($p<0.05$ for all comparisons (NDA Amendment: Table 15.3.2.2.8: 3).

Table 7.3.1: 6 Yearly Event Rate of Gastrointestinal Bleeding Events – RE-LY Study (randomized set)

	DE 110 N (%)	DE 150 N (%)	Warfarin N (%)
Number of randomized subjects	6015	6076	6022
Any GI bleeds	600 (5.41)	681 (6.13)	452 (4.02)
GI Major bleeds (%/year)	134 (1.14)	186 (1.57)	125 (1.07)
GI Life threatening MBEs	67 (0.57)	94 (0.79)	57 (0.49)

In case of recurrent event, the first event was considered
For subjects with event, subject-years= (first onset date - date of randomization + 1) / 365.25
For subjects without event, subject-years= (study termination date - date of randomization + 1)/365.25
Yearly event rate (%) = # of subjects with event / subject-years * 100.
Any GI bleeds included adjudicated major GI bleeds and non-adjudicated minor GI bleeds.
Source: NDA Amendment; Table 15.3.2.2.8: 1

Major bleeding events by baseline demographics

Major bleeding rates are presented in the following sections with rates provided in different categories of various baseline characteristics including status of prior VKA use, age, gender, creatinine clearance and several other characteristics.

Major bleeding events by baseline demographics - Vitamin K antagonist use in RE-LY

The yearly event rate of a major bleeding event was generally similar within treatment groups, although the DE 150 BID estimate appears higher for the first 12-15 months for VKA-naïve subjects (Table 7.3.1: 3).

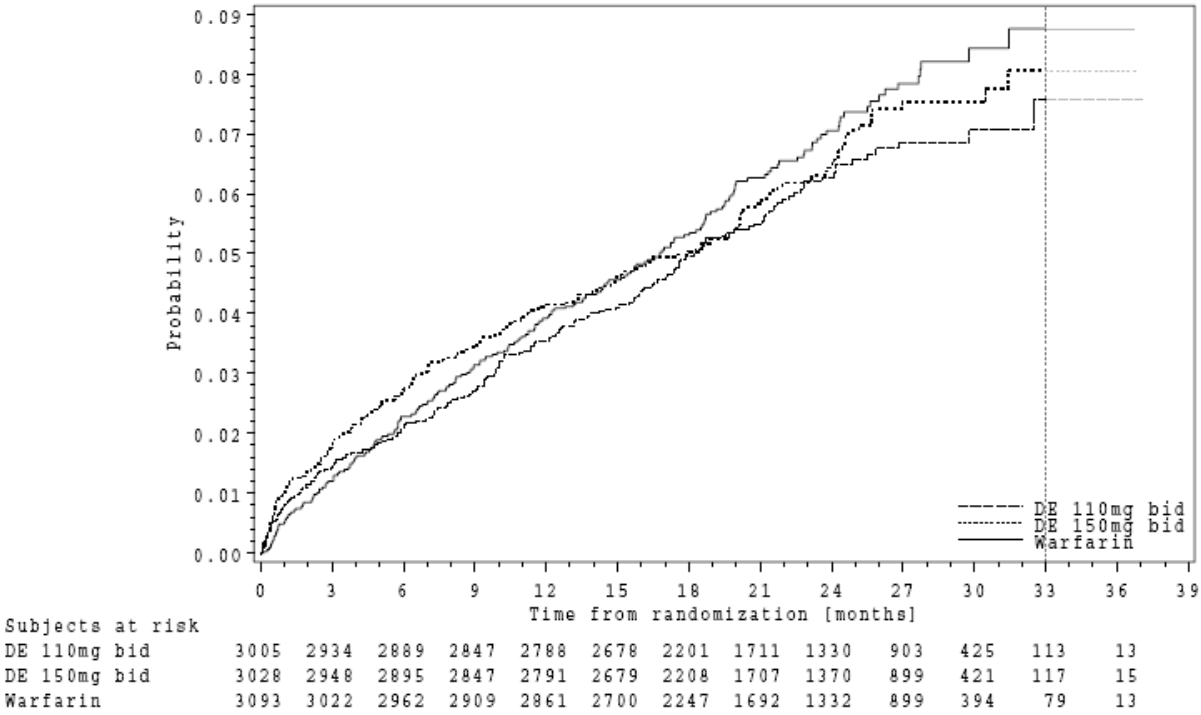


Figure 7.3.1: 3 Kaplan-Meier Estimate of Time to First Major Bleed by Prior VKA Class Use – VKA Naive

Source: NDA Amendment; Figure 15.3.2.2.1: 1

The KM estimate for the DE 110 BID group is clearly lower than the DE 150 BID and warfarin groups throughout the entire RE-LY study in the VKA-experienced cohort (Figure 7.3.1: 4). The DE 150 BID and warfarin curves are similar and cross several times.

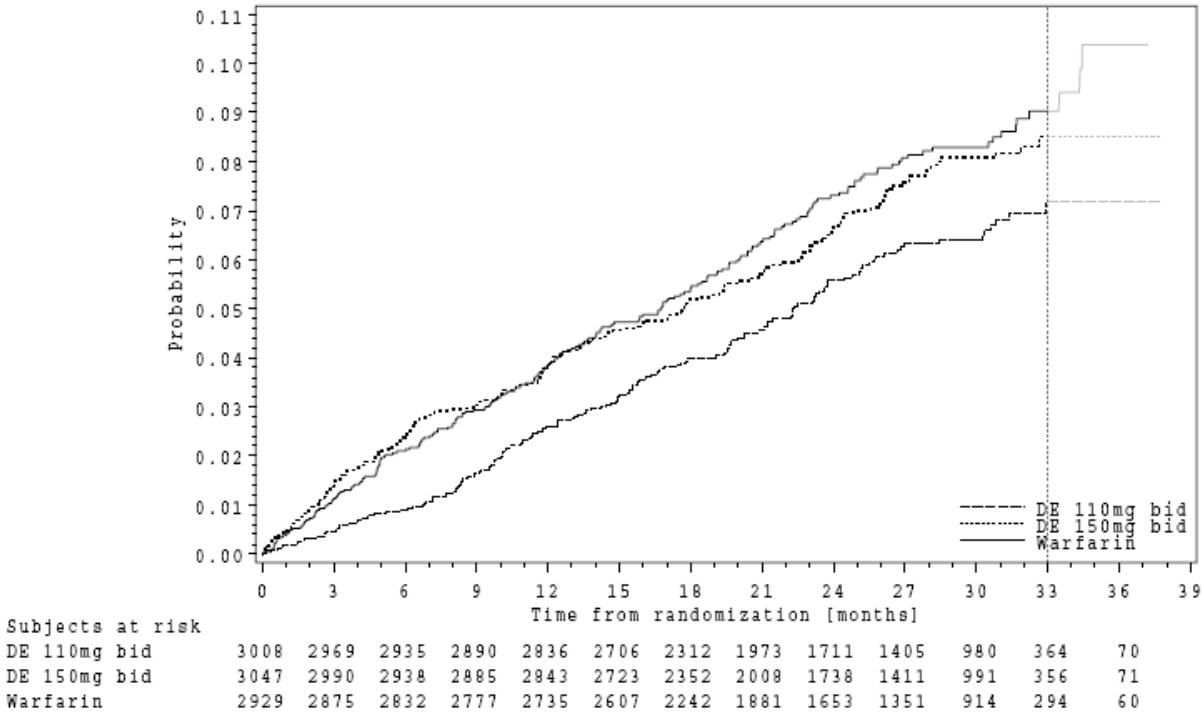


Figure 7.3.1: 4 Kaplan-Meier Estimate of Time to First Major Bleed by Prior VKA Class Use – VKA Experienced

Source: NDA Amendment; Figure 15.3.2.2.1: 1

There was little difference in the yearly rates of MBEs between VKA-naïve and experienced subjects in all treatment groups. Similarly, whether or not subjects were on a VKA or not at randomization, or had prior difficulty with INR control or did not, there were no large differences in the yearly rate of MBEs between these cohorts. Subjects that had a bleeding episode while previously on VKA had more bleeding than subjects that never had bleeding on warfarin, irrespective of their treatment in RE-LY (DE or warfarin) (Table 7.3.1: 7).

Table 7.3.1: 7 Yearly Event Rate of Major History of Prior VKA use

	DE 110 BID		DE 150 BID		Warfarin	
	# Subjects	Subjects with events (%)	# Subjects	Subjects with events (%)	# Subjects	Subjects with events (%)
VKA use class[1]						
Naive	3005	176 (3.11)	3028	190 (3.33)	3093	205 (3.57)
Experienced	3008	166 (2.66)	3047	209 (3.30)	2929	216 (3.57)
Total duration of VKA use at entry (months)						
0 (never used)	1868	103 (2.93)	1909	112 (3.13)	1972	121 (3.29)
0< and ≤ 1	824	53 (3.43)	817	54 (3.50)	811	64 (4.34)
1< and ≤2	310	20 (3.38)	300	24 (4.16)	307	19 (3.27)
2< and ≤3	186	12 (3.32)	183	16 (4.51)	171	17 (4.99)
3< and ≤6	356	18 (2.54)	338	31 (4.53)	332	23 (3.46)
6< and ≤12	376	12 (1.55)	423	18 (2.10)	434	34 (3.90)
>12	2090	124 (2.83)	2103	144 (3.25)	1992	142 (3.40)
VKA use status at randomization						
Not on VKA	2264	131 (3.08)	2316	146 (3.35)	2344	150 (3.43)
On VKA	3751	211 (2.76)	3760	253 (3.30)	3678	271 (3.65)
Bled on VKA in the past[2]						
No	2993	165 (2.76)	3046	196 (3.22)	2943	201 (3.47)
Yes	395	33 (4.06)	394	31 (3.74)	396	42 (5.16)
Major bleed	45	8 (9.53)	43	5 (5.70)	44	7 (9.05)
Minor bleed	341	25 (3.50)	338	24 (3.35)	335	34 (4.85)
Unknown	8	0 (0.00)	13	2 (7.77)	17	1 (2.87)
Difficulty with INR control in the past[2]						
No	2676	168 (3.12)	2735	176 (3.18)	2638	198 (3.78)
Yes	472	21 (2.17)	476	36 (3.75)	470	33 (3.49)
Unknown	242	9 (2.01)	231	15 (3.37)	232	13 (3.04)

1 Naïve subjects: received ≤2 months of oral anticoagulant during subject's lifetime prior to randomization. Experienced subjects: received >2 months of oral anticoagulant prior to randomization. All 18,113 randomized subjects are included above while 18,040 were treated with one of the three study medications.
2 Bleed and difficulty with INR control only include subjects who used VKA prior to randomization.
In case of recurrent event, the first event was considered.
Yearly event rate (%) = # of subjects with event / subject-years * 100.
Source: NDA Amendment; Table 15.3.2.2.1: 1

The only baseline characteristic with a significant treatment interaction was age. Yearly major bleed rates by baseline characteristics and demographics are presented in Table 7.3.1: 8.

Table 7.3.1: 8 Yearly Major Bleed Rates by Baseline Characteristics – RE-LY Study

	DE 110 BID		DE 150 BID		Warfarin	
	# Subjects	Subjects with events (%)	# Subjects	Subjects with events (%)	# Subjects	Subjects with events (%)
Age (years)						
<80	5044	244 (2.43)	5019	273 (2.73)	5034	331 (3.35)
>=80	971	98 (5.25)	1057	126 (6.24)	988	90 (4.70)
Gender						
Male	3865	225 (2.92)	3840	268 (3.37)	3809	273 (3.63)
Female	2149	117 (2.79)	2236	141 (3.23)	2213	148 (3.46)
Ethnicity						
White	4208	255 (3.02)	4268	297 (3.48)	4203	275 (3.28)
Black	52	2 (2.02)	57	6 (4.99)	67	10 (8.23)
Asian	955	41 (2.25)	965	42 (2.26)	955	68 (3.80)
Other	799	44 (2.88)	786	54 (3.57)	797	68 (4.52)
Hispanic or Latino	421	12 (1.66)	416	17 (2.37)	407	19 (2.75)
Region						
USA, Canada	2166	186 (4.19)	2200	217 (4.81)	2167	209 (4.72)
Central Europe	707	24 (1.74)	706	25 (1.84)	706	24 (1.77)
Western Europe	1544	58 (1.87)	1555	73 (2.33)	1552	80 (2.59)
Latin America	320	11 (2.01)	320	15 (2.72)	316	17 (3.18)
Asia	923	39 (2.22)	933	39 (2.17)	926	66 (3.82)
Other	355	24 (3.60)	362	30 (4.42)	355	25 (3.79)
CrCl (ml/min)						
<30	15	0 (0.00)	32	7 (13.31)	30	0 (0.00)
30>= and <50	1136	120 (5.65)	1156	116 (5.27)	1051	112 (5.68)
50>= and <80	2714	154 (2.87)	2777	182 (3.34)	2806	206 (3.78)
>=80	1899	57 (1.49)	1882	80 (2.09)	1877	94 (2.49)

In case of recurrent events, the first event was considered. All 18,113 randomized subjects are included above, while 18,040 subjects were treated with one of the three study treatments; subjects with missing CRF entries in one or more categories are not included above but this information is available in the Table cited below.
Yearly event rate (%) = # of subjects with event / subject-years * 100.
Source: NDA Amendment, Table 15.3.2.2.2:1; NDA Sequence 0132, Table 2.9

Age

A significant statistical interaction for the risk of major bleeds with treatment was observed for age ≥80 years when comparing both doses of dabigatran to warfarin (NDA Amendment; Table 15.3.2.2.4: 3; p<0.0038). For subjects <80 years of age, DE 110 BID and DE 150 BID had a lower rates of major bleeds compared to warfarin (2.43%, 2.73%, 3.35%, respectively; however, subjects ≥80 years of age treated with DE 150 BID had a 1/3 higher rate of major bleeds compared to warfarin and approximately a 1% higher absolute rate than DE 110 BID (5.25%, 6.24% and 4.70%, respectively; Table 7.3.1: 9). The hazard ratio for DE 150 BID vs warfarin was 1.35 and the lower bound of the CI exceeded 1.0, while the hazard ratio for DE 110 BID vs Warfarin was 1.12, the lower bound of the 85% CI was 0.84 (NDA Sequence 0132, Table 2.10).

Sex

No gender differences in bleeding were observed despite the fact that DE plasma levels in females are generally between 20 and 40% higher than those in males in all populations studied.

Ethnicity

DE 110 BID showed the lowest yearly event rate of major bleeds for whites, blacks and other ethnicity classes compared to DE 150 BID and warfarin. In the relatively few black subjects in RE-LY, the yearly event rate varied widely, with DE 110 BID showing the lowest risk, followed by DE 150 BID and by warfarin (2.02% DE 110 BID, 4.99% DE 150 BID, and 8.23% warfarin; Table 7.3.1: 9).

In Asians, major bleed rates were similar for both DE doses and were significantly less than warfarin (2.25% DE 110 BID, 2.26% DE 150 BID, and 3.80% warfarin; Table 7.3.1: 9).

Hispanic or Latino subjects had the lowest yearly major bleed event rate in those receiving DE 110 BID; the rate for DE 150 BID was slightly lower compared to warfarin (1.36% DE 110 BID, 2.37% DE 150 BID and 2.75% warfarin; Table 7.3.1: 9).

Region

Major bleeding occurred more frequently in USA/Canada than in any other region for all three treatment groups. Major bleed rates were about double compared to the rate in Western Europe for all treatment groups despite a relatively small difference in overall TTR for warfarin treated subjects.

In Asia, there were comparable yearly major bleed rates for both DE groups. Despite the lower levels of INR control seen in Asia, the risk of a major bleed was higher for warfarin than both DE groups (2.22% DE 110 BID, 2.17% DE 150 BID and 3.82% warfarin; Table 7.3.1: 9).

CrCl

Renal impairment is associated with a higher risk of bleeding. In subjects with moderate renal impairment (CrCl 30-50 mL/min), bleeding rates for DE 110 BID and DE 150 BID were comparable to warfarin. For subjects in which CrCl ≥50 mL/min, major bleed rates were lower for both DE 110 BID and DE 150 BID subjects compared to warfarin (Table 7.3.1: 9).

Major bleeding events by age, CrCl, gender, and ASA use (covariate interactions)

A Cox regression model was used to compare the hazard ratio of major bleeds of DE 110 BID vs. warfarin and DE 150 BID vs. warfarin. The model included treatment, age at entry (years), CrCl at entry, gender, ASA use and treatment by covariate interactions. These factors were selected since they do have a potential for an interaction with the treatments in RE-LY.

The hazard ratio of major bleeds (DE vs. warfarin) increases as age increases. Treatment by age interaction is highly significant with or without other covariates in the model. The hazard ratio of DE 150 BID vs. warfarin is higher than DE 110 BID vs. warfarin with increasing age. For the DE 150 dose, the hazard ratio is above 1.0 when age is approximately 80 years, suggesting that a dose adjustment could be considered in this situation. The hazard ratio of major bleed for DE 150 BID vs warfarin is similar for the different CrCl values (Figure 7.3.1: 5; note that dotted line indicated by the CRCl = 80mL/min rate is almost completely overlaid by the solid line for the CRCl = 72.9 mL/min overall mean rate). For DE 110 BID vs. warfarin, subjects with lower baseline CrCl values tend to have a larger hazard ratio (Figure 7.3.1: 6; note dashed line across from the DE 110 mg label).

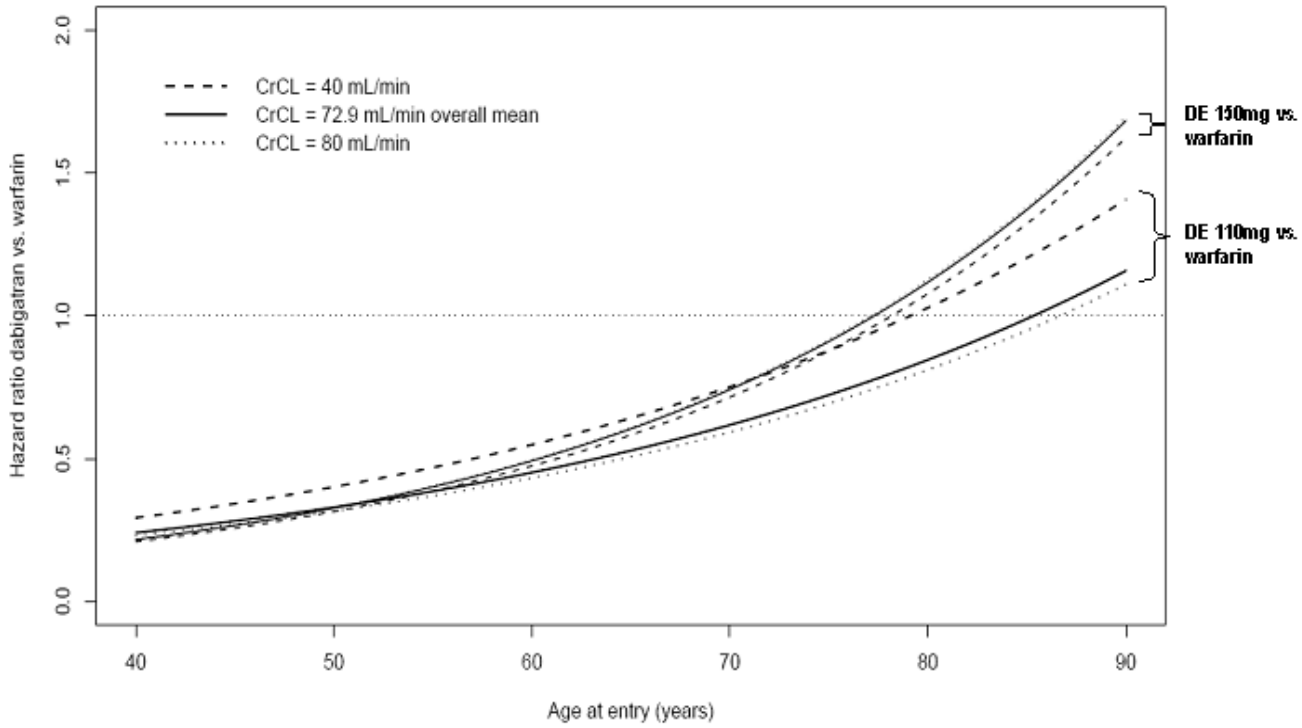


Figure 7.3.1: 5 Hazard Ratio of Major Bleed (DE vs. warfarin) by Continuous age at Selected CrCl Values – RE-LY Study

Source: NDA Sequence 0000, SCS Appendix 7, Table 2.1.1.1.7.3

Baseline CrCl, when analyzed alone, shows a statistically significant interaction with treatment. The hazard ratio of major bleeds appears to decrease as baseline CrCl increases (Figure 7.3.1: 6). However, the interaction is not statistically significant when treatment by age interaction is included in the model. This is more obvious in the DE 150 BID vs. warfarin comparison, for which the treatment by CrCl interaction is negligible (Figure 7.3.1: 6, in right panel and shown as nearly a flat curve). For the DE 110 BID vs. warfarin comparison, the

treatment by CrCl interaction decreased slowly as CrCl increased (Figure 7.3.1: 6, right panel). Statistical significance was not reached for the differences observed.

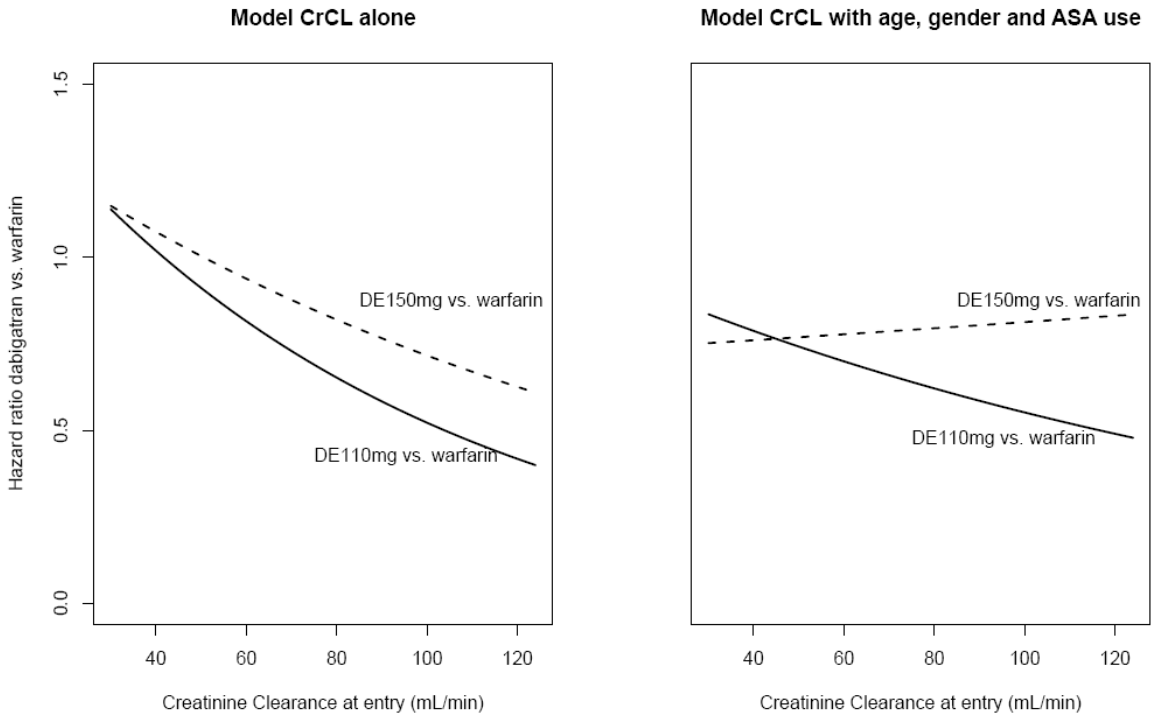


Figure 7.3.1: 6 Hazard Ratio of Major Bleed (DE vs. Warfarin) by Continuous CrCl Values with Parameters Estimated From Two Models: (left figure) from Model with Treatment and Treatment by CrCl Interaction Only; (right figure) from Model with Age, CrCl, gender, ASA use During Study, and All Two-factor Interaction Terms – RE-LY

Source: NDA Sequence 0000, SCS Appendix 7, Table 2.1.1.1.7.2 and Table 2.1.1.1.7.3

ASA use during the study had a strong effect on bleeding risk. Subjects who took ASA at least once during the study almost doubled the risk of a major bleed (hazard ratio = 1.91; $p<0.001$) compared with those who did not use ASA during the study. However, ASA use does not interact with treatment (treatment by ASA interaction was not statistically significant), i.e., there was no difference of the ASA effect across DE doses or warfarin (NDA Amendment; Figure 15.2.3.3: 4 and Figure 15.2.3.3: 5).

Bleeding outcomes by gender were not significantly different. Male subjects had an equal risk of a major bleed compared to female subjects despite the higher plasma levels in female. For DE 110 vs warfarin the hazard ratio was 0.80 for both genders. For DE 150 vs. warfarin the hazard ratio for both genders was ~0.94. (NDA Amendment; Figure 15.3.2.2.2: 1-3).

Bleeding events by stroke risk factors

The frequencies of major bleeds by baseline stroke risk factors and $CHADS_2$ score for RE-LY are shown in Table 7.3.1: 9. Factors which increased the risk for stroke also generally predicted an increased risk of major bleeding. Higher risk for major bleeds was reported in those subjects who were elderly (>75 or >80 years) and those subjects >65 years who also had an additional risk factor of DM or CAD.

Major bleed rates increased with increasing $CHADS_2$ scores for each treatment group. Subjects treated with DE 110 BID had the lowest rate of major bleeds across all $CHADS_2$ scores except for zero, which had few subjects (Table 7.3.1: 9). There was a lower incidence of major bleeds for both DE doses compared to warfarin for almost every $CHADS_2$ score categories. The exception was a higher yearly frequency reported for DE 150 BID for the $CHADS_2$ scores of ≥3 (Table 7.3.1: 9).

Table 7.3.1: 9 Yearly Event Rate of Major Bleeds by Baseline Stroke Risk Factors – RE-LY Study

	DE 110 BID		DE 150 BID		Warfarin	
	# Subjects	Subjects with events (%)	# Subjects	Subjects with events (%)	# Subjects	Subjects with events (%)
Stroke/SEE/TIA						
No	4706	270 (2.91)	4718	285 (3.06)	4735	320 (3.45)
Yes	1308	72 (2.76)	1358	114 (4.20)	1287	101 (4.00)
Left ventricular ejection <=40%						
No	2299	122 (2.72)	2326	151 (3.32)	2337	173 (3.85)
Yes	649	42 (3.43)	652	28 (2.24)	630	37 (3.09)
Symptomatic heart failure (NYHA>=2)						
No	4372	239 (2.73)	4434	301 (3.38)	4397	301 (3.45)
Yes	1641	103 (3.26)	1640	97 (3.10)	1623	120 (3.90)
Age >=75 years						
No	3666	138 (1.89)	3610	153 (2.12)	3599	215 (3.03)
Yes	2349	204 (4.44)	2466	246 (5.12)	2423	206 (4.39)
Age >=65 years and diabetes mellitus						
No	4837	246 (2.57)	4952	282 (2.87)	4827	319 (3.36)
Yes	1177	96 (4.14)	1124	117 (5.34)	1195	102 (4.41)
Age >=65 years and CAD						
No	4553	211 (2.35)	4617	256 (2.82)	4565	279 (3.14)
Yes	1461	131 (4.51)	1459	143 (4.86)	1457	142 (4.87)
Age >=65 years and hypertension						
No	1976	84 (2.13)	2003	76 (1.90)	1943	115 (3.01)
Yes	4038	258 (3.24)	4073	323 (4.02)	4079	306 (3.84)
$CHADS_2$ score						
1	1809	69 (1.88)	1815	81 (2.20)	1707	98 (2.90)
2	2088	121 (2.98)	2136	127 (3.04)	2229	144 (3.31)
≥3	1966	147 (3.80)	1979	188 (4.86)	1931	172 (4.61)

In case of recurrent events, the first event was considered. All 18,113 randomized subjects are included above, while 18,040 subjects were treated with one of the three study medications; subjects with missing CRF entries in one or more categories are not included above but this information is available in the Tables cited below.
Yearly event rate (%) = # of subjects with event / subject-years * 100.
Source: NDA Amendment; Table 15.3.2.2.4: 1 and Table 15.3.2.2.5: 1

The pattern of major bleed rates across treatment groups was generally similar in subjects with each type of AF (NDA Amendment; Table 15.3.2.2.4: 6).

Bleed rates by baseline medication use - major bleeds and any bleeds

For baseline medication categories (antithrombotic, antihypertensive, "any blocker", metabolic/anti-inflammatory, and "any other drug"), both DE doses showed a lower range of frequency of major bleeding 2.87%/year to 3.28%/year for DE 110 BID, a range of 3.40%/year to 3.93%/year for DE 150, and compared to a range of 3.65%/year to 4.05%/year for warfarin (NDA Amendment; Table 15.3.2.2.3: 1).

A higher risk of bleeds was reported with baseline use of the P-gp inhibitor amiodarone; the frequency was 2.96%/year for DE 110 BID, 3.05%/year for DE 150 BID, and 2.80%/year for warfarin (NDA Amendment; Table 15.3.2.2.3:1). This difference did not persist for in trial use of amiodarone (NDA Amendment Table 15.3.2.2.3: 3)

For any bleeding, across the same baseline medication categories evaluated for major bleeds, DE treatment consistently resulted in lower frequencies of "any bleeding" compared to warfarin (NDA Amendment; Table 15.3.2.2.3:2).

Major Bleeding Sensitivity Analyses

The protocol prespecified that a TTR cutoff of 65% be analyzed to demonstrate the effect of DE on bleeding when compared to bleeding in subjects with well-controlled (TTR≥65%) warfarin INR levels. However, in the most recent AF trial with ximelegatran (SPORTIF V), the mean TTR achieved was 68%. Therefore, the same post-hoc analysis was performed for the cutoff of TTR ≥ 68%. (Table 7.3.1: 10).

Subgroups defined only on a post-randomization basis may introduce bias, especially if they are derived for only one treatment group. When selecting subjects with better INR control, there is likely a bias toward including warfarin subjects from centers with better outcomes and those centers may provide a better overall standard of medical care so that interpretation of such analyses must be done with caution. Nominal p values are presented. For the TTR ≥ 68% analysis more than half of all warfarin treated subjects in RE-LY have been removed from this analysis. The absolute differences in yearly major bleed rates between all treatment groups for both TTR cut off values were small. Yearly major bleed rates are presented in the following table (Table 7.3.1: 10).

Table 7.3.1: 10 Yearly Event Rates of Major Bleeding Related to Subject Warfarin Control, Safety Set

	DE 110 BID	DE 150 BID	Warfarin
TTR threshold ≥ 65%			
Subjects	5983	6059	3194
Subject-years	10242	10261	6175
Major Bleeds: N(%)	295 (2.88)	350 (3.41)	179 (2.90)
TTR threshold ≥ 68%			
Subjects	5983	6059	2807
Subject-years	10242	10261	5414
Major bleeds: N(%)	295 (2.88)	350 (3.41)	146 (2.70)

Source: NDA Sequence 0148, Table 2.13.2.2.1 and NDA Amendment Table 15.3.2.1: 13

The analyses also showed that poor INR control was associated with higher event rates with warfarin treatment (annual major bleed rate of 4.28% in the converse set of 2982 subjects with INR TTR < 68%, NDA Sequence 0148, Table 2.13.2.2.3). DE 110 BID had comparable hazard ratios (near 1.00) compared to very well controlled warfarin (either TTR ≥ 65% or TTR ≥ 68%). DE 150 BID compared to well controlled warfarin (TTR ≥ 65%) had a lower bound of the 95% CI that was less than 1.00, however, when compared to well controlled warfarin (TTR ≥ 68%) the lower bound of the confidence interval exceeded 1.00 (Table 7.3.1: 11).

Table 7.3.1: 11 Major Bleeding Related to Subject Warfarin Control via TTR >=65% and TTR >=68% for INR Levels of 2-3, Hazard Ratios and 95% CI

	DE 110 vs Warfarin	**DE 150 vs Warfarin**
TTR>=65%		
Hazard Ratio	0.97	1.15
95% CI	0.80, 1.16	0.96, 1.38
P-value	0.7121	0.1291
TTR>=68%		
Hazard Ratio	1.04	1.24
95% CI	0.85, 1.27	1.02, 1.50
P-value	0.7026	0.0305

The Cox regression model for these analyses included baseline $CHADS_2$ as a covariate.
Source: NDA Sequence 0148, Table 2.13.2.2.2 and NDA Amendment 15.3.2.1: 14

7.4 PHASE III SPAF STUDY RE-LY – OVERALL ADVERSE EVENTS

In the RE-LY trial, outcome events (stroke, MI, deaths, SEE, PE, and TIA) were analyzed as efficacy endpoints while major bleeding was analyzed as the key safety endpoint. Therefore, these outcome events were not routinely separately reported and/or analyzed as AEs unless they were specifically categorized as related to a study medication by an investigator. Although RE-LY had a PROBE design, all investigators and subjects were aware of their assignment to either dabigatran (but not the specific dose) or warfarin. Although all outcome events were independently adjudicated, there may have been biases when it came to investigator reporting of AEs as well as when investigators chose to discontinue study medication.

The AEs reported in RE-LY were not unexpected, considering the enrolled study population. This study was in an elderly population (mean age was 71.5 years at baseline) treated with an anticoagulant, and receiving multiple concomitant medications, and often with concomitant illnesses. In general, the AE profile of DE was comparable to warfarin, with the exception of gastrointestinal AEs, which were reported more frequently with DE treatment. The AEs presented below were from the safety dataset (on treatment) (Table 7.4: 1).

The overall incidence of reported AEs was similar across the 3 treatment groups, although slightly higher in both DE groups (DE 110 BID [78.6%] DE 150 BID [78.3%] warfarin [75.9%]; NDA Amendment, 15.3.2.6:30.) For overall AEs, the SOCs with the highest incidence of AEs for both dabigatran-treated subjects and for warfarin-treated subjects were

GI disorders, infections and infestations, and general disorders (Table 7.4: 1). The most frequently occurring AEs (in MedDRA preferred terms) for DE 110, DE 150, and warfarin-treated subjects, respectively, were dyspnea (8.3%, 8.7%, 9.2%), dizziness (7.6%, 7.6%, 9.2%), and peripheral edema (7.5%, 7.3%, 7.6%). Warfarin-treated subjects had the highest incidence in all of these AEs (Table 7.4: 1).

GI AEs were reported the most frequently for DE 110, DE 150 and warfarin (34.6%, 34.5%, 24.1%, respectively; Table 7.4: 1). The most frequently reported GI AEs (preferred terms) for DE 110, DE 150, and warfarin groups, respectively, were diarrhea (5.9%, 6.1%, and 5.5%) and dyspepsia (6.2%, 5.7%, and 1.4%).

Table 7.4: 1 Adverse Events as Preferred Terms Reported in ≥5.0% of Subjects for Any Treatment – RE-LY Study

Preferred term	DE 110 BID N (%)	DE 150 BID N (%)	Warfarin N (%)
Total with AEs	4703 (78.6)	4746 (78.3)	4551 (75.9)
Dizziness	457 (7.6)	458 (7.6)	554 (9.2)
Dyspnea	498 (8.3)	526 (8.7)	551 (9.2)
Edema peripheral	446 (7.5)	442 (7.3)	453 (7.6)
Fatigue	370 (6.2)	367 (6.1)	353 (5.9)
Cough	320 (5.3)	310 (5.1)	346 (5.8)
Chest pain	287 (4.8)	355 (5.9)	342 (5.7)
Back pain	295 (4.9)	289 (4.8)	331 (5.5)
Arthralgia	248 (4.1)	313 (5.2)	329 (5.5)
Diarrhea	355 (5.9)	367 (6.1)	328 (5.5)
Atrial fibrillation	303 (5.1)	313 (5.2)	327 (5.5)
Nasopharyngitis	315 (5.3)	309 (5.1)	327 (5.5)
Urinary tract infection	242 (4.0)	252 (4.2)	316 (5.3)
Upper respiratory tract infection	266 (4.4)	262 (4.3)	297 (5.0)
Dyspepsia	368 (6.2)	345 (5.7)	83 (1.4)

Percentages were calculated using total number of subjects per treatment as the denominator
MedDRA version 12.0 used for reporting terms.
Source data: NDA Amendment; Table 15.3.2.6: 30

7.4.1 Serious Adverse Events

In the RE-LY study, the total subjects reporting SAEs were similar across all treatment groups: 1263 (21.1%), 1290 (21.3%), and 1357 (22.6%) for DE 110 BID, DE 150 BID, and warfarin, respectively. The SAEs reported the most frequently as preferred terms were: cardiac failure congestive, pneumonia, atrial fibrillation, and cardiac failure (Table 7.4.1: 1).

Table 7.4.1: 1 Serious Adverse Events Reported in ≥0.5% of Subjects for Any Treatment – RE-LY Study

Preferred term	DE 110 BID N (%)	DE 150 BID N (%)	Warfarin N (%)
Number of subjects	5983 (100.0)	6059 (100.0)	5998 (100.0)
Total with SAEs	1263 (21.1)	1290 (21.3)	1357 (22.6)
Atrial fibrillation	64 (1.1)	55 (0.9)	74 (1.2)
Cardiac failure congestive	83 (1.4)	58 (1.0)	73 (1.2)
Cardiac failure	51 (0.9)	62 (1.0)	65 (1.1)
Pneumonia	74 (1.2)	70 (1.2)	62 (1.0)
Chest pain	29 (0.5)	45 (0.7)	46 (0.8)
Dyspnoea	38 (0.6)	43 (0.7)	45 (0.8)
Angina pectoris	29 (0.5)	30 (0.5)	45 (0.8)
Fall	22 (0.4)	29 (0.5)	43 (0.7)
Gastrointestinal hemorrhage	38 (0.6)	55 (0.9)	41 (0.7)
Renal failure acute	42 (0.7)	38 (0.6)	35 (0.6)
Syncope	33 (0.6)	31 (0.5)	34 (0.6)
Anemia	34 (0.6)	47 (0.8)	33 (0.6)
Dehydration	15 (0.3)	22 (0.4)	31 (0.5)
Prostate cancer	25 (0.4)	32 (0.5)	29 (0.5)
Renal failure	15 (0.3)	19 (0.3)	27 (0.5)

Percentages were calculated using total number of subjects per treatment as the denominator.
MedDRA version 12.0 used for reporting terms.
Source data: NDA Amendment; Table 15.3.2.6: 1, Table 15.3.2.6: 2

7.4.2 Adverse Events Leading to Treatment Discontinuation

In the RE-LY study, more DE subjects discontinued study medication due to AEs compared with warfarin subjects. AEs that resulted in discontinuation of treatment mirrored the types of SAEs that were reported most frequently in this study, SOCs of cardiac disorders, infections and infestations, and GI disorders. Table 7.4.2: 1 displays the number of subjects with AEs leading to treatment discontinuation with a ≥0.5% occurrence by MedDRA preferred term.

Discontinuation of treatment due to GI disorders occurred more frequently in both DE groups compared to warfarin, with dyspepsia resulting in discontinuation most often. Other GI events that resulted in a higher proportion of discontinuations in DE subjects include (in the same respective groups) GI hemorrhage, nausea, abdominal pain upper, and diarrhea.

Table 7.4.2: 1 AEs Leading to Treatment Discontinuation Reported in ≥0.5% of Subjects by Preferred Term – RE-LY Study

Preferred term	DE 110 BID N (%)	DE 150 BID N (%)	Warfarin N (%)
Number of subjects	5983 (100.0)	6059 (100.0)	5998 (100.0)
Total with AEs leading to treatment discontinuation	1138 (19.0)	1242 (20.5)	939 (15.6)
Anaemia	43 (0.7)	61 (1.0)	39 (0.7)
Gastrointestinal haemorrhage	39 (0.7)	55 (0.9)	37 (0.6)
Dyspnoea	37 (0.6)	43 (0.7)	33 (0.6)
Fall	14 (0.2)	18 (0.3)	32 (0.5)
INR increased	2 (0.0)	3 (0.0)	29 (0.5)
Hematuria	27 (0.5)	36 (0.6)	26 (0.4)
Cardiac failure congestive	29 (0.5)	20 (0.3)	26 (0.4)
Pneumonia	33 (0.6)	24 (0.4)	22 (0.4)
Chest pain	17 (0.3)	29 (0.5)	21 (0.4)
Nausea	41 (0.7)	42 (0.7)	20 (0.3)
Diarrhoea	36 (0.6)	36 (0.6)	20 (0.3)
Renal failure acute	30 (0.5)	21 (0.3)	18 (0.3)
Rectal haemorrhage	20 (0.3)	29 (0.5)	15 (0.3)
Dizziness	32 (0.5)	27 (0.4)	13 (0.2)
Renal failure	27 (0.5)	26 (0.4)	12 (0.2)
Abdominal pain upper	31 (0.5)	36 (0.6)	7 (0.1)
Dyspepsia	57 (1.0)	57 (0.9)	2 (0.0)

Percentages were calculated using total number of subjects per treatment as the denominator.
MedDRA Version 12.0
Source data: NDA Amendment; Table 15.3.2.6: 4

7.4.3 Deaths

In RE-LY, all 1371 deaths were adjudicated for cause of death. Because outcome events, including death, were captured as adjudicated efficacy measures (Section 6.4.3.7), some exemptions from expedited safety reporting were in place during the conduct of the trial. The incidence and yearly rate for all-cause death was 446 (3.75%), 438 (3.64%) and 487 (4.13%) in the DE 110 BID, DE 150 BID and the warfarin groups, respectively (Table 6.4.3.7: 1).

Deaths were only reported as SAEs when they were considered related to study treatment by the investigator. Investigators reported adverse events for 365 subjects that had a fatal outcome. The incidence of fatal AEs was 2.0%, 1.8%, and 2.2% for DE 110 BID, DE 150 BID, and warfarin, respectively. The SOCs with the highest percentage of subjects with AEs leading to death were neoplasms, cardiac disorders, and infections and infestations; the incidence of AEs within each SOC was similar across treatment groups (NDA Amendment; Table 15.3.2.6.2: 5). According to internal assessments by the sponsor, three warfarin subjects died of hepatic failure compared to one DE 110 BID subject and no DE 150 BID subjects.

7.4.4 Hepatic Function Monitoring and Hepatic Safety

In recent years, the detection of signals of severe drug induced liver injury (DILI) has led to the denial of drug approval, marketing withdrawal or cessation of development for several

promising drugs. In order to facilitate the detection of meaningful signals of liver injury in premarketing development, the FDA recently published a guidance document (P09-12413). The guidance addresses relevant biochemical signals indicative of liver injury. Serum transaminase elevations (ALT and AST) in particular are considered a highly sensitive signal for the potential of a drug to cause DILI. A more specific signal of DILI potential is a higher rate of marked peak transaminase elevations, ie, > 10x upper limit of normal (ULN). The best predictor of severe DILI, however, is the finding of transaminase elevations >3x ULN with total bilirubin >2x ULN in the absence of indictors of cholestasis. This is referred to as Hy's Law in recognition of the contributions of the late Dr. Hyrum Zimmerman to the field of DILI (R10-1341). The guidance document emphasizes the importance of Hy's Law and its key elements: "The single clearest (most specific) predictor found to date of a drug's potential for severe hepatotoxicity, however, is the occurrence of a small number of cases of hepatocellular injury (aminotransferase elevation) accompanied by increased serum total bilirubin (TBL), not explained by any other cause, such as viral hepatitis or exposure to other hepatotoxins, and without evidence of cholestasis, together with an increased incidence of aminotransferase (AT) elevations in the overall trial population compared to control."

This section addresses the incidence rates of transaminase elevations of various magnitudes, eg, >3x, 5x, 10x, 20x ULN, transaminase elevations with total bilirubin elevations, bilirubin elevations alone, hepatic AEs, SAEs, cases of liver failure and liver-related deaths in dabigatran-and comparator-treated cohorts. The results from two different frequencies of liver test monitoring in RE-LY (more intense vs. less intense) in detecting signals of liver injury is also included.

As a result of the identification in 2004 of severe hepatotoxicity associated with the use of another direct thrombin inhibitor, ximelagatran, increased surveillance of laboratory liver tests (LFT) was added to all ongoing and planned DE trials.

The treatment duration in dabigatran non-SPAF trials has generally been limited to 6 months or less. In these trials the rates of ALT/AST >3x, >5x and >10x ULN have been low and similar across a range of dabigatran doses (50 mg BID - 225 mg BID and 300 mg QD). The rates seen with dabigatran have been comparable to the control treatment groups with either enoxaparin or warfarin. Most importantly there have been no post-treatment signals observed for as long as several months after completion of study drug treatment. As a result, this briefing document will focus on the hepatic safety data from Phase II and III trials in subjects with atrial fibrillation. The primary focus will be on the RE-LY trial (Study 1160.26, U09-3249-01) in which 18,113 subjects were followed for up to 3 years. This indication constitutes the largest exposure dataset for hepatic safety of dabigatran (Table 7.4.4: 1).

Table 7.4.4: 1 Exposure in Atrial Fibrillation Trials

	DE 50 QD	DE 50 BID	DE 150 QD	DE 110 BID	DE 150 BID	DE 300 QD	DE 300 BID	Warfarin
Phase II Trials								
Subjects Treated (N)	1	105	102	46	414	90	161	132
1160.20, 1160.42, 1160.49 (total subject-yrs)	0.1	23.7	60.4	9.7	854.5	242.0	82.5	29.3
Phase III Trial								
Subjects Treated (N)				5983	6059			5998
1160.26 (RE-LY) (total subject-yrs)				10242.1	10261.2			10659.3

Source: SPAF NDA Sequence 0000, SCS, Table 1.2.1.1.1: 1 and NDA Amendment, Table 15.3.1: 1

Phase II Trials in Subjects with Atrial Fibrillation

Three Phase II trials (1160.20 [PETRO] U06-1615-02; 1160.42 [PETRO-EX] U06-3419-01; and 1160.49 U07-3126) have been conducted in subjects with atrial fibrillation. Study 1160.20 (PETRO) compared the safety and efficacy of nine different doses of dabigatran (ranging from 50 mg BID to 300 mg BID with and without aspirin) versus warfarin after 12 weeks of treatment. A total of 502 subjects were randomized; with 20 to 99 subjects being assigned to each of the treatment groups. LFT testing was done at Screening, Weeks 1, 4, 8, 12 and if required at Week 13. Three dabigatran subjects (0.7%) had an ALT/AST value >3x ULN versus none for warfarin. For one of these subjects (Subject No. 1056) the ALT/AST elevation was >5x ULN with an accompanying increase in Alkaline Phosphatase (AP). The subject was diagnosed with cholecystolithiasis. The values returned to normal after discontinuation of study drug. There were no potential Hy's Law cases in this study. All of the subjects who received dabigatran (except the DE 50mg QD dose group) and completed 1160.20 could roll over into the open-label extension Study 1160.42 (PETRO-EX). Subjects in this study were assigned to one of four-dose groups of dabigatran (150mg QD, 150mg BID, 300mg QD, 300mg BID) and were treated for up to 5 years. A total of 361 subjects were enrolled. LFT testing was performed monthly for the first 6 months and then every 3 months until end of year 4 and then every 6 months until the end of the study. A total of 19 (1.5%) subjects experienced an ALT/AST value >3x ULN at some point in the study; 11 of these subjects had an ALT/AST value >5x ULN with 2 of the 11 had an ALT/AST value >10x ULN. The first subject (Subject No. 1005) had the LFT elevation 3 years and 8 months after starting dabigatran treatment and this was accompanied with urinary retention. The LFT values declined after discontinuation of dabigatran. The second subject (Subject No. 1636) had an ALT/AST >10x ULN 11 weeks into the PETRO study and was rolled over into PETRO-EX. The ALT/AST elevation was accompanied with an elevation in AP and diagnosed as chronic calculous cholecystitis with gallstone pancreatitis. The LFT elevations improved following laparoscopic cholecystectomy. The breakdown of subjects experiencing an ALT/AST value >3x ULN by dose was as follows: 150 mg BID = 14 (1.7%) subjects; 300 mg QD = 4 (1.7%) subjects; and 300 mg BID = 2 (2.4%) subjects. One subject experienced an ALT/AST increase in two different dabigatran dose groups and is counted twice. Three subjects (Subject Nos. 1018, 1059, 1528) with ALT/AST >3x ULN with total bilirubin >2x ULN within 30 days were identified. Two subjects were treated with DE 150

BID and one with dabigatran 300 QD. In all three cases, alternate causes for LFT elevations were reported (worsening of gall stones, cholestasis, and cholelithiasis).

Finally, Study 1160.49 (U07-3126) assessed the pharmacodynamics and safety of two dabigatran doses (110mg BID and 300mg BID) versus warfarin after 12 weeks of treatment in Japanese subjects with atrial fibrillation. A total of 150 subjects were randomized; with 53 to 62 subjects being assigned to each of the treatment groups. LFT testing was done at Screening, Randomization and at Weeks 4, 8, 12 and if required at Week 13. No subjects had an ALT/AST value >3x ULN or met the criteria to be a potential Hy's Law case.

Phase III trial in Subjects with Atrial Fibrillation

In the RE-LY trial, surveillance initially included monthly monitoring of LFTs during the first 12 months of treatment. In addition, a hepatic monitoring algorithm was implemented, which mandated weekly monitoring of subjects with emergent ALT, AST or Alkaline Phosphatase (AP) elevations of >2x ULN, with additional clinical and laboratory evaluations for liver disease, until all values fell below 2x ULN. Protocol specified diagnostic evaluations were required for subjects with ALT/AST >3x ULN or total bilirubin >2x ULN. Investigators were instructed to discontinue study medication for subjects with confirmed ALT/AST elevations of >5x ULN, or ALT/AST elevations of >3x ULN associated with total bilirubin elevations of >2x ULN within 30 days, or for any signs or symptoms of hepatic injury (e.g., jaundice, fatigue, nausea, vomiting, loss of appetite, new onset of itching, upper abdominal pain, especially right upper quadrant abdominal pain).

Overall safety, including hepatic safety, for the RE-LY study was periodically reviewed by an external, independent data safety monitoring board (DSMB; which included an academic Hepatologist member). Based on a protocol-specified DSMB examination of unblinded liver function test (LFT) data after 6,000 subjects had been randomized and followed for at least 6 months, the RE-LY DSMB recommended that monthly monitoring was no longer required. Subsequently, after FDA Division of Cardio-Renal Drug Products concurrence was obtained, and hepatic safety laboratory monitoring was reduced to months 1, 3, 6, 9, 12 during first year of treatment and every 4 months thereafter.

7.4.4.1 Laboratory Serum Transaminase and Bilirubin Elevations in RE-LY

The Phase III RE-LY study included 18,113 subjects with a planned treatment period of 1 to 3 years. The median exposure to dabigatran and warfarin in RE-LY was 1.78 – 1.88 years (NDA Amendment, Table 15.3.1: 1) with more than 80% of subjects treated with dabigatran or warfarin for 1-3 years.

Summary of laboratory serum transaminase and bilirubin elevations in this section used the LFT safety set. This data set included all randomized subjects who took at least one dose of study medication. The analyses using this data set included all serum ALT/AST and bilirubin elevations that occurred between the date of first study medication to the date of study termination.

Table 7.4.4.1: 1 summarizes serum ALT/AST and bilirubin elevations in RE-LY. The incidence of transaminase elevations was low and similar across treatment groups. The frequency of ALT/AST >3x ULN was 2.0%, 1.7% and 2.1% for DE 110 BID, DE 150 BID, and warfarin subjects, respectively. The frequency of ALT/AST >5x ULN was low (0.6 – 0.8%) and similar across treatment groups. Examination of elevations >10x ULN and >20x ULN, which may provide early signals of severe DILI, show similar low rates (0.0% - 0.3%) for dabigatran and warfarin. Elevations of bilirubin >2x ULN in the atrial fibrillation population were mostly isolated and showed similar frequencies in each treatment group.

Table 7.4.4.1: 1 ALT/AST and Bilirubin Elevations – RE-LY Study (LFT safety set)

LFT elevation	DE 110 BID N (%)	DE 150 BID N (%)	Warfarin N (%)
Total treated	5983 (100.0)	6059 (100.0)	5998 (100.0)
ALT/AST >3x ULN	118 (2.0)	106 (1.7)	125 (2.1)
ALT/AST >5x ULN	36 (0.6)	45 (0.7)	50 (0.8)
ALT/AST >10x ULN	9 (0.2)	16 (0.3)	20 (0.3)
ALT/AST >20x ULN	1 (0.0)	3 (0.1)	9 (0.2)
Bilirubin >2x ULN	114 (1.9)	106 (1.7)	116 (1.9)
ALT/AST >3x ULN + Bilirubin >2x ULN within 30 days	11 (0.2)	14 (0.2)	21 (0.4)

LFT elevations occurring between the first dose of study medication and study termination, regardless of whether subjects were on or off study medication or if the elevation was present at baseline.
Source: NDA Amendment Table 15.3.3.1: 1 and NDA Sequence 0149, Table 2.9.4: 1

The cumulative probability of subjects having laboratory elevations of ALT/AST >3X ULN, and >10X ULN are shown in Figures 7.4.4.1: 1 and 7.4.4.1: 2, respectively. This demonstrates that dabigatran 110 mg and 150 mg treatments have the same or a lower cumulative risk than warfarin. In contrast to ximelagatran, which is also a direct thrombin inhibitor, the risk with dabigatran is similar to warfarin without any excess of events or clustering of early or late events.

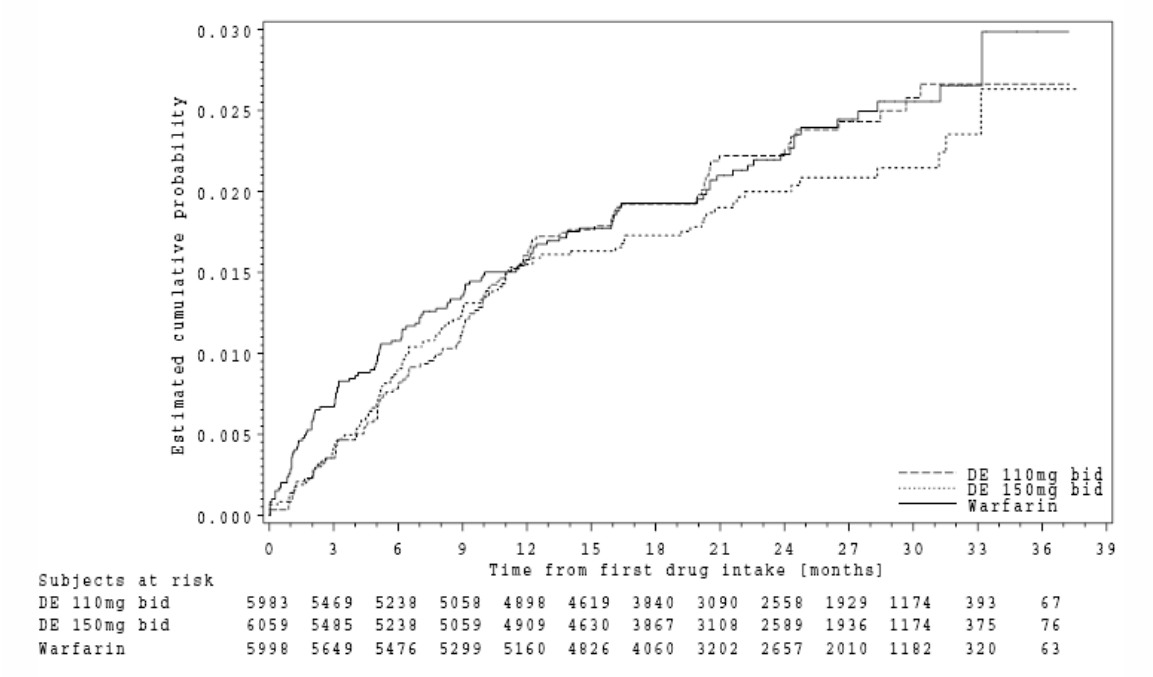


Figure 7.4.4.1: 1 Kaplan-Meier estimates for first occurrence of ALT/AST >3x ULN – RE-LY Study (LFT safety set)

Source: NDA Amendment Figure 15.3.3.1: 3

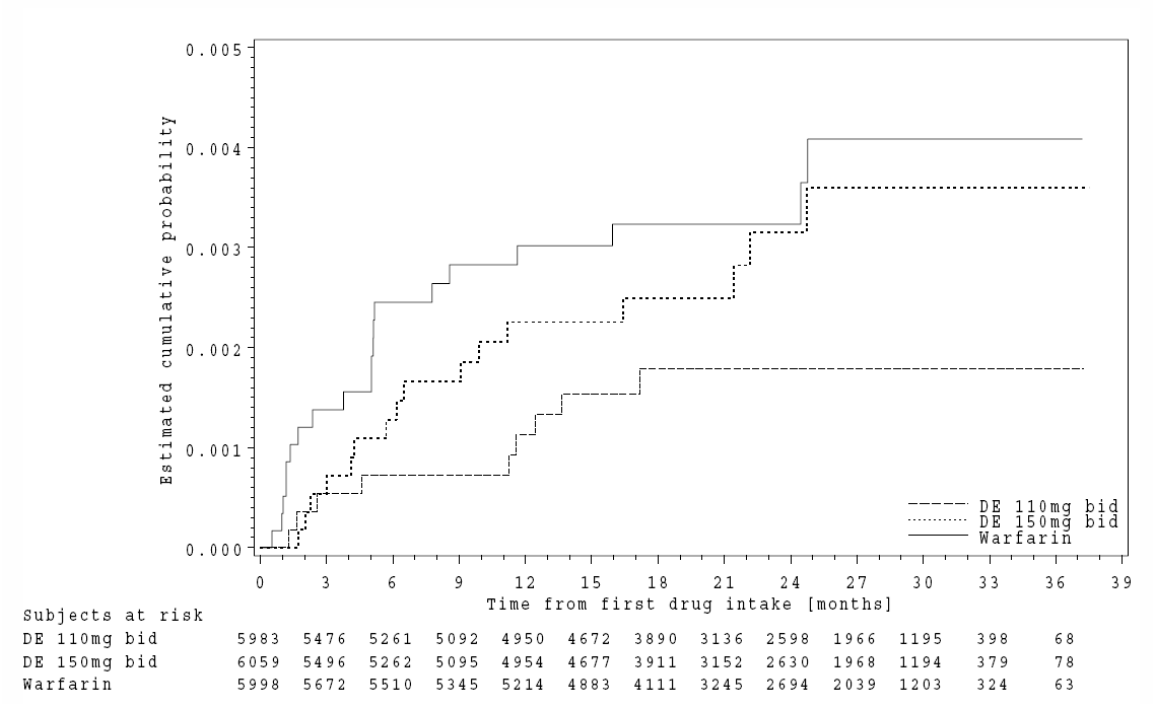


Figure 7.4.4.1: 2 Kaplan-Meier estimates for ALT/AST >10x ULN – RE-LY Study (LFT safety set)

Source: NDA Sequence 0149, Figure 2.9.4: 2

7.4.4.2 Potential Hy's Law signal detection in RE-LY

Laboratory results that fulfil the definition of a potential Hy's Law case (ALT/AST >3x ULN associated with a total bilirubin >2x ULN) are described in this section. The definition used here for screening potential Hy's Law cases is more conservative than the FDA Guidance on DILI (P09-12413) because it did not exclude events associated with significant cholestasis, i.e., associated with a >2x elevation in alkaline phosphatase.

A useful tool in assessing DILI is a scatter plot of maximal ALT/AST value at any during the trial period versus maximal bilirubin at any time during the trial period. The scatter plot is divided into quadrants based on the laboratory value thresholds defining Hy's Law which provides a rapid, visual perspective of those cases where liver injury may have become sufficiently severe as to cause loss of hepatic function. The timeframe of maximal ALT/AST values and maximal total bilirubin values may not be contemporaneous in such a plot, e.g., a maximal ALT/AST elevation may have occurred months earlier or later than a maximal total bilirubin elevation; therefore clinical review is required to provide a complete assessment.

Figure 7.4.4.2: 1 is a log–log plot of all subjects' maximal ALT/AST and maximal bilirubin values. The right upper quadrant in this figure displays potential Hy's Law cases with ALT/AST >3x ULN with bilirubin >2x ULN occurring within 30 days. Many of the RE-LY cases found in the right upper quadrant include cholestatic events with concurrent elevations of serum alkaline phosphatase such as cholangitis, choledocholithiasis, acute cholecystitis or obstruction due to neoplasm. Isolated cases of bilirubin elevations are seen in the RE-LY population as may be found in subjects with Gilbert's UGT1A1 polymorphism (left upper quadrant) or in subjects with congestive heart failure (R10-1324).

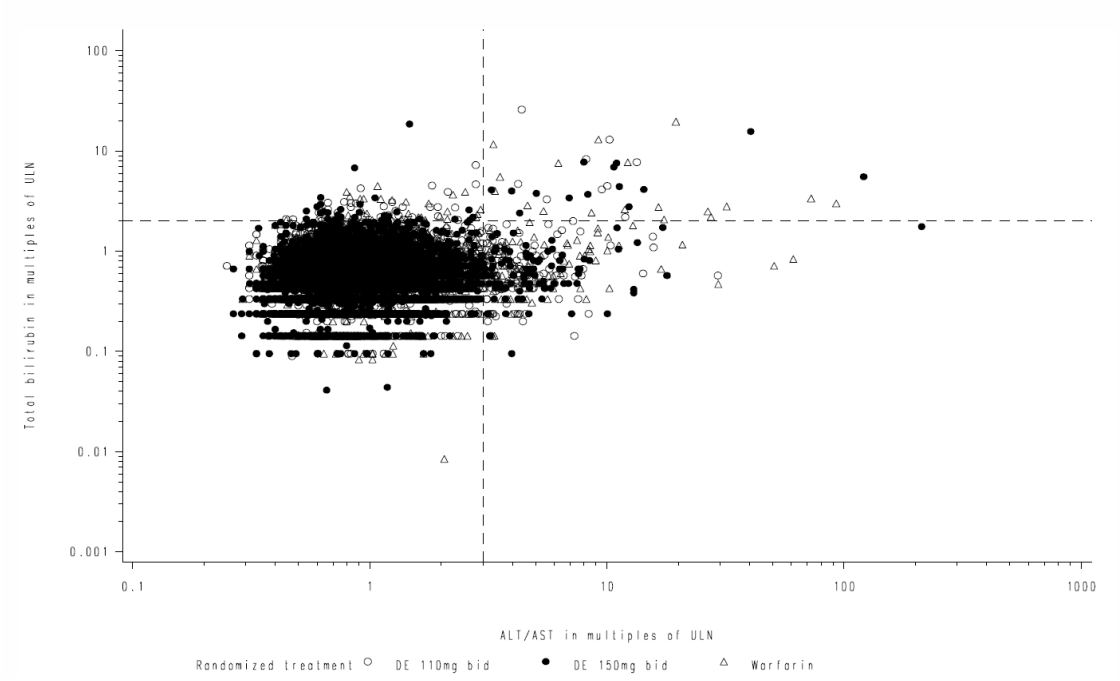


Figure 7.4.4.2: 1 Scatter plot of maximal ALT/AST with maximal bilirubin within 30 days – RE-LY Study (LFT safety set)

Source: NDA Sequence 0149, Figure 2.9.6: 1

As shown in Table 7.4.4.2: 1, the frequency of potential Hy's Law cases was approximately double in warfarin treated subjects as compared to both DE dose groups. There were 46 potential Hy's Law cases with 11, 14 and 21 in DE 110 BID, DE 150 BID and warfarin groups, respectively. The majority of events occurred on study drug with only a few cases occurring more than 30 days from time of study drug discontinuation.

Table 7.4.4.2: 1 Number of subjects with potential Hy's Law cases by time of occurrence relative to discontinuation of study medication – RE-LY Study (LFT safety set)

	DE 110 BID N (%)	DE 150 BID N (%)	Warfarin N (%)
Total Treated	5983 (100.0)	6059 (100.0)	5998 (100.0)
Total number of subjects with potential Hy's Law cases	11 (0.2)	14 (0.2)	21 (0.4)
Occurrence on study drug	8 (0.1)	13 (0.2)	21 (0.4)
On study drug	8 (0.1)	8 (0.1)	15 (0.3)
Within 30 days off study drug*	0 (0.0)	5 (0.1)	5 (0.1)
< = 3 days	0 (0.0)	3 (0.0)	3 (0.1)
3 < and < = 6 days	0 (0.0)	2 (0.0)	2 (0.0)
Occurrence >30 days off study drug*	3 (0.1)	1 (0.0)	1 (0.0)
30 < and <= 60 days	3 (0.1)	0 (0.0)	0 (0.0)
60 < and <= 90 days	0 (0.0)	0 (0.0)	0 (0.0)
> 90 days	0 (0.0)	1 (0.0)	1 (0.0)

* Onset time measured from the date of drug discontinuation (permanent or temporary).
Source: NDA Amendment Table 15.3.3.1: 2

Figure 7.4.4.2: 2 illustrates the cumulative probability of ALT/AST elevations >3x ULN with total bilirubin of >2x ULN within 30 days (potential Hy's Law cases). Both DE dose groups are associated with a lower numerical risk, though not statistically significant, compared with warfarin.

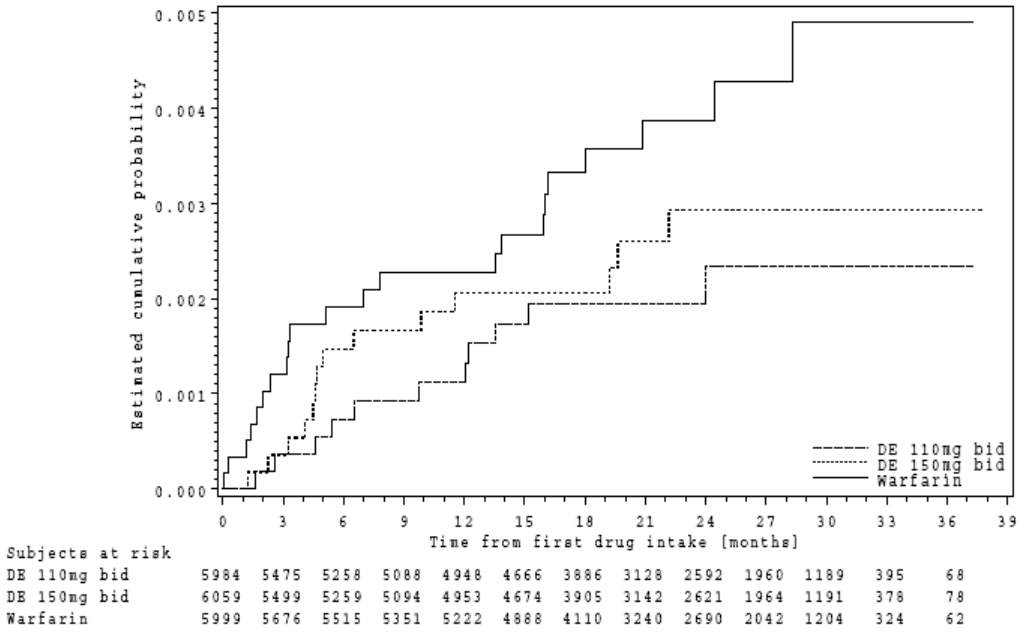


Figure 7.4.4.2: 2 Kaplan-Meier Estimate of the First Occurrence of Abnormal LFT (ALT/AST >3x ULN with Total Bilirubin >2x ULN within 30 days) – RE-LY Study

Source: NDA Amendment, Figure 15.3.3.1: 1

The laboratory detection of potential Hy's Law cases was further assessed with clinical data in order to appreciate whether each event was the result of study drug DILI, alternate hepatotoxic concomitant medication, and disease affecting the hepatobiliary system or another underlying pathophysiologic process, e.g., sepsis or neoplasm.

After completion of the RE-LY trial, the 46 potential Hy's Law cases were evaluated for causality in a blinded manner by an independent external DILI expert, Dr. James Lewis (Director of Hepatology, Georgetown University Medical Center, Washington, DC). All subject data and source documents were compiled into detailed case narratives and then were blinded by redacting information that could lead to identification of the treatment assignment for each subject. The reviewer used a structured expert opinion process similar to that recently described by the NIH-sponsored DILI Network (R10-1325) to assign a level of probability that the study drug was responsible for the hepatic finding. The probability levels are: a) highly probable, b) probable, c) possible, d) unlikely or e) excluded/not related.

The external DILI expert blinded assessment identified 3 cases that were graded as "possibly" related: Subject No. 0059018, DE 150; Subject No. 1292005, warfarin and Subject No. 1678011, warfarin. The remaining 43 cases were evaluated as either "unlikely or excluded/not related" and attributed to underlying disorders, e.g., cholelithiasis, congestive heart failure, cardiogenic shock, septic shock, pancreatic cancer, etc. The expert reviewer's summaries of the 3 possibly related Hy's Law cases are described below.

Subject No. 0059018 (DE 150 bid): An 80 year old Black female with atrial fibrillation, coronary artery disease, mitral regurgitation and hypertension. The subject discontinued study drug on day 36 after a major GI bleed requiring transfusions. Two days later the following LFTs were noted: ALT 6.9x ULN, AST 4.3x ULN with bilirubin >2x ULN (mostly indirect) with normal alkaline phosphatase. A positive dechallenge occurred when stopping the study drug. Ultrasound showed gallstones and a common bile duct (CBD) of 9 mm diameter without changes of acute cholecystitis. Magnetic resonance cholangiopancreatography (MRCP) showed possible sludge or small stones. A repeat ultrasound 6 weeks later still showed gallstones without any dilation of the CBD. ALT and AST values returned to normal 6 weeks later and bilirubin was approaching its normal limits. Possible alternative causes include gallstones, use of a statin, macrolide antibiotics and/ or parenteral anticoagulants.

Subject No. 1292005 (warfarin): A 47 year old Asian male with atrial fibrillation, coronary artery disease and heart failure was noted on day 59 to have ALT 2xULN, AST 3x ULN with bilirubin 2.3x ULN and normal alkaline phosphatase. He had started taking herbs for erectile dysfunction a few days before. LFTs resolved upon discontinuation of these herbs. The elevation of causality was confounded by the use of the herbal therapy. This could represent a form of drug tolerance as the ALTs declined while the subject remained on warfarin.

Subject No. 1678011 (warfarin): A 78 year old Asian male with atrial fibrillation, stroke/thromboembolic disease and hypertension was noted to have on Day 97 ALT 3.8x ULN, AST 4.2x ULN with bilirubin elevation 2.1x ULN (30 days later) with normal alkaline phosphatase 1.5x ULN. He was diagnosed with hepatitis B on Day 97. Warfarin was temporarily stopped on Day 104, restarted on Day 135 and permanently discontinued 3 days later. He was being treated with lamivudine when hepatitis B surface antigen (HBsAg) and elevated ATs were noted; no viral load was assessed; ATs did not normalize. Warfarin was temporarily restarted but there was no further increase in ALT observed.

Impact of LFT Monitoring in RE-LY – More Intense versus Less Intense

The RE-LY trial offered a unique opportunity to retrospectively evaluate the effectiveness of more intense (monthly) LFT monitoring during the first year of therapy compared to a less intense LFT monitoring frequency.

Based on a protocol-specified DSMB examination of unblinded LFT data after 6,000 subjects had been randomized and followed for at least 6 months, the RE-LY DSMB indicated that monthly monitoring during the first year was no longer required. This recommendation had concurrence by the FDA Division of Cardio-Renal Drug Products. Subsequently, LFT monitoring was reduced to months 1, 3, 6, 9, 12 during first year of treatment and every 4 months thereafter.

Table 7.4.4.2: 2 shows the comparison of those who received monthly more intensive LFT monitoring (i.e., first 6000 pts) for the first year and every 4 months thereafter to those subjects who enrolled later and were followed with less frequent (i.e., less intensive) LFT monitoring. The table shows that the exposure adjusted yearly event rate of ALT/AST >3x, >5x, >10x ULN and of potential Hy's cases are remarkably similar between the two LFT monitoring cohorts.

Table 7.4.4.2: 2 More Intense versus Less Intense Liver Function Test Monitoring – RE-LY Study (safety set)

	DE 110 mg bid		DE 150 mg bid		Warfarin	
	First 6000 pts	Excluding First 6000 pts	First 6000 pts	Excluding First 6000 pts	First 6000 pts	Excluding First 6000 pts
	N (% events per subject-yr)	N (% events per subject-yr)	N (% events per subject-yr)	N (% events per subject-yr)	N (% events per subject-yr)	N (% events per subject-yr)
Subjects Treated	1986	3997	1996	4063	1993	4005
Subject years	4956	6861	5002	6975	4918	6815
ALT/AST >3x ULN	49 (0.99)	69 (1.01)	43 (0.86)	63 (0.90)	46 (0.94)	79 (1.16)
ALT/AST >5x ULN	12 (0.24)	24 (0.35)	15 (0.30)	30 (0.43)	23 (0.47)	27 (0.40)
ALT/AST >10x ULN	3 (0.06)	6 (0.09)	3 (0.06)	13 (0.19)	10 (0.20)	10 (0.15)
Bilirubin > 2x ULN	47 (0.95)	67 (0.98)	41 (0.82)	65 (0.93)	47 (0.96)	69 (1.01)
ALT/AST >3x ULN + Bilirubin >2x ULN	5 (0.10)	6 (0.09)	5 (0.10)	9 (0.13)	11 (0.22)	10 (0.15)

Source: NDA Sequence 0155, Tables 2.9.1: 2 and 2.9.1: 3

A similar analysis comparing hepatobiliary SAEs between the two LFT monitoring cohorts found no differences in yearly event rates between treatment groups within each cohort or across the two cohorts.

These analyses re-affirm the DSMB decision which was subsequently accepted by FDA that less intense LFT monitoring as would be done in any Phase III cardiovascular development program was appropriate for the atrial fibrillation population studied in RE-LY. These data also demonstrate that more intense LFT monitoring did not identify an incremental number of subjects with potential hepatic signals of possibly liver injury. No relevant differences were observed between dabigatran and warfarin when comparing the more intense and less intense LFT monitoring cohorts. Overall, the hepatic profile of dabigatran is comparable to warfarin a drug recognized as having rare, if any, hepatotoxicity, and which does not require routine LFT monitoring (R10-1340).

7.4.4.3 Hepatobiliary Adverse Events in RE-LY

In RE-LY, the incidence of hepatobiliary adverse events (AE) was similar between subjects treated with DE 110, DE 150 and warfarin. The incidence of serious AEs and AEs resulting in discontinuation was also similar between groups as shown in Table 7.4.4.3: 1.

Table 7.4.4.3: 1 Overview of Hepatobiliary Adverse Events – RE-LY Study (safety set)

	DE 110 BID N (%)	DE 150 BID N (%)	Warfarin N (%)
Number of subjects	5983 (100.0)	6059 (100.0)	5998 (100.0)
Subjects with any AE	4703 (78.6)	4746 (78.3)	4551 (75.9)
Subjects with hepatobiliary AEs	121 (2.0)	123 (2.0)	132 (2.2)
Subjects with hepatobiliary AEs leading to discontinuation of trial drug	22 (0.4)	24 (0.4)	25 (0.4)
Subjects with hepatobiliary SAEs	25 (0.4)	28 (0.5)	25 (0.4)
Subjects with hepatobiliary AEs leading to death	4 (0.1)	1 (0.0)	5 (0.1)
Hepatic failure	1 (0.0)	0 (0.0)	3 (0.1)
Hepatic cirrhosis	1 (0.0)	0 (0.0)	0 (0.0)
Hepatitis	1 (0.0)	0 (0.0)	0 (0.0)
Ischemic hepatitis	0 (0.0)	0 (0.0)	1 (0.0)
Jaundice	0 (0.0)	1 (0.0)	0 (0.0)
Cholecystitis	1 (0.0)	0 (0.0)	1 (0.0)

A subject may be counted in more than one serious criterion.
Source: NDA Amendment Tables 15.3.2.6: 1, 2, 4 and 5

Four subjects experienced hepatic failure with fatal outcomes in the RE-LY study. Of these, one was treated with DE 110 BID (Subject No. 545006) and the three remaining received warfarin (Subjects Nos. 0133011, 0388040, 0113002). Additionally, one subject treated with DE 110 died from acute hepatitis attributed to urinary tract infection treated with levaquin (Subject No. 0704002). A brief description of each of the four cases of hepatic failure and hepatitis that resulted in death is provided below.

Subject No. 545006 (DE 110 BID): A 66 year old male was randomized to dabigatran 110 mg twice daily and started his medication on 04Nov2006. Medical history was notable for alcoholism, hypertension, diabetes mellitus with peripheral polyneuropathy (PNP), ataxia cerebellar and cirrhosis of the liver. Concomitant medications included: insulin, metformin, bisoprolol, ramipril and Pantoloc. On 11Jul2007, the subject experienced pneumonia followed by acute renal failure and septic shock. On 26Jul2007, he experienced liver failure followed by respiratory failure. On 02Aug2007, he was diagnosed with pancreatic cancer with metastases to peritoneum, pleura and multiple metastasis of liver. The subject received treatment for acute renal failure, septic shock, pneumonia and respiratory failure which included continuous hemofiltration, antibiotic therapy, and artificial respiration. Dabigatran was permanently stopped around 21Jul2007. The events had a fatal outcome.

Subject No. 0133011 (warfarin): A 70 year old female was randomized to warfarin and started medication on 18Oct2006. Medical history was notable for heart failure and hypertension. Concomitant medications included: aspirin, beta blocker, calcium channel blocker and diuretics. The subject was hospitalized on 16Jun2008 with edema, tricuspid value regurgitation, and coronary artery disease. Subject was diagnosed with right heart failure due to malposition of pacemaker leads. Study medication was discontinued on 22Oct2008. She underwent open heart surgery on 23Oct2008 with tricuspid valve replacement, CABG, partial maze revision of pacemaker pocket, and removal of right atrial appendage. The subject

expired on 29Oct2008 (7 days after discontinuing warfarin) from complications of tricuspid value regurgitation leading to cardiac cirrhosis and ultimately liver failure.

Subject No. 0388040 (warfarin): A 78 year old male was randomized to warfarin and started medication on 26Mar 2007. Medical history was non-significant at time of entry. Concomitant medications included: digoxin and Flomax. The subject died 15Oct2007 on study treatment (204 days) due to non-vascular alcoholism/liver failure.

Subject No. 0113002 (warfarin): A 58 year old male was randomized to warfarin and started medication on 4Jan2007. Medical history was notable for coronary artery disease, heart failure, diabetes mellitus, hypertension, aortic and mitral valve regurgitation, decreased LV ejection fraction (25%). Concomitant medications included: ARB, vancomycin piperacillin/tazobactam, beta blocker, digoxin, diuretic, insulin, oral hypoglycemic, proton pump inhibitors, statin. On 15 Aug 2007, he presented to the hospital with foul-smelling discharge from bilateral lower extremity lesions and a two day history of lethargy. His BUN/Creatinine was 100/3.4, INR > 14 and elevated transaminases. Warfarin was permanently discontinued. On 21 Aug 2007, the subject met the definition of potential Hy's Law with AST 125 U/L (3x ULN) and bilirubin 5.7 mg/dL (4.8x ULN). Abdominal ultrasound 21 Aug 2007 indicated he had chronic parenchymal liver disease with mild hepatomegaly. The subject deteriorated with respiratory failure requiring artificial respiration, cardiogenic shock, and non-vascular, multi-organ system failure. The events resulted in fatal outcome on 22Aug2007 (10 days after last dose of warfarin).

Subject No. 0704002 (DE 110 BID): A 74 year old male was randomized to DE 110 BID and started medication on 22Jun2006. On 05Oct2008, the subject experienced asthenia, pneumonia, and renal insufficiency and low albumin requiring hospitalization. On 06Oct2008, the subject was started on Levaquin (levofloxacin). He developed an acute toxic hepatitis on 09Oct2008 leading to fatal outcome on 13Oct2008. Dabigatran was stopped on 08Oct2008. Based on the temporal relationship and known hepatotoxic effect, the Investigator assessed event to Levaquin.

Hepatobiliary adverse events leading to study drug discontinuation are summarized in Table 7.4.4.3: 2. The number of subjects reporting each preferred term was low and the numbers were balanced when comparing the dabigatran groups to the warfarin group.

Table 7.4.4.3: 2 Hepatobiliary disorders leading to treatment discontinuation – RE-LY Study (safety set)

System organ class/ Preferred term	DE 110 BID N (%)	DE 150 BID N (%)	Warfarin N (%)
Hepatobiliary disorders	22 (0.4)	24 (0.4)	25 (0.4)
Cholecystitis	3 (0.1)	6 (0.1)	6 (0.1)
Cholelithiasis	4 (0.1)	6 (0.1)	3 (0.1)
Hepatic failure	1 (0.0)	0 (0.0)	3 (0.1)
Hepatic function abnormal	3 (0.1)	0 (0.0)	0 (0.0)
Hyperbilirubinaemia	0 (0.0)	1 (0.0)	3 (0.1)
Jaundice	0 (0.0)	5 (0.1)	4 (0.1)
Bile duct obstruction	0 (0.0)	0 (0.0)	2 (0.0)
Biliary colic	0 (0.0)	1 (0.0)	0 (0.0)
Cholangitis	1 (0.0)	0 (0.0)	0 (0.0)
Cholangitis acute	1 (0.0)	0 (0.0)	2 (0.0)
Cholecystitis acute	1 (0.0)	0 (0.0)	1 (0.0)
Cholecystitis chronic	0 (0.0)	0 (0.0)	1 (0.0)
Cholestasis	0 (0.0)	1 (0.0)	1 (0.0)
Cytolytic hepatitis	0 (0.0)	1 (0.0)	0 (0.0)
Gallbladder pain	1 (0.0)	0 (0.0)	0 (0.0)
Hepatic cirrhosis	2 (0.0)	0 (0.0)	0 (0.0)
Hepatic lesion	1 (0.0)	0 (0.0)	0 (0.0)
Hepatic pain	1 (0.0)	0 (0.0)	0 (0.0)
Hepatic steatosis	1 (0.0)	1 (0.0)	0 (0.0)
Hepatitis	2 (0.0)	1 (0.0)	0 (0.0)
Hepatomegaly	1 (0.0)	0 (0.0)	0 (0.0)
Hepatotoxicity	0 (0.0)	0 (0.0)	1 (0.0)
Liver disorder	2 (0.0)	2 (0.0)	0 (0.0)

A subject may be counted in more than one category.
Source: NDA Amendment Table 15.3.2.6: 4

In RE-LY, hepatobiliary adverse events leading to treatment discontinuation were similar both qualitatively and quantitatively in dabigatran and warfarin treatment groups.

Post marketing experience data for liver safety obtained through spontaneous reporting is presented in Section 7.7 of this briefing document.

Conclusions on Dabigatran Hepatic Safety

The hepatic safety of dabigatran has been evaluated across studies in multiple indications with the largest safety database derived from the RE-LY trial (Study 1160.26, U09-3249-01) where 18,113 subjects were randomized to one of 2 blinded doses of dabigatran (110 or 150 BID) or warfarin and treated for up to 3 years (20,503.3 subject-years with dabigatran and 10,659.3 with warfarin).

As described in FDA Guidance on DILI (P09-12413), there are several key assessments deemed essential in ascertaining whether a signal exists for the risk of severe drug induced liver injury. The first is to determine if an excess of transaminase elevations >3x ULN, and in particular high peak levels >10x ULN, are observed with study drug compared to comparator

medication. In sharp contrast to ximelagatran, dabigatran has no excess of >3x ULN or higher ALT/AST elevations >10x ULN compared to warfarin. Also in contrast to ximelagatran, the time course of transaminase elevations with dabigatran has no tendency for clustering either shortly after initiation of the drug or later during its administration or after stopping treatment. The pattern of ALT/AST elevations seen with dabigatran parallel that seen with warfarin, a drug recognized as having rare, if any, hepatotoxicity.

In the most critical assessment, the number of "potential" Hy's cases was shown to be similar in all treatment groups. Blinded external DILI expert evaluation identified three attributable Hy's Law cases: two in subjects treated with warfarin and one subject treated with dabigatran. In all three cases the level of probability was deemed only "possible" because of significant confounding conditions and concomitant medications.

Liver function test monitoring during the initial portion of RE-LY was intensive with monthly testing during the first year and every 4 months thereafter. After 6,000 subjects had been randomized and followed for at least 6 months, the RE-LY DSMB recommended that monthly monitoring was no longer required and the FDA concurred. This recommendation was then implemented. An analysis comparing event rates per subject-year of exposure on the first 6000 subjects who underwent more intensive monitoring versus subjects who followed a less intensive monitoring schedule was performed. No relevant differences were observed in the detection of significant hepatic events between dabigatran and warfarin when comparing data from subjects who followed with more intense versus less intense LFT monitoring schedules. Overall, the hepatic profile of dabigatran was comparable to warfarin a drug recognized as having rare, if any, hepatotoxicity and which does not require routine LFT monitoring (R10-1340).

In conclusion, systematic liver function testing in atrial fibrillation trials confirms that the hepatic safety profile of dabigatran is comparable to warfarin. No excess event rate for liver injury has been found based on transaminase elevations of any grade, with or without associated elevations of bilirubin. Hepatobiliary adverse events were similar and balanced across study treatments.

7.4.5 Gastrointestinal Events and Other Events

GI disorders, Infections and Infestations, and General disorders were the SOCs with the highest incidence of reported AEs for both DE and warfarin subjects in the RE-LY study (Table 7.4: 1).

Subjects treated with DE had higher incidences of anemia compared with subjects treated with warfarin (3.0%, 3.4%, and 2.7% for DE 110 BID, DE 150 BID, and warfarin, respectively, NDA Amendment; Table 15.3.2.6: 7.) This, in combination with a slightly higher incidence of GI hemorrhage (1.1%, 1.3%, and 0.9% for DE 110 BID, DE 150 BID, and warfarin, respectively), is consistent with the results of the adjudicated bleeding events. DE subjects had a lower incidence of AEs associated with minor bleeding (hematoma, epistaxis, ecchymosis, fall and contusion) compared with warfarin.

Dyspepsia and gastritis

Dyspepsia was reported more frequently for DE 110 BID and DE 150 BID subjects compared with warfarin (6.2%, 5.7%, and 1.4%, respectively). Gastritis was reported in 2.5%, 2.1%, and 1.5% of DE 110 BID, DE 150 BID, and warfarin subjects, respectively (Table 7.4.5: 1). A Kaplan-Meier analysis shows that the risk for dyspepsia with dabigatran occurred very early in the first few weeks but subsequently the onset rates paralleled that of warfarin (Figure 7.4.5: 1).

PTs in MedDRA that were similar to dyspepsia and may define the same symptom were clustered to get an estimate of the overall occurrence of this AE (Table 7.4.5: 1). Two clusters were defined separately, “dyspepsia-like symptoms” (which include dyspepsia, upper abdominal pain, abdominal pain, abdominal discomfort, and epigastric discomfort) and “gastritis-like symptoms” (which include gastritis, gastroesophageal reflux disease, esophagitis, erosive gastritis, gastric hemorrhage, hemorrhagic gastritis, and hemorrhagic erosive gastritis). These two clusters were also pooled. Symptoms similar to dyspepsia were reported in a higher number of dabigatran-treated subjects compared with warfarin. The same pattern was observed for symptoms similar to gastritis.

Gastritis-like symptoms were associated with an increased risk of a major GI bleed by 3- to 4-fold and any bleed by 2- to 3-fold for all treatments (Table 7.4.5: 2). Dyspepsia-like symptoms were not associated with an increased risk of major bleeds for DE treated subjects; however, the probability of any bleeds increased slightly.

Discontinuation of treatment due to dyspepsia occurred more frequently in DE subjects (2.1%/year, 2.0%/year, and 0.6%/year for DE 110 BID, DE 150 BID, and warfarin, respectively, NDA Amendment; Table 15.3.2.8: 3). The reporting of dyspepsia or gastritis as an SAE was infrequent; however, gastritis was reported as an SAE more often on DE than for warfarin (0.4%/year and 0.3%/year vs. 0.2%/year, DE 110 BID, DE 150 BID and warfarin, respectively). Concomitant ASA increased event rates for both DE and warfarin, but there is no evidence of a synergistic effect.

Table 7.4.5: 1 Frequency of Subjects with Dyspepsia-like and Gastritis-like Symptoms – RE-LY Study

Preferred term/Investigator term	DE 110 BID N (%)	DE 150 BID N (%)	Warfarin N (%)
Number of subjects	5983 (100.0)	6059 (100.0)	5998 (100.0)
Total with dyspepsia/gastritis	983 (16.4)	940 (15.5)	470 (7.8)
Dyspepsia-like symptoms[1]	761 (12.7)	738 (12.2)	354 (5.9)
Dyspepsia	368 (6.2)	345 (5.7)	83 (1.4)
Abdominal pain upper	177 (3.0)	170 (2.8)	80 (1.3)
Abdominal pain	130 (2.2)	137 (2.3)	141 (2.4)
Abdominal discomfort	119 (2.0)	112 (1.8)	64 (1.1)
Epigastric discomfort	40 (0.7)	40 (0.7)	9 (0.2)
Gastritis-like symptoms[1]	297 (5.0)	257 (4.2)	142 (2.4)
Gastritis	147 (2.5)	127 (2.1)	87 (1.5)
Gastroesophageal reflux disease	117 (2.0)	99 (1.6)	46 (0.8)
Esophagitis	32 (0.5)	27 (0.4)	8 (0.1)
Gastritis erosive	21 (0.4)	19 (0.3)	3 (0.1)
Gastric hemorrhage	0 (0.0)	4 (0.1)	3 (0.1)
Gastritis hemorrhagic	5 (0.1)	4 (0.1)	3 (0.1)
Hemorrhagic erosive gastritis	2 (0.0)	0 (0.0)	0 (0.0)

[1] Represents a composite of sponsor-identified AEs (preferred terms) that were similar and likely reported in the same subject.
Percentages were calculated using total number of subjects per treatment as the denominator. Incidences >0 with percentages = 0 are less than 0.05% and rounded down to 0.
MedDRA Version 12.0 used for reporting terms
Source: NDA Amendment; Table 15.3.2.8: 1

The KM curves for time to first dyspepsia are presented in the next figure (Figure 7.4.5: 1).

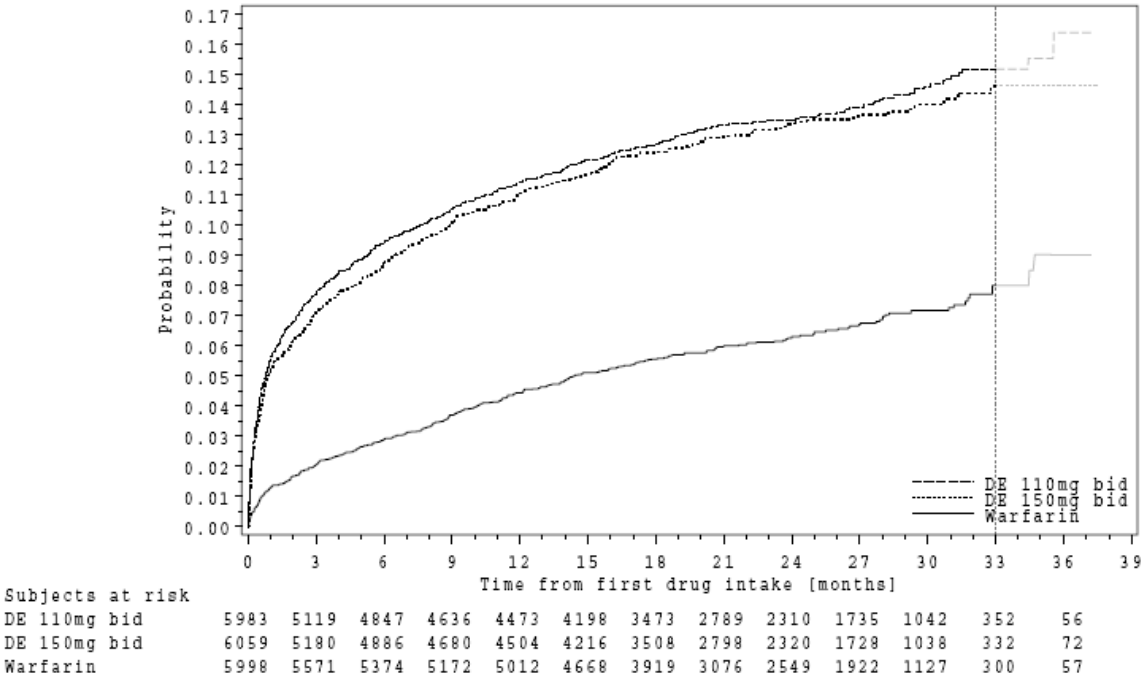


Figure 7.4.5: 1 Kaplan-Meier Estimates of Time to First Dyspepsia – RE-LY Study

Source: NDA Amendment; Figure 15.3.2.8: 1

There were more subjects having dyspepsia-like symptoms and gastritis-like symptoms on DE than warfarin (Table 7.4.5: 1). However, the percentages of subjects with dyspepsia-like symptoms had a lower rate of GI bleeding on both DE doses compared to warfarin. For those with gastritis-like symptoms, subjects on DE 110 had fewer bleeds than warfarin subjects while there were more bleeds when exposed to DE 150 (Table 7.4.5: 2).

Table 7.4.5: 2 Subjects with GI Bleeding Events for Subjects with Symptoms of Dyspepsia or Gastritis – RE-LY Study

	DE 110 BID		DE 150 BID		Warfarin	
	Number of subjects N	Subjects with events N (%)	Number of subjects N	Subjects with events N (%)	Number of subjects N	Subjects with events N (%)
Subjects with GI major bleed	5983	119 (2.0)	6059	161 (2.7)	5998	111 (1.9)
Subjects with any GI bleed	5983	558 (9.3)	6059	638 (10.5)	5998	428 (7.1)
Subjects with dyspepsia-like symptoms[1]						
and GI major bleeds	761	14 (1.8)	738	20 (2.7)	354	12 (3.4)
and any GI bleeds	761	96 (12.6)	738	83 (11.2)	354	45 (12.7)
Subjects with gastritis-like symptoms[1]						
and GI major bleeds	297	21 (7.1)	257	27 (10.5)	142	13 (9.2)
and any GI bleeds	297	59 (19.9)	257	66 (25.7)	142	32 (22.5)
Subjects with dyspepsia/gastritis-like symptoms[1]						
and GI major bleeds	983	31 (3.2)	940	43 (4.6)	470	23 (4.9)
and any GI bleeds	983	137 (13.9)	940	137 (14.6)	470	71 (15.1)

1 Represents a composite of sponsor-identified AEs (preferred terms) that were similar and likely reported in the same subject.
Source: NDA Amendment; Table 15.3.2.8: 5

7.5 ADDITIONAL SAFETY EXPERIENCE

7.5.1 Temporary Interruptions of dabigatran therapy

According to the RE-LY clinical trial protocol (dated 12 Sept 2005), dabigatran treatment could be continued until 24 hours before any prospective surgery. The protocol was revised in Amendment 5 (dated 07 Aug 2008) to highlight the importance of renal function relative to the clearance of dabigatran (P10-02803). It provided guidance for the management of subjects based on the risk of bleeding as a function of their CrCl level and on the type of surgery planned. Warfarin was to be stopped 5 days before the procedure and was to be started as soon as clinically feasible in the post procedural period. Patients could be managed with or without bridging anticoagulant therapy. Under this regimen, temporary interruptions for surgery or procedures occurred in 4623 (25.6%) subjects (NDA Sequence 0132, Table 17.1). More than half of these subjects, were from the US or Canada, approximately 20% were from Western Europe and the balance from the rest of the world. The mean age was 72.5 years, the mean $CHADS_2$ score did not differ from the overall population ($CHADS_2$ = 2.1).

More subjects in the dabigatran groups were managed without bridging anticoagulant therapy as compared to subjects in the warfarin group (79.3% and 77.4% for DE 110mg bid and DE 150 mg bid, respectively, vs. 65.7% for warfarin; NDA Sequence 0132, Table 17.2). When considering the time between last dose until surgery or procedure for all treatment interruptions (temporary and permanent) was shorter in DE 110 mg BID and DE 150 mg BID

subjects compared to warfarin subjects with 30.1% and 30.6% of dabigatran subjects undergoing surgery/procedure within 2 days after last drug intake compared to only 6.4% of warfarin subjects (Table 7.5.1: 1).

Table 7.5.1: 1 Treatment Interruptions -Time Since Last DE Dose and Surgery/procedure

Time since last dose to time of surgery/procedure	DE 110 BID (%)	DE 150 BID (%)	Warfarin (%)	Total (%)
≤2 days	749 (30.1)	807 (30.6)	162 (6.4)	1718 (22.5)
>2 and ≤5 days	534 (21.5)	572 (21.7)	660 (26.2)	1766 (23.1)
>5 days	208 (8.4)	210 (8.0)	640 (25.4)	1058 (13.9)

Source: NDA Amendment, Table 15.1.5: 8
Surgery/procedure with missing time was not included in the calculation

Thromboembolic complications and bleeding are the major concerns in the perioperative setting in subjects with oral anticoagulant therapy (P10-02622). Patients with AF are at a higher risk of stroke within 30 days after surgery as compared to non-AF subjects (R10-1346). Therefore, a time period of 30 days after surgery/intervention was chosen to analyze outcome events potentially related to intervention in RE-LY.

The occurrence rates of strokes/SEE events were similar across treatment groups, occurring infrequently in the 30 days after a temporary treatment interruption (Table 7.5.1: 2).

Table 7.5.1: 2 Subjects with Outcome Events 30 Days Post-surgery/Procedure

	DE 110mg BID (%)	DE 150mg BID (%)	Warfarin (%)	Total (%)
Subjects with interruptions for procedure/surgery	1501	1554	1568	4623
Stroke/SEE	8 (0.5)	6 (0.4)	14 (0.9)	28 (0.6)
Major Bleed	60 (4.0)	80 (5.1)	78 (5.0)	218 (4.7)
Minor bleed	140 (9.3)	160 (10.3)	151 (9.6)	451 (9.8)
Death	8 (0.5)	6 (0.4)	5 (0.3)	19 (0.4)

Note: Total N=4623
Source: NDA Sequence 0132, Table 17.6

There were relatively few subjects undergoing emergency surgery/procedures in RE-LY. There were no imbalances between treatment groups in those undergoing emergency group.

Conclusion

Discontinuation of DE for between 24 and 48 hours is generally appropriate for elective procedures and/or diagnostic testing. Temporary interruptions for a surgery or procedure

occurred in 4623 (25.6%) subjects (NDA Sequence 0132, Table 17.1). Over 90% of the treatment interruptions were done for elective procedures. More subjects in the DE groups were managed without bridging anticoagulant therapy as compared to subjects in the warfarin group (79.3% and 77.4% for DE 110mg BID and DE 150 mg BID, respectively, vs. 65.7% for warfarin; NDA Sequence 0132, Tables 17.2, 17.8, and 17.9). Strokes, MIs and bleeding events occurred at comparable frequencies in all treatment groups within the 30 days following a temporary treatment interruption. Sufficient information is available to recommend strategies to manage DE treatment interruptions for elective, urgent and emergency situations, whether or not short term bridging anticoagulant therapy (e.g., UFH and/or LMWH) is needed.

7.5.2 Switching Anticoagulant Therapy Between Dabigatran and Other Anticoagulants

When subjects receiving DE need to undergo elective procedures or diagnostic testing, bridging anticoagulant therapy with either unfractionated heparin or a low molecular weight heparin can be appropriate in subjects at higher risk of having a stroke. Additionally, subjects may be transitioned from warfarin to DE treatment as was done for more than one third of the subjects in RE-LY and subjects may need to transition from DE to warfarin, as was done for many of the subjects that permanently discontinued DE treatment in RE-LY.

Switching therapy from Vitamin K antagonist to dabigatran etexilate

In the RE-LY trial, subjects who were receiving warfarin or other Vitamin K antagonists (VKAs) and who were randomized to dabigatran, were only to initiate DE after the INR was below 2.0 (U09-3249-01). At the start of DE treatment in RE-LY, 7,511 subjects switched from VKAs to DE (NDA Amendment: Table 15.2.3.1: 1)

Using this approach in RE-LY allowed a simple approach for transitioning subjects from warfarin to DE. There was no early surge in the occurrence of strokes or bleeding (see Figure 6.3: 1 and Figure 7.3.1: 4)

Switching therapy from dabigatran etexilate to LMWH or from unfractionated heparin to dabigatran therapy

The switch from enoxaparin to dabigatran has been tested in a Phase I Study (1160.78, U09-1230-01). After a 24-hour washout of enoxaparin PD, levels of dabigatran were mainly not affected. On the other hand, to ensure anticoagulant activity, it is advised to initiate dabigatran etexilate when the next dose of parenteral anticoagulant would have been due, approximately 12 hours (AF population) or 24 hours (VTE prevention in orthopaedic population) after the last dose of the parenteral anticoagulant depending on the dosing regimen, once or twice daily. This schedule may be generally applied to LMWH or unfractionated heparin (UFH).

The Cmax of dabigatran etexilate is about 2 hours after ingestion and PK correlates with measurements of pharmacodynamic activity (P08-05411). Therefore, to allow for the appropriate pharmacodynamic effect of dabigatran, dabigatran etexilate should be taken

0-2 hours prior to the time that the next dose of the alternate therapy would be due, or at the time of discontinuation in case of continuous treatment (eg, intravenous UFH).

The RE-COVER study, a "venous thromboembolism (VTE) treatment trial" with 2539 subjects delivers additional supportive clinical evidence. All subjects were to receive parenteral anticoagulants for at least 5 days prior to switching to either double-blind warfarin or DE 150 BID. The regimen described above was utilized in this study.

Switching therapy from dabigatran etexilate treatment to LMWH, heparin or warfarin

When switching from dabigatran etexilate to another anticoagulant, the other anticoagulant should be started when the next scheduled dose of dabigatran etexilate would have been due. Given the BID dosing regimen established for DE, introduction (switching) of another anticoagulant should occur approximately 12 hr following the last dose of DE. This will result in continuous anticoagulant protection. These recommendations were given in the RE-LY trial protocol and resulted in the effective management of transitions from DE to LMWH and/or warfarin (U09-3249-01).

7.5.3 Long-term Data in SPAF Other Than RE-LY

A total of 432 subjects were treated with dabigatran etexilate in the Phase II study (PETRO, 1160.20, U06-1615-02) and in the extension study (PETRO-EX, 1160.42, U06-3419-01, All subjects treated with dabigatran etexilate were included in the safety analysis for this long-term data. The total exposure to dabigatran etexilate was 1250 subject-years. Since over 50% of the entered subjects remained on treatment for more than 4 years, the long-term extension study demonstrated that dabigatran etexilate was generally well tolerated with prolonged use.

The primary safety endpoint was bleeding. Bleeding was generally dose-related with higher incidences in subjects taking 150 mg BID or more of dabigatran etexilate and additionally an increased risk of bleeding with concomitant ASA use. The only exception was the rate of major bleeding in the 150 mg QD group, but the total number of subjects and total exposure in this group was relatively small.

The incidence of liver enzyme elevations was generally low. ALT and AST increases greater than 3x ULN were found at 2.3% per year across all treatments. Five subjects were reported to have ALT and AST increases >3x ULN with concomitant bilirubin elevations >1.2x ULN and only 3 subjects with concomitant bilirubin elevations of 2x ULN. In all cases, the liver enzymes returned to normal, with the exception of 1 subject with pancreatic cancer and liver metastasis.

During the trial, the 300 mg BID dose of dabigatran etexilate proved to have an unacceptably high incidence of both major bleeding (7% per year) and any bleeding (59.7% per year) compared to the other treatment regimens. This was noted by the Data Safety and Monitoring Board, and subsequently the 300 mg BID dose was eliminated from the trial. Similarly, the incidence of thromboembolic events for the 150 mg QD dose was unacceptably high, and this dose was also eliminated from the trial. These subjects were switched to 300 mg per day, either 150 mg BID or 300 mg QD which comprises the largest subject exposure in the trial.

This met the trial objective of defining the maximum tolerated dose and the minimum effective dose.

Dabigatran etexilate at 300 mg per day was generally well tolerated. The study provided long-term exposure data to support the safety of dabigatran etexilate with chronic use.

7.5.4 Dabigatran therapy after cardioversion

In RE-LY, 1255 subjects had at least one cardioversion: 409 in the DE 110 treatment group (6.8% of randomized subjects), 415 on DE 150 (6.8%), and 431 on warfarin (7.2%) (Table 7.5.4: 3, NDA Sequence 0132 Table 3.3 and Table 3.4). Most of these procedures were electrical cardioversions, with less than 1.5% in any group undergoing pharmacological cardioversion.

Fifty-nine to 66% of subjects receiving DE had their last dose within 24 hours of the procedure, and 52 to 60% within 12 hours of the procedure, indicating that the majority of subjects randomized to dabigatran were on treatment at the time of the procedure.

There were relatively few outcome events within the first 30 days after cardioversion of subjects receiving DE. Strokes occurred in 2, 1, and 1 subject for DE 110, DE 150 and warfarin, respectively. Deaths occurred in 3, 1, and zero subjects, respectively (NDA Sequence 0132 Table 3.1).

7.6 NON-SPAF PHASE II STUDIES - BLEEDING EVENTS

In Phase II SPAF trials, the DE 300 BID dose level was administered alone or concomitantly with ASA. The number of major bleeds as well as major or clinically relevant bleeds increased with increasing ASA dose. These high rates of bleeding occurred in Trial 1160.20 (U06-1615-02). Following the review and recommendation of the DSMB, the two treatment groups (DE 300 BID alone and with concomitant ASA) were terminated in the extension trial (1160.42, U06-3419-01).

In previous trials of DE for VTE prevention, DE doses ranged from DE 50 BID to DE 225 BID and DE 300 QD and were compared to either enoxaparin or placebo. As seen in SPAF trials, MBE rates increased with increasing dose.

7.7 NON-SPAF PHASE II STUDIES - DISCONTINUATION DUE TO ADVERSE EVENTS

In the SPAF Phase II trial, 1160.20 (U06-1615-02), 5.8% of subjects discontinued the study due to adverse events. The DE 300 BID doses were associated with higher discontinuation rates due to AEs than lower DE doses (DE 150 BID and DE 50 BID).

The Phase II VTE trials demonstrated similar results as the rate of subjects that discontinued treatment due to AEs ranged from 4.1% to 9.2%, with the highest rates seen in the higher dose DE groups (U02-1716, U03-1309, U04-1195-01, and U07-3436-01).

7.8 POST MARKETING

Dabigatran etexilate is approved in 74 countries worldwide for primary prevention of VTE events in subjects who have undergone major orthopedic surgery. The dosing regimen for this indication is 110 mg on the day of surgery, followed by 220 mg once daily for 10 days after total knee replacement (TKR) or 28-35 days after total hip replacement (THR). In subjects with moderate renal impairment, the recommended dose of DE is reduced to 150 mg QD.

From 18 March 2008 (international birthday) to 31 May 2010, approximately 280,000 subjects have been treated with DE based on worldwide "ex-factory" sales data for number of capsules sold, assuming a mean treatment duration of 30 days.

From 18 March 2008 to 15 June 2010, a total of 1157 (554 serious and 603 non-serious) cases containing 1918 adverse events (914 serious and 1004 nonserious) were received by Boehringer-Ingelheim from spontaneous, health authority, literature, and observational study sources. This includes health care provider confirmed, as well as consumer cases, independent of causal assessment to DE treatment.

The reported AEs received during post marketing safety surveillance are presented in Table 7.8: 1.

Table 7.8: 1 Incidence of Post Marketing Adverse Events by MedDRA System Organ Class Greater Than 2 Percent

System Organ Class	Percent
Injury, poisoning, and procedural complications	16.2
GI disorders	16.2
Vascular disorders	12.7
Investigations	10.4
General disorders/admin site conditions	8.3
Respiratory, thoracic, mediastinal disorders	6.3
Skin and subcutaneous tissue disorders	5.3
Surgical and medical procedures	3.5
Nervous system disorders	3.5
Renal and urinary disorders	3.4
Infections and infestations	2.8
Blood and lymphatic system disorders	2.6

Source: Boehringer Ingelheim Global Drug Safety Database

Forty-four (3.8%) of the 1157 cases contained a fatal event: thrombotic/embolic event (11 cases), general disorder SOC event (11 cases), GI hemorrhage event (6 cases), cardiac events (6 cases). intracranial hemorrhage event (3 cases), infection event (3 cases), blood and lymphatic SOC event (2 cases), injury, poisoning, procedural SOC event (1 case), and hepatobiliary SOC event (1 case).

A total of 334 (28.9%) cases contained at least 1 bleeding event. Within the total cases, 189 cases contained at least 1 serious bleeding event. Of the total 334 cases, 112 were GI hemorrhage events (6 fatal), 8 were intracranial hemorrhages (3 fatal), and 214 were "other hemorrhages" (0 fatal).

Additionally, 10 cases of ischemic cerebrovascular disease were reported with no fatalities.

Using the SMQ "Hepatic Disorders", 73 cases were retrieved. Of these 73 cases, 22 only contained coagulation abnormalities, considered to reflect the mode of action of DE. Of the remaining 51 cases, 36 reported isolated increased hepatic enzymes, 8 reported increased hepatic enzymes and increased bilirubin, 2 reported increased bilirubin without increased hepatic enzymes, and 5 reported "other hepatic disorders". Within these 51 cases, 2 potential Hy's Law cases were assessed as possibly related to DE by the sponsor.

Acute MI/acute coronary syndrome was reported in 8 cases (2 fatal). In 3 of these 8 cases, the subject had stopped DE before the time of the event for 3 days, 4 days, and 1 month, respectively.

The collection and evaluation of the postmarketing data continues as part of the routine monitoring program.

7.9 OVERDOSE

There is only limited clinical experience with overdose to date. Overdose following administration of DE may lead to hemorrhagic complications due to its pharmacodynamic properties. A specific antidote antagonizing the pharmacodynamic effect of DE is not available.

Doses of DE beyond those recommended expose the subject to an increased risk of bleeding. Excessive anticoagulation may require discontinuation of DE. In the event of hemorrhagic complications, treatment must be discontinued and the source of bleeding investigated. Since dabigatran is excreted predominantly by the renal route, adequate diuresis must be maintained. Appropriate standard treatment, e.g., surgical hemostasis as indicated and blood volume replacement, should be undertaken. In addition, consideration may be given to the use of fresh whole blood or fresh frozen plasma. As dabigatran has low plasma protein binding and is not sequestered in red blood cells, it is dialyzable; however, there is limited clinical experience in using dialysis in this setting.

Activated prothrombin complex concentrates (e.g., FEIBA) or recombinant Factor VIIa or concentrates of coagulation factors II, IX or X may be considered. There is some experimental evidence to support the role of these agents in reversing the anticoagulant effect of dabigatran but their usefulness in clinical settings has not yet been systematically demonstrated. Consideration should also be given to administration of platelet concentrates in cases where thrombocytopenia is present or long acting antiplatelet drugs have been used. All symptomatic treatment has to be given according to the physician's judgement.

DE administration is contraindicated in cases of severe renal impairment.

7.10 CONCLUSIONS

- DE 150 BID had a 7% non-significant lower risk of major bleeding compared with warfarin (p=0.3146) for the primary safety endpoint of major bleeding.

- DE 110 BID had a 20% lower risk of major bleeding compared with warfarin (p=0.0026).

- DE 110 BID had a 14% lower risk of major bleeds compared with DE 150 BID (p=0.043) for this blinded comparison.

- Both DE doses reduced the rate of life-threatening bleeds compared to warfarin, 33% (yearly rate = 1.24%; p=0.0001) and 20% (yearly rate = 1.49%; p=0.0305) for DE 110 BID and DE 150 BID, respectively.

- Intracranial hemorrhage risk decreased 70% for DE 110 BID compared to warfarin (p<0.0001) and 59% for DE 150 BID compared to warfarin (p<0.0001).

- Both DE doses resulted in a relative risk reduction in all bleeding (major +minor) compared to warfarin. For DE 110 BID, the risk reduction was 22% (p<0.0001) and for DE 150 BID the risk was reduced 9% vs warfarin (p=0.0016). DE 110 BID led to significantly less bleeding (relative reduction =14%) than DE 150 BID (p<0.0001) with this blinded comparison.

- Subjects treated with DE 150 BID had a higher incidence of major bleeding events within the gastrointestinal tract when compared with warfarin (yearly rate = 1.57% versus 1.07%).

- Bleeding is increased in the elderly in all treatment groups. In subjects ≥80 years, the risk of major bleeding for DE 110 BID was reduced compared to DE 150 BID by approximately an absolute 1%/year from 6.24%/year on DE 150 BID to 5.25%/year on DE 110 BID and was more similar to the warfarin rate of 4.70%/year. The benefit of DE versus warfarin in this subgroup for ICH and hemorrhagic stroke was maintained.

- The use of ASA nearly doubled the risk of major bleeds across all treatment groups, but did not change the relative risks. There were no concurrent medications that differentially increased major bleeds across treatment groups.

- GI AEs were more frequent for DE than for warfarin, with no difference between DE doses.

- AEs leading to discontinuation were more frequent in the DE groups compared to warfarin (19% of subjects for DE 110 BID, 20.5% for DE 150 BID, and 15.6% for warfarin). Gastrointestinal bleeding contributed to discontinuations on DE treatment. Discontinuations due to dyspepsia and related symptoms occurred more frequently on DE compared to warfarin, but were seldom reported as SAEs.

- RE-LY has evaluated effective bridging strategies when switching from DE to and from LMWH and warfarin without significant risk of major bleeding and the occurrence of stroke or other outcome events.

8. RISK/BENEFIT ANALYSIS

Anticoagulants have a profile where increased efficacy can be obtained but at the cost of increased bleeding. The remarkable and unexpected outcome in RE-LY was that DE 150 BID both reduced the incidence of the primary efficacy endpoint stroke/SEE and reduced the incidence of intracranial hemorrhage including hemorrhagic stroke as well as life-threatening bleeding, bleeding into a critical area or organ, and total bleeding compared to warfarin. There were some other findings, including an increase in GI adverse events, (although these resulted in relatively few study drug discontinuations) and a modest imbalance in MIs, both favouring warfarin. The overall balance between the above noted results clearly establishes a positive risk benefit profile for DE for use in the prevention of stroke and SEE in all subjects who are eligible to receive warfarin with the use of the lower tested dose (DE 110 BID), having a better risk benefit profile in those at least 80 years of age.

8.1 RISKS OF DABIGATRAN TREATMENT

The principal risk of anticoagulation is bleeding with the observed yearly event rates provided below.

Table 8.1: 1 Yearly Event Rate of Bleeding - RE-LY Study

	DE 110 BID N (%)	DE 150 BID N (%)	Warfarin N (%)
Adjudicated Bleeds			
Number of randomized subjects	6015	6076	6022
Subject-years	11899	12033	11794
Major bleeds (%/year)	342 (2.87)	399 (3.32)	421 (3.57)
Life threatening MBEs	147 (1.24)	179 (1.49)	218 (1.85)
Other MBEs	218 (1.83)	248 (2.06)	226 (1.92)
ICH[1]	27 (0.23)	38 (0.32)	90 (0.76)
Minor bleeds[2]	1566 (13.16)	1787 (14.84)	1931 (16.37)
Any bleeds[2]	1754 (14.74)	1993 (16.56)	2166 (18.37)

[1] ICH includes subdural and subarachnoid bleeds in addition to intracerebral bleeds.
[2] Investigator-reported bleeding events. Minor bleeds were not adjudicated.
There were 18,040 subjects that received at least one dose of study medication to be evaluable for bleeding analyses in the safety set. In case of a recurrent event of the same category, the first event was considered.
Subject-years = sum (date of study termination - date of randomization +1) of all randomized subjects / 365.25.
Yearly event rate (%) = # of subjects with event / subject-years * 100.
Source data: NDA Amendment; Table 15.3.2.1: 1, Table 15.3.2.1: 2

Dabigatran exposure was evaluated during RE-LY by measurements of peak and trough plasma concentrations. There was a relationship between dabigatran plasma concentrations and the risk of bleeding (Table 8.1: 2). DE subjects with major bleeds had on average about a 50% higher trough dabigatran plasma concentration than those with no reported bleeding event. Additionally, the risk of bleeding was influenced by other factors, in particular age as bleeding risk increased in all three treatment groups with increasing age (Table 7.3.1: 8).

Table 8.1: 2 Trough Plasma Dabigatran Concentrations by Type of Bleeding Event in RE-LY

	Trough total dabigatran plasma concentration [ng/mL]				
	Major bleed	**Any bleed**	**No bleed**	**DE 110 BID**	**DE 150 BID**
N	323	2319	5899	4227	4222
Mean	141	111	92.4	81.3	114
CV [%]	69.0	74.9	73.5	72.4	71.6
SD	97.7	83.0	67.9	58.9	81.9

Source: NDA Amendment, Table 11.5.2.3.1 and Table 11.5.2.1: 1

The relationship between the risk of stroke and dabigatran trough plasma concentrations is more pronounced when considering ischemic strokes/SEE rather than all strokes (Figure 4.6: 2). Note that the slope of the curves decreases with increasing dabigatran plasma concentrations. There is relatively little difference in stroke risk across a wide range of higher dabigatran trough concentrations, but age continues to influence stroke risk substantially. DE doses greater than 150 mg BID (median trough concentration of DE 150 BID was 93 ng/mL) would be expected to result in very modest reductions in stroke risk/SEE, while increasing all categories of bleeding more prominently.

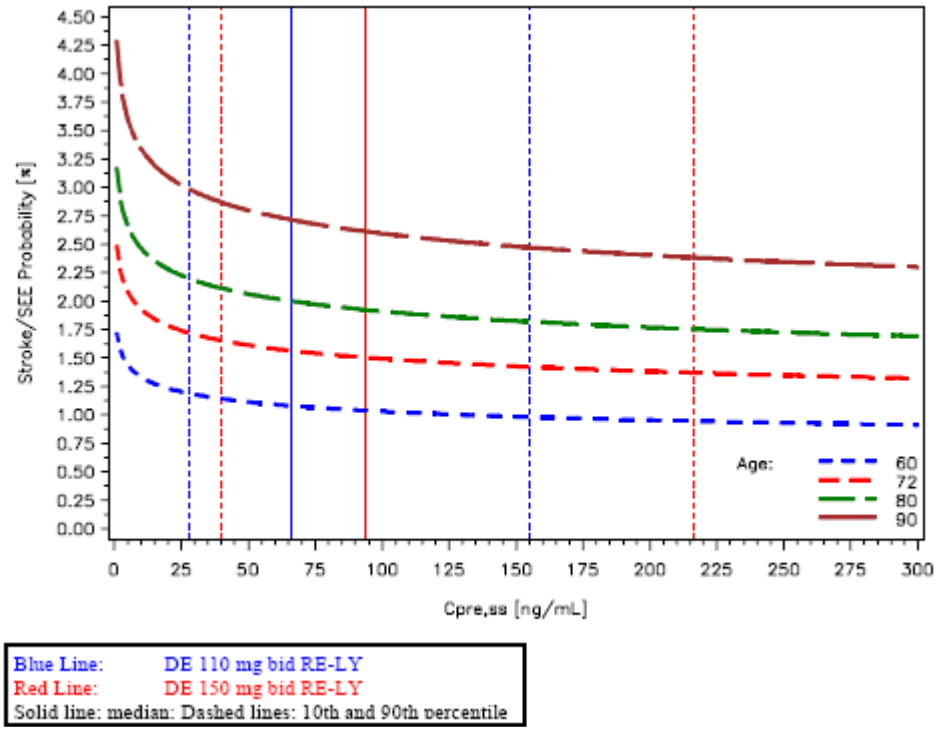


Figure 8.1: 1 Effects of Age and DE Dose on Stroke Risk

Source: U10-3483-01

ASA administered during the study had a strong effect on the risk of bleeding, which almost doubled compared with those who did not use ASA during the study. However, this increase of bleeding risk by ASA use was observed for all three treatment groups regardless of age or creatinine clearance. Similarly, renal impairment increased the risk of bleeding but again there was no treatment interaction and the use of DE 150 BID compared to warfarin did not disproportionately increase stroke or bleeding risk in the RE-LY subjects.

Several Phase I studies demonstrated that there was an interaction with increased exposure to dabigatran when various P-gp inhibitors. For example, verapamil at steady state and single dose amiodarone increased dabigatran exposure by about 50%. These results were not replicated in the clinical setting during the RE-LY study. In particular, co-administration of verapamil and amiodarone with DE only produced modest increases in dabigatran plasma levels of about 20 and 13%, respectively, which were not associated with any substantial increase in bleeding or AE. Dosing modifications in RE-LY when co-administering DE with P-gp inhibitors was generally not done. It may be appropriate to space the timing of administration of DE and P-gp inhibitors to minimize the chance of interaction. A risk for increased bleeding due to an increased dabigatran exposure with administration of P-gp inhibitors cannot be ruled out.

Gastrointestinal bleeding was more frequent on DE, notably major GI bleeding with DE 150 BID compared to warfarin (1.5% vs. 1%) although overall fatal bleeding was less frequent on both DE doses.

Dyspepsia and related symptoms were twice as frequent on DE as warfarin (12-13% vs. 6%) but this was seldom reported as a serious adverse event and led to discontinuation of treatment in approximately 2% of subjects compared to 1% on warfarin.

The absolute risk of MI was low (0.6 to 0.8%/year), but was greater on DE (relative risks about 1.30 for both DE groups compared to warfarin). There were similar numbers of MIs identified on both DE doses. Approximately 20% of MIs occurred after discontinuation of study drug and a portion of the overall observed imbalance occurred during this period.

8.2 BENEFITS OF DABIGATRAN TREATMENT

DE 110 BID and DE 150 BID have both been shown to be non-inferior to warfarin for the prevention of stroke and systemic embolism in subjects with AF. DE 150 BID has been demonstrated to be superior to warfarin for the prevention of stroke/systemic embolism with a hazard ratio of 0.65 and a p-value for superiority of <0.0001. All sensitivity analyses (i.e., on-treatment comparison of DE 150 mg BID vs warfarin, including only those with better INR [>65% and >68%] control, etc.) confirmed the robust results.

Both DE doses significantly reduced the occurrence of hemorrhagic stroke by over two thirds compared to warfarin ($p<0.0001$). In addition, ICH was reduced by over 50% for both DE 110 BID and DE 150 BID compared to warfarin (both DE 110 BID and DE 150 BID; $p<0.0001$).

Hazard ratios for death and vascular death ranged between 0.85 and 0.91 for both DE doses compared to warfarin with those on DE 150 BID consistently lower than those on DE 110 BID. Only one comparison, DE 150 BID vs warfarin had a nominal p value below 0.05 (DE 150 BID vs warfarin for vascular death). The occurrence of vascular deaths, particularly those due to strokes as well as deaths associated with bleeding occurred less frequently on DE 150 BID than warfarin.

Bleeding is discussed in the RISK section above, yet multiple categories of bleeding were observed less frequently with both DE 110 and DE 150 compared to warfarin.

Hazard ratios, confidence intervals and p-values comparing some of the groups shown in Table 8.1: 1 are found in the following table (extracted from NDA Amendment, Table 15.3.2.1: 9).

Table 8.2: 1 Hazard Ratios and 95% CI for Various Categories of Bleeding

		DE 110 BID vs Warfarin	**DE 150 BID vs Warfarin**	**DE 110 BID vs DE 150 BID**
Adjudicated major bleeds	Hazard ratio (SE)	0.80 (0.06)	0.93 (0.07)	0.86 (0.06)
	95% CI	0.70, 0.93	0.81, 1.07	0.75, 1.00
	P-value	0.0026	0.3146	0.0429
Adjudicated life-threatening bleeds	Hazard ratio (SE)	0.67 (0.07)	0.80 (0.08)	0.80 (0.09)
	95% CI	0.54, 0.82	0.66, 0.98	0.67, 1.03
	P-value	0.0001	0.0305	0.0915
Adjudicated ICH	Hazard ratio (SE)	0.30 (0.06)	0.41 (0.08)	0.72 (0.18)
	95% CI	0.19, 0.45	0.28, 0.60	0.44, 1.18
	P-value	<0.0001	<0.0001	0.1875
Investigator reported any bleeds	Hazard ratio (SE)	0.78 (0.03)	0.91 (0.03)	0.86 (0.03)
	95% CI	0.73, 0.83	0.85, 0.96	0.81, 0.92
	P-value	<0.0001	0.0016	<.0001

In case of recurrent event, the first event was considered.
Source: NDA Amendment; Table 15.3.2.1: 9_NEW

DE 150 BID compared to warfarin had hazard ratios less than 1.00 for all above categories of bleeding and statistically significant differences were observed for any bleeds, life-threatening bleeds and ICH. DE 110 BID consistently and significantly had less bleeding in all above categories compared to warfarin and similarly versus DE 150 BID. The DE 110 BID vs DE 150 BID comparisons (DE doses were double-blinded during RE-LY) all had very similar hazard ratios for each category of bleeding above, demonstrating a clear and consistent dose response relationship for bleeding between the two DE dosing regimens.

A significant statistical interaction for the risk of major bleeds with treatment was observed in the elderly. A cut point at an age ≥80 years was selected because this is near the point where the DE 150 BID vs warfarin hazard ratio for major bleeding becomes greater than 1.00 and there was essentially no greater reduction in the occurrence of strokes comparing DE 150 BID to DE 110 BID in those at least 80 years of age (see Figure 8.2: 1). When comparing both doses of DE to warfarin, there was a strong treatment interaction for age, p<0.0038). For

subjects <80 years of age, DE 110 BID and DE 150 BID had a lower rate of major bleeds compared to warfarin (2.4%, 2.7% and 3.4%, respectively; however, subjects ≥80 years of age treated with DE 150 BID had an approximately 1% absolute increase in annual major bleed rates compared with the DE 110 BID group, which had a rate closer to that of warfarin (5.2%, 6.2% and 4.7%, for DE 110, DE 150 and warfarin, respectively; NDA Sequence 0132, Table 2.9).

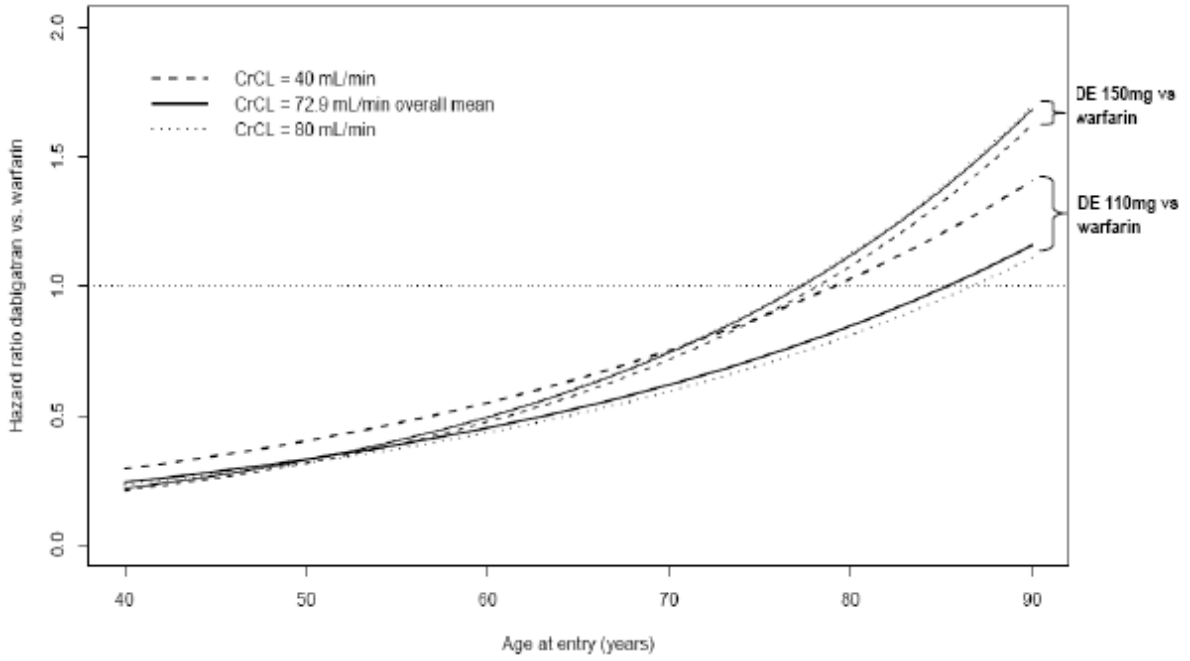


Figure 8.2: 1 Hazard Ratio of Major Bleed (DE vs. warfarin) by Continuous age at Selected CrCl Values – Re-LY Study

Source: NDA Sequence 0000, SCS Appendix 7, Table 2.1.1.1.7.3

Increasing age is associated with an increased stroke risk. Dabigatran plasma concentrations are inversely related to the occurrence of stroke in the elderly.

- The effect of age on stroke risk appears to be greater than the effect of changing dabigatran plasma concentrations.
- Increasing plasma dabigatran concentrations lowers the stroke risk, although at concentrations above 50 ng/mL this effect is modest.
- The relative risk reduction is comparable across ages.

The recommendation to tailor doses for patients with different bleeding and stroke risk profiles, specifically recommending the use of DE 110 BID in those at least 80 years of age is demonstrated by the RE-LY data.

Treatment interruptions are common in those receiving chronic anticoagulation, as was the case in RE-LY where 25% of subjects had at least one temporary treatment interruption. For those undergoing surgery or procedures, outcome events (strokes and death) occurred at similar frequencies in both DE groups compared to warfarin, whether or not bridging therapy was given, and whether or not procedures were elective or done on an emergent basis.

Analyses of virtually every subgroup (i.e., medical history, stroke risk factors, baseline medications, $CHADS_2$ score, renal impairment, gender, concomitant use of P-gp inhibitors, prior VKA use (including at study entry, whether never used or warfarin naïve as defined in the RE-LY protocol) had no subgroup by treatment interaction indicating a consistency of the effects of DE in reducing strokes compared to warfarin. There was a treatment interaction with age, which has resulted in the recommendation for the use of DE 110 BID in those >80 years.

8.3 BENEFIT/RISK CONCLUSIONS

The DE doses tested in RE-LY, DE 110 BID and DE 150 BID, were both non-inferior, and DE 150 BID was superior to warfarin for prevention of the primary endpoint, stroke/SEE. Both DE doses profoundly reduced the risk of hemorrhagic stroke and intracranial bleeding compared to warfarin and DE 150 BID also reduced ischemic strokes compared to warfarin. There were lower hazard ratios for both DE groups compared to warfarin for all-cause mortality and vascular mortality. The double-blind comparison between DE 110 BID and DE 150 BID demonstrated statistically and clinically important between-group differences in multiple bleeding endpoints with all having similar hazard ratios for these comparisons For the primary efficacy endpoint (stroke/SEE) the blinded comparison of DE 150 BID and DE 110 BID demonstrated the superiority of DE 150 BID as well. These results clearly show that the measures put in place to prevent ascertainment and other biases were successful during this trial with blinded DE doses and open-label warfarin.

Use of DE 110 BID should be considered in subjects at least 80 years of age, a cut point when the hazard ratio for major bleeding of DE 150 BID compared to warfarin exceeds 1.00, while the hazard ratios for stroke/SEE prevention for both DE 150 BID and SE 110 BID compared to warfarin are comparable. For both DE doses compared to warfarin, the risk of gastrointestinal bleeding is increased in the elderly, especially with DE 150 BID in subjects ≥80 years. This accounts for most of the excess bleeding in the elderly compared to warfarin. The risk of extracranial bleeding on dabigatran in the elderly (≥80 years) can also be minimized by use of the lower DE 110 BID dose.

Reduced creatinine clearance increases dabigatran plasma levels. This may increase bleeding risk especially in the elderly. Age is an independent and more powerful predictor of bleeding risk. There is also a relationship between dabigatran plasma concentration and stroke prevention, which is stronger in older subjects. The balance between bleeding and efficacy favours the use of DE 110 BID instead of DE 150 BID in those at least 80 years of age.

Discontinuation of treatment due to dyspepsia occurred more frequently in DE subjects (2.1%/year, 2.0%/year, and 0.6%/year for DE 110 BID, DE 150 BID, and warfarin,

respectively) but was infrequent. The reporting of dyspepsia or gastritis as an SAE was uncommon.

The incidence of MI was higher for both DE groups than for warfarin, but it was not dose-dependent and was low in all treatment groups (0.6 – 0.8% per year). At present, there is no explanation for this difference.

The superiority of DE 150 BID versus INR-adjusted warfarin (2.0 – 3.0) for stroke/SEE prevention, together with the reduced frequency of severe and clinically important bleeding (i.e., ICH) as well as minor bleeding is consistent across a wide range of subgroups and demographic characteristics and highly clinically relevant. The only exception is in the elderly, where the DE 110 BID dose is recommended to prevent stroke/SEE with a lower risk of extracranial major bleeding.

The fear of the occurrence of ICH is a major factor in the under-use of anticoagulation in moderate to high risk subjects with AF. Although there is a modest increase in GI bleeding with the DE 150 BID dose compared to warfarin and an increased rate of MIs (0.2%/year), this is more than counterbalanced by the superiority of the DE 150 BID in preventing both ischemic and hemorrhagic strokes and intracranial haemorrhages. These data strongly support the registration of both DE 150 BID and DE 110 BID for prevention of stroke/SEE. In the elderly (≥ 80 years of age), DE 110 BID should be the recommended dose.

9 OVERALL SUMMARY AND CONCLUSIONS

Dabigatran etexilate has been administered to over 25,000 subjects in ongoing and completed clinical trials and is marketed for the prevention of venous thromboembolic events in subjects undergoing elective total hip and knee replacement surgery in over 70 countries outside the US. Dabigatran has a constant relationship between the pharmacokinetic (plasma levels) and pharmacodynamic response (aPTT, thrombin time, ecarin clotting time) in animals and multiple human populations (i.e., healthy volunteers, subjects undergoing orthopaedic surgery, subjects being treated for deep vein thrombosis with and without pulmonary embolism and subjects with atrial fibrillation).

Two blinded doses of DE were selected for inclusion in the Phase III RE-LY study. This strategy allowed the comparison of both blinded dabigatran doses to open-label warfarin as well as a blinded comparison of the two dabigatran etexilate dose strengths to assess the dose-response relationship for both safety (i.e., bleeding) and efficacy and to strengthen the trial design and increase the reliability and robustness of the results. The INR control (TTR was 64.4% for warfarin overall and 66.9% in USA/Canada) was comparable to recent warfarin trials (SPORTIF III and V, ACTIVE-W, AMADEUS).

The most important results from RE-LY are:

- DE 150 BID:
    - significantly reduced the risk of the primary efficacy endpoint, stroke and systemic embolism compared to warfarin (HR 0.65, 97.5% CI 0.51 – 0.83, p = 0.0001)
    - significantly reduced the risk of intracranial hemorrhage compared to warfarin (HR 0.41, 95% CI 0.28 - .060, p < 0.0001)
    - decreased the incidence of ischemic strokes, hemorrhagic strokes, vascular mortality and all bleeding events compared to warfarin (all nominal p-values < 0.05)
    - and warfarin had a comparable number of major bleeds (HR 0.93, 95% CI 0.81 – 1.07, p = 0.32). There were more major GI bleeds and total GI bleeds on DE 150 BID than on warfarin.
- DE 150 BID significantly reduced the risk of the primary efficacy endpoint, stroke and systemic embolism compared to DE 110 BID in this blinded comparison (HR DE 110 BID/DE 150 BID 1.39, 95% CI 1.11 – 1.73, p = 0.0041)
- DE 110 BID:
    - was non-inferior to warfarin for reducing the risk of stroke and systemic embolism (HR 0.90, 97.5% CI, 0.71 – 1.13, p < 0.0001)

  - significantly reduced major bleeding, life-threatening bleeding, intracranial hemorrhage, hemorrhagic stroke and any bleeding compared to warfarin (all p values < 0.003)

  - significantly reduced major and all bleeding compared to DE 150 BID in this blinded comparison

- The hazard ratios comparing the blinded DE 110 BID to DE 150 BID doses were consistent and comparable (around 0.85 or lower) when assessing all categories of bleeding.

- For subjects at least 80 years of age, DE 110 BID had similar effect on stroke/SEE as DE 150 BID but with less bleeding (all severity categories and for all locations) and therefore had a better benefit/risk profile than both DE 150 BID and warfarin, and is thus appropriate for use in this population

- GI AEs such as dyspepsia and nausea occurred more frequently in DE treated subjects but there were no other important differences in the reported AEs between the treatment groups

- There was a small imbalance in the annual rate of MIs favouring warfarin but the annual rate in each treatment group was < 1%

- LFT abnormalities and potential Hy's Law cases occurred less commonly on both blinded DE doses compared to warfarin

- The RE-LY results were robust with all sensitivity and subgroup analyses essentially having similar results.

The dabigatran etexilate SPAF development program has demonstrated that fixed doses of DE administered without monitoring is an excellent alternative to warfarin in the entire group of AF subjects for whom warfarin therapy can be considered.

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