DISCLAIMER STATEMENT

The attached package contains background information prepared by the Food and Drug Administration (FDA) for the panel members of the Cardiovascular and Renal Drugs Advisory Committee. The FDA background package often contains assessments and/or conclusions and recommendations written by individual FDA reviewers. Such conclusions and recommendations do not necessarily represent the final position of the individual reviewers, nor do they necessarily represent the final position of the Review Division or Office. We have brought the dabigatran New Drug Application to this advisory committee in order to gain the Committee's insights and opinions, and the background package may not include all issues relevant to the final regulatory recommendation and instead is intended to focus on issues identified by the Agency for discussion by the advisory committee. The FDA will not issue a final determination on the issues at hand until input from the advisory committee process has been considered and all reviews have been finalized. The final determination may be affected by issues not discussed at the advisory committee meeting.

Questions

Dabigatran

September 20, 2010

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration

The Advisory Committee is asked to opine on the approvability of dabigatran, a direct thrombin inhibitor, to reduce the risk of stroke and systemic embolus in patients with atrial fibrillation.

The support for this claim comes primarily from RE-LY, in which 18113 subjects with persistent, paroxysmal, or persistent atrial fibrillation (about one-third each) were randomized to open-label warfarin or to one of two blinded doses of dabigatran. The trial ran until 450 events accrued, about 3 years. Important results were as follows:

		Patient-years			**HR vs Warf**	
		Warf 11794	**D110 11899**	**D150 12033**	**D110**	**D150**
Primary	Stroke/SEE	1.7%	1.5%	1.1%	0.90 (0.74-1.10)	0.65 (0.52-0.81)
	Stroke	1.6%	1.4%	1.0%	0.91 (0.74-1.12)	0.64 (0.51-0.80)
	Rankin >1					
	Rankin >3					
	Rankin 6					
	SEE	0.2%	0.1%	0.1%	0.71 (0.36-1.37)	0.61 (0.30-1.21)
Deaths	Total				0.91 (0.80-1.03)	0.88 (0.77-1.00)
	Vascular					
	Stroke					
	Hemorr					
	Non-vasc					
Bleeding	Fatal[1]					
	Intracranial[2]	0.8%	0.2%	0.3%		
	Symptomatic[1]					
	Surgery[1, 2]					
	Inotrope[1, 2]					
	≥4 units[1]					
	≥5 g/dL[1]					
	[1]Life-threat	1.9%	1.2%	1.5%		
	[2]GUSTO Sev		0.6%	0.9%		

1. Please comment on the adequacy of the design of RE-LY.
    - 1.1. Was open-label warfarin reasonable?
    - 1.2. Incorporating at least two doses of dabigatran is laudable, but were reasonable doses selected?

Last saved Tuesday, 24 August 2010 at 08:03

1.3. The primary analyses were non-inferiority of each dose against warfarin. The sponsor set a non-inferiority margin at 1.46, while the Agency has, using a slightly different analysis but the same set of reference studies, argued consistently for a margin of 1.38. Should RE-LY have been allowed to proceed?

1.4. Should end point events be counted off treatment and following crossover from dabigatran to warfarin?

1.5. Are there other study design issues?

2. Please comment on the adequacy of the conduct of RE-LY.

2.1. Was warfarin used in a manner that made the comparison with dabigatran fair?

2.2. Was follow-up for end point events adequate in all treatment groups?

2.3. Was follow-up for adverse events, particularly hepatotoxicity and bleeding, adequate in all treatment groups?

2.4. Are there any other study conduct issues?

3. Please comment on effectiveness. Is dabigatran effective in reducing the combined risk of stroke and systemic embolus? If so, …

3.1. … do both stroke and systemic embolus contribute to the effect?

3.2. … is effectiveness demonstrated at both doses?

3.3. … is the 150-mg dose unequivocally superior to warfarin?

4. Please comment on safety.

4.1. What should labeling say about the risk of hepatotoxicity?

4.2. Is the risk of bleeding unequivocally lower on dabigatran 110 mg than on warfarin? If so, what classes of bleeding did you use to conclude that?

4.3. Is the risk of bleeding similar on dabigatran 150 mg and warfarin?

4.4. Are there any other major safety issues?

5. VOTE: Should dabigatran be approved for the treatment of atrial fibrillation? If so, …

5.1. … at what doses?

5.2. … is there a claim of superiority to warfarin?

5.3. … Are there any important limitations on use?

6. Please comment on the benefit of stroke reduction versus the risk of bleeding.

6.1. Bleeding can lead to fixed or long-term sequelae—death, stroke, MI, renal injury.

6.1.1. Were such sequelae worse in one treatment group than another?

6.1.2. Were such sequelae more common in subjects following a bleed?

6.2. Bleeding that does not lead to long-term sequelae can still require hospitalization, need for surgery, or need for transfusion. How many bleeds without long-term sequelae does it take to offset one stroke? Please comment by stroke severity?

6.3. Please weight the relative clinical importance of the following in deciding the merits of one treatment modality versus another:

Death (CV or all cause?)
Stroke
  Rankin >1
  Rankin >3
  Rankin 6
Systemic embolus
Bleeding
  Intracranial (only symptomatic?)
  Requiring surgery
  Requiring inotrope
  Requiring ≥4 units
  >5 g/dL

6.4. Has the dose-response relationship for dabigatran been adequately defined? If not what doses would you like to see in a future study

		Events (N)			Patient-years			HR vs Warf	
		Warf 6022	**D110 6015**	**D150 6076**	**Warf 11794**	**D110 11899**	**D150 12033**	**D110**	**D150**
Primary	Stroke/SEE	202	183	134	1.7%	1.5%	1.1%	0.90 (0.74-1.10)	0.65 (0.52-0.81)
	Stroke	186	171	122	1.6%	1.4%	1.0%	0.91 (0.74-1.12)	0.64 (0.51-0.80)
	Rankin >1	119	109	73					
	Rankin >3	80	71	55					
	Rankin 6	58	47	42					
	SEE	21	15	13	0.2%	0.1%	0.1%	0.71 (0.36-1.37)	0.61 (0.30-1.21)
Deaths	Total	487	446	438				0.91 (0.80-1.03)	0.88 (0.77-1.00)
	Vascular	317	289	274					
	Stroke	44	30	23					
	Hemorr	18	11	14					
	Non-vasc	170	157	164					
Bleeding	Fatal[1]								
	Intracranial[2]	90	27	38	0.8%	0.2%	0.3%		
	Symptomatic[1]								
	Surgery[1, 2]								
	Inotrope[1, 2]								
	≥4 units[1]								
	≥5 g/dL[1]								
	[1]Life-threat	218	147	179	1.9%	1.2%	1.5%		
	[2]GUSTO Sev		74	106		0.6%	0.9%		

CLINICAL REVIEW

Application Type	NDA
Application Number(s)	022-512
Priority or Standard	Priority
Submit Date(s)	December 15, 2009 (Initial) April 19, 2010 (Resubmission)
Received Date(s)	As above
PDUFA Goal Date	October 19, 2010
Division / Office	Cardiovascular and Renal Products/ODE1
Reviewer Name(s)	Nhi Beasley (Safety) Aliza Thompson (Efficacy)
Review Completion Date	August 25, 2010
Established Name	Dabigatran
(Proposed) Trade Name	Pradaxa
Therapeutic Class	Anticoagulant
Applicant	Boehringer-Ingelheim
Formulation(s)	Oral
Dosing Regimen	110 and 150 mg BID
Indication(s)	Prevention of stroke and systemic embolism in atrial fibrillation
Intended Population(s)	Adults

Table of Contents

1 RECOMMENDATIONS/RISK BENEFIT ASSESSMENT 9
1.1 Recommendation on Regulatory Action 9
1.2 Risk Benefit Assessment 9
1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies . 15
1.4 Recommendations for Postmarket Requirements and Commitments 16
2 INTRODUCTION AND REGULATORY BACKGROUND 16
2.1 Product Information 16
2.2 Tables of Currently Available Treatments for Proposed Indication 17
2.3 Availability of Proposed Active Ingredient in the United States 17
2.4 Important Safety Issues with Consideration to Related Drugs 17
2.5 Summary of Presubmission Regulatory Activity Related to Submission 18
3 ETHICS AND GOOD CLINICAL PRACTICES 19
3.1 Submission Quality and Integrity 19
3.2 Compliance with Good Clinical Practices 22
3.3 Financial Disclosures 24
4 SIGNIFICANT EFFICACY/SAFETY ISSUES RELATED TO OTHER REVIEW DISCIPLINES 24
4.1 Chemistry Manufacturing and Controls 24
4.2 Clinical Microbiology 24
4.3 Preclinical Pharmacology/Toxicology 25
4.4 Clinical Pharmacology 25
4.4.1 Mechanism of Action 25
4.4.2 Pharmacodynamics 25
4.4.3 Pharmacokinetics 27
5 SOURCES OF CLINICAL DATA 28
5.1 Tables of Studies/Clinical Trials 28
5.2 Review Strategy 28
5.3 Discussion of Individual Studies/Clinical Trials 29
5.3.1 Study Design and Objectives 29
5.3.2 Study Duration/Dates 29
5.3.3 Study Sample Size and Power Considerations 29
5.3.4 Study Population 30
5.3.5 Procedures 30
5.3.5.1 Liver monitoring 31
5.3.5.2 Anticoagulation initiation, maintenance and monitoring 31
5.3.5.3 Treatment of bleeds 32
5.3.5.4 Emergency and elective surgery 33
5.3.5.5 Discontinuation of study medication and follow-up of subjects 33
5.3.6 Endpoints 34

5.3.7 Statistical Analysis Plan 36
5.3.7.1 Primary endpoint analysis as specified in the 2005 protocol (and TSAP) 36
5.3.7.2 Secondary endpoint analysis as specified in the 2005 protocol (and TSAP) .. 37
5.3.8 Identification of potential endpoint events 37
5.3.9 Protocol Amendments: 39
5.3.10 Adjudication process 41

6 REVIEW OF EFFICACY 44

6.1 Indication 48
6.1.1 Methods 49
6.1.2 Demographics 49
6.1.3 Subject Disposition 51
6.1.4 Analysis of Primary Endpoint(s) 53
6.1.5 Analysis of Secondary Endpoints(s) 57
6.1.7 Subpopulations and concomitant medications 63
6.1.8 Analysis of clinical information relevant to dosing recommendations 66
6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects 69
6.1.10 Additional Efficacy Issues/Analyses 69
6.1.10.1 Warfarin administration and INR control 69
6.1.10.2 Analyses pertaining to RE-LY's open-label design 76

7 REVIEW OF SAFETY 80

7.1 Methods 80
7.1.1 Studies/Clinical Trials Used to Evaluate Safety 80
7.1.2 Categorization of Adverse Events 81
7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence 81
7.2 Adequacy of Safety Assessments 81
7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations 81
7.2.2 Explorations for Dose Response 83
7.2.3 Special Animal and/or In Vitro Testing 83
7.2.4 Routine Clinical Testing 83
7.2.5 Metabolic, Clearance, and Interaction Workup 83
7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class .. 83
7.3 Major Safety Results 83
7.3.1 Deaths 83
7.3.2 Nonfatal Serious Adverse Events 84
7.3.2.1. Major Bleeding 84
7.3.2.2. Summary of non-bleeding SAEs 100
7.3.3 Dropouts and/or Discontinuations 101
7.3.4 Significant Adverse Events 102
7.3.5 Drug induced liver injury 102
7.4 Supportive Safety Results 111
7.4.1 Common Adverse Events 111
7.4.2 Laboratory Findings 113

7.4.3 Vital Signs 113
7.4.4 Electrocardiograms (ECGs) 113
7.4.5 Special Safety Studies/Clinical Trials 113
7.4.6 Immunogenicity 113
7.5 Other Safety Explorations 113
7.5.1 Dose Dependency for Adverse Events 113
7.5.2 Time Dependency for Adverse Events 113
7.5.3 Drug-Demographic Interactions: Eldery 114
7.5.4 Drug-Disease Interactions: Renal impairment 115
7.6 Additional Safety Evaluations 116
7.6.1 Human Carcinogenicity 116
7.6.2 Human Reproduction and Pregnancy Data 116
7.6.3 Pediatrics and Assessment of Effects on Growth 117
7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound 117
7.7 Interruptions for elective surgeries/procedures 119

9 APPENDICES 122

9.1 Literature Review/References 122
9.2 Labeling Recommendations 123
9.3 Advisory Committee Meeting 123
9.4 Efficacy of Warfarin 123
9.5 Rankin Scale 128
9.6 RE-LY protocol additional information 129
9.6.1. Full Inclusion/Exclusion Criteria 129
9.6.2. Liver abnormality follow-up 131
9.7 Additional information on FDA liver review 132
9.9 Timing of events following medication discontinuation 134
9.10 RE-LY Follow-up visit CRF 136

Table of Tables

Table 1. Definitions of terms 10
Table 2. Analyses of net benefit 11
Table 3. Net benefit: event rate per subject-year follow-up 12
Table 4. Event rate per subject-year follow up in dabigatran treatment arms 13
Table 5. Dabigatran etexilate mesylate product information 17
Table 6. Regulatory advice 18
Table 7. Numbers of subjects identified by quality checks 21
Table 8. Additional outcome events identified by quality checks 21
Table 9. Sites closed for cause by sponsor 22
Table 10. Events at site 251 23
Table 11. Sites for which DSI received complaints 23
Table 12. Key pharmacokinetic attributes 28
Table 13. Nomogram for initiating warfarin 32
Table 14. Nomogram for warfarin maintenance 32
Table 15. Sponsor's algorithm for stopping dabigatran before surgery 33
Table 16. Definitions of key efficacy outcome events 35
Table 17. Meta-analyses of historical placebo-controlled trials 37
Table 18. RE-LY protocol amendments 39
Table 19. Demographics historical warfarin trials vs. RE-LY 45
Table 20. Stroke incidence per 100 subject-years in historical trials 45
Table 21. Demographics and stroke incidence in RE-LY, ACTIVE W and SPORTIF trials 46
Table 22. Baseline demographics 49
Table 23. Baseline medication use 51
Table 24. Disposition of subjects 52
Table 25. Number of subjects with strokes/SEE 54
Table 26. Strokes excluded by the statistical analysis plan 54
Table 27. Hazard ratios for stroke/SEE 55
Table 28. "As treated" analysis of the primary endpoint 56
Table 29. Yearly event rate for strokes and SEE 56
Table 30. Hazard ratios for components of primary endpoint 57
Table 31. Investigator-reported Rankin scores at 3-6 months 57
Table 32. Hazard ratios for secondary endpoints 58
Table 33. Yearly event rate (%) for stroke,SEE, PE, MI and vascular death 58
Table 34. Number of deaths by treatment arm 59
Table 35. Deaths excluded by the sponsor’s statistical analysis plan 59
Table 36. Hazard ratios for all cause mortality 60
Table 37. Adjudicated and investigator-reported cause of death 61
Table 38. Results of vital status queries* 62
Table 39. Changes in the use of proton pump inhibitor therapy during RE-LY 65
Table 40. Proton Pump Inhibitor use and the risk of ischemic stroke 65
Table 41. Aspirin use and the risk of ischemic stroke 66
Table 42. Phase 2 studies in patients with atrial fibrillation 67

Table 43. Incidence of secondary efficacy endpoints in PETRO-EX (1160.42)..... 68
Table 44. Interruptions of study medication..... 70
Table 45. Mean percent of time INR 2 to 3..... 71
Table 46. Mean percent of time INR>4 71
Table 47. Mean percent of time INR<2 72
Table 48. Mean percent of time INR <1.5 72
Table 49. Analyses by quartile of center-level INR control 73
Table 50. Investigator-reported vs. adjudicated strokes, TIAs and SEE..... 76
Table 51 Investigator-reported vs. adjudicated major bleeds 77
Table 52. Review of adjudicated SEE 78
Table 54. Relative and absolute risk by vitamin K antagonist use..... 94
Table 55. Risk of bleeding compared to warfarin subjects with INR in range (2-3) ≥ 65% of the time 95
Table 56. Yearly event rate of major bleeds by medication use during the study..... 96
Table 57. Yearly event rate of major bleeds by concomitant p-gp inhibitor during treatment period safety set 97
Table 58. Location of adjudicated major bleeds 98
Table 59. Risk of serious and any GI bleed..... 99
Table 60. Reason given for reporting event as SAE 100
Table 61. Liver test abnormalities in randomized population..... 104
Table 62. Summary of severity (SEV) of DILI injury scores..... 106
Table 63. Summary of likelihood (LIK) of DILI injury scores..... 106
Table 64. Liver test ratios in probable DILI subject 107
Table 65. Premature discontinuations with elevated aminotransaminases 108
Table 66. Three postmarketing cases under review..... 109
Table 67. Frequency of ALT monitoring in treated subjects, n (%)..... 110
Table 68. Frequency of dyspepsia and gastritis 111
Table 69. Frequency of dyspepsia and gastritis by aspirin use 112
Table 70. Frequency and yearly event rate of major bleed in elderly (age ≥ 75 years) 114
Table 71. Net benefit comparison of dabigatran doses in elderly..... 115
Table 72. Frequency and yearly event rate for major bleeds by baseline renal function 116
Table 73. Frequency and yearly event rate for stroke/SEE by baseline renal function 116
Table 74. Corrective therapies used in subjects with adjudicated major bleed 117
Table 75. Corrective therapies used for adjudicated major bleeds in subjects that died 118
Table 76. Corrective therapies used for adjudicated major bleeds in subjects that did not die 119
Table 77. Summary of bridging therapy for subjects with interruptions of anticoagulant for surgery/procedure..... 119
Table 78. Summary of surgery/procedures for subjects used pre-procedural bridging therapy 120
Table 79. Summary of outcome events for subjects without bridging therapy for surgery/procedure..... 121

Table 80. Summary of outcome events for subjects using emergency procedure for surgery/procedure 121
Table 81. Rankin Scale 128
Table 82. Completeness and Information scores for 55 liver cases 133
Table 83. Strokes or SEEs occurring off of therapy 134
Table 84. Major bleeds occurring off of study medication 135

Table of Figures

Figure 1. Chemical structure dabigatran etexilate mesylate 16
Figure 2. Overview of dataflow for subjects with potential events 20
Figure 3. Relationship between dabigatran (BIBR 953) concentration and aPTT, ECT, Thrombin time, and INR 26
Figure 4. ECT and APTT and the probability of a life-threatening bleed within 1 year in RE-LY 27
Figure 5. Days of follow- up based on pulse data 53
Figure 6. Kaplan Meier estimate of time to first stroke/SEE 55
Figure 7. Stroke/SEE hazard ratios by baseline characteristics 64
Figure 8. Percent time in therapeutic range vs. frequency of monitoring 74
Figure 9. Events by frequency of monitoring and level of INR control 75
Figure 10. Days to last medication 82
Figure 11. Time to first major bleed 88
Figure 12. Time to first life threatening bleed 89
Figure 13. Time to first GUSTO severe bleed 90
Figure 14. Time to first ICH 91
Figure 15. Dabigatran 110 mg v. warfarin subgroup analysis 92
Figure 16. Dabigatran 150 v. warfarin subgroup analysis (baseline demographics) 93
Figure 17. Time to first major bleed, warfarin subjects with INR 2-3 ≥ 65% of the time. 95
Figure 18. Time to first major GI bleed 99
Figure 19. Dabigatran concentrations in four subjects during a major bleed (red) and not during a major bleed (blue) 100
Figure 20. Maximum ALT vs. maximum total bilirubin per subject 103
Figure 21. Days to reach potential Hy's criteria (n=25) 105
Figure 22. Regional population in RE-LY 110
Figure 23. Time to first dyspepsia/gastritis 112
Figure 24. Impact of age on major bleeding in subjects with normal renal function 114
Figure 25. Impact of renal function on major bleeding in subjects less than 65 years old 115

1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

Dabigatran should be approved for the prevention of stroke and systemic embolism in patients with atrial fibrillation. The 150 mg dose of dabigatran should be approved but not the 110 mg dose. A superiority claim over warfarin should not be granted.

1.2 Risk Benefit Assessment

Reviewer's comment: This section focuses on key analyses related to net benefit. A more thorough discussion of RE-LY's efficacy and safety findings, the adequacy of anticoagulation in the warfarin arm, the PROBE design and effects on mortality can be found in the Reviews of Efficacy and Safety (Sections 6 and 7, respectively).

Dabigatran etexilate is an orally available, reversible, direct thrombin inhibitor with a proposed indication for the prevention of stroke and systemic embolism in patients with atrial fibrillation. In support of this indication, the sponsor conducted the RE-LY trial, a large (~18,000 subjects), randomized, non-inferiority study of unblinded warfarin administration and blinded administration of two doses of dabigatran (110 mg and 150 mg). RE-LY's primary endpoint was a composite of adjudicated stroke and systemic embolism. The sponsor's primary analysis, conducted on the ITT population, established efficacy. Compared to warfarin treated subjects, the HR was 0.66 (95% CI 0.53 to 0.82, p<0.003 for superiority) in the dabigatran 150 arm and 0.91 (95% CI 0.74 to 1.11, p<0.0001 for non-inferiority) in the 110 arm.

Bleeding was the only important safety concern that we identified in RE-LY. Relative to warfarin, dabigatran 150 mg was not associated with an increased risk of adjudicated major bleeds (HR of 0.93, 95% CI 0.81, 1.07) whereas dabigatran 110 mg was associated with fewer major bleeding events (HR of 0.80, 95% CI 0.68, 0.90, p<0.003).[1] How a major bleed, as defined in RE-LY (see table below), compares in clinical significance to a stroke is questionable. To assess the net benefit of dabigatran (relative to warfarin, and the two doses relative to one another), a finer classification of both types of events is perhaps needed.

The sponsor defined subtypes of adjudicated bleeding and stroke events (e.g., life threatening bleeds, GUSTO-severe, intracranial hemorrhage [ICH], disabling and fatal strokes) using information submitted by investigators. There are limitations to this approach. Investigators may not have uniformly applied or reported the necessary

1 The RE-LY definition of major bleed is the same as ISTH (International Society on Thrombosis and Haemostasis).

information to create the classification. For example, Rankin scores[2], used to define the severity of a stroke, were not consistently reported by site investigators. It is also not clear how investigators defined a symptomatic bleed or whether or not investigators used similar criteria. Such limitations impose a level of imprecision on the analyses of net benefit that follow and future development programs should perhaps strive to implement a more uniform and formal process for identifying those events of greatest clinical importance.

Table 1. Definitions of terms

Term	Definition
Adjudicated major bleed	Satisfying at least one: bleeding associated with a reduction in hemoglobin of at least 2 grams per deciliter or leading to a transfusion of at least 2 units of blood or packed cells; symptomatic bleeding in a critical area or organ (intraocular, intracranial, intraspinal or intramuscular with compartment syndrome, retroperitoneal bleeding, intra-articular bleeding or pericardial bleeding)
Adjudicated life-threatening bleed (sub classification of major bleed)	An adjudicated major bleed meeting at least one of the following criteria: fatal; symptomatic intracranial bleed; reduction in hemoglobin of at least 5 grams per deciliter; transfusion of at least 4 units of blood or packed cells, associated with hypotension requiring the use of intravenous inotropic agents; required surgical intervention
GUSTO severe	An adjudicated ICH event; An adjudicated major bleed with at least one of the following criteria: associated with hypotension requiring use of intravenous inotropic agents; required surgical intervention to stop bleeding
ICH	Includes adjudicated hemorrhagic stroke or adjudicated major bleed that was symptomatic intracranial
Adjudicated fatal or disabling stroke	Adjudicated stroke with initial Rankin* score of 3 or greater

*The Rankin scale runs from no symptoms (0) to death (6). A Rankin score of 3 represents moderate disability (requires some help, but able to walk unassisted); a copy of the scale is provided in the appendix.

In the analyses of “net benefit” shown below, dabigatran’s effects on various composite endpoints (composites of different types of bleeding, stroke and non-CNS systemic embolism events) were explored. These composite endpoint analyses suggest a favorable profile for dabigatran relative to warfarin. With respect to the two doses of dabigatran, no clear and consistent differences are seen between the 150 mg and 110

2 The reported Rankin scores in this review are based on the Modified Rankin Scale; an overview of this scale can be found in the appendix.

mg dose using these definitions of "net benefit". As shown below, net benefit does not strongly or consistently favor one or the other dabigatran arm; the confidence intervals for the 150 mg to 110 mg comparisons are also, for the most part, broad and cross one, raising questions about which dabigatran dose better balances safety against efficacy.

Table 2. Analyses of net benefit

Net Benefit		**D110 vs. warfarin**	**D150 vs. warfarin**	**D150 vs. D110**
Adjudicated life threatening bleed or stroke/SEE	HR	0.82	0.77	0.94
	95% CI	0.71, 0.96	0.66, 0.90	0.80, 1.11
	p-value	0.01	0.001	0.47
Adjudicated life threatening bleed or disabling or fatal stroke	HR	0.81	0.80	0.99
	95% CI	0.68, 0.96	0.68, 0.96	0.83, 1.19
	p-value	0.02	0.01	0.94
ICH or stroke/SEE	HR	0.79	0.63	0.79
	95% CI	0.66,0.96	0.52,0.77	0.64, 0.98
	p-value	0.02	<0.0001	0.03
ICH or disabling or fatal stroke	HR	0.71	0.61	0.85
	95% CI	0.56, 0.91	0.48, 0.78	0.65, 1.11
	p-value	0.006	<0.0001	0.24
GUSTO-severe or disabling or fatal stroke	HR	0.74	0.74	1.00
	95% CI	0.60,0.91	0.60,0.91	0.81,1.24
	p-value	0.0034	0.0035	0.99
Major bleed or stroke/SEE	HR	0.87	0.88	1.01
	95% CI	0.77, 0.99	0.78, 1.00	0.89,1.15
	p-value	0.03	0.04	0.87

Analyses excluding SEE produced similar/near identical point estimates, 95% confidence intervals and p-values and hence are not shown.

Table 3. Net benefit: event rate per subject-year follow-up

Event	D110 (n=6015)		D150 (n=6076)		W (n=6022)	
	# events	%/yr	# events	%/yr	# events	%/yr
Adjudicated life threatening bleed or stroke/SEE	302	2.5	288	2.4	364	3.1
Adjudicated life threatening bleed or disabling or fatal stroke	233	2.0	234	1.9	285	2.4
ICH or stroke/SEE	195	1.6	157	1.3	243	2.1
ICH or disabling or fatal stroke	117	1.0	101	0.8	162	1.4
GUSTO-severe or disabling or fatal stroke	163	1.4	165	1.4	218	1.9
Major bleed or stroke/SEE	485	4.1	494	4.1	550	4.7

Annual event rate calculated using sponsor's study termination date and randomization date for all randomized subjects.

Dose: While the composite endpoint analyses show very similar findings for the two doses of dabigatran, these findings are reached via different pathways/effects on the bleeding vs. stroke components of the composite. The yearly event rate for all of the events shown is low and the likely imprecision in the estimate of these event rates limits conclusions about the absolute risk of one event versus another. Nonetheless, we believe these analyses suggest that the 150 mg dose provides greater net benefit than the 110 mg dose. At the 110 mg dose, the rate of important stroke events (fatal/disabling strokes) perhaps still exceeds the rates of some of the worst bleeding events (e.g., GUSTO severe bleeds and ICH). At the 150 mg dose, the point estimate for the rate of life threatening and GUSTO severe bleeds begins to meet or exceed the point estimate for the stroke rate (overall and subset adjudicated to be ischemic or of uncertain classification). At this dose, the rates of disabling and hemorrhagic strokes and ICH also move closer, suggesting that a dose greater than 150 mg might result in an increase in clinically important bleeding events that could outweigh any benefit gained from stroke reduction.

Figure 1. Event rate per subject-year follow up

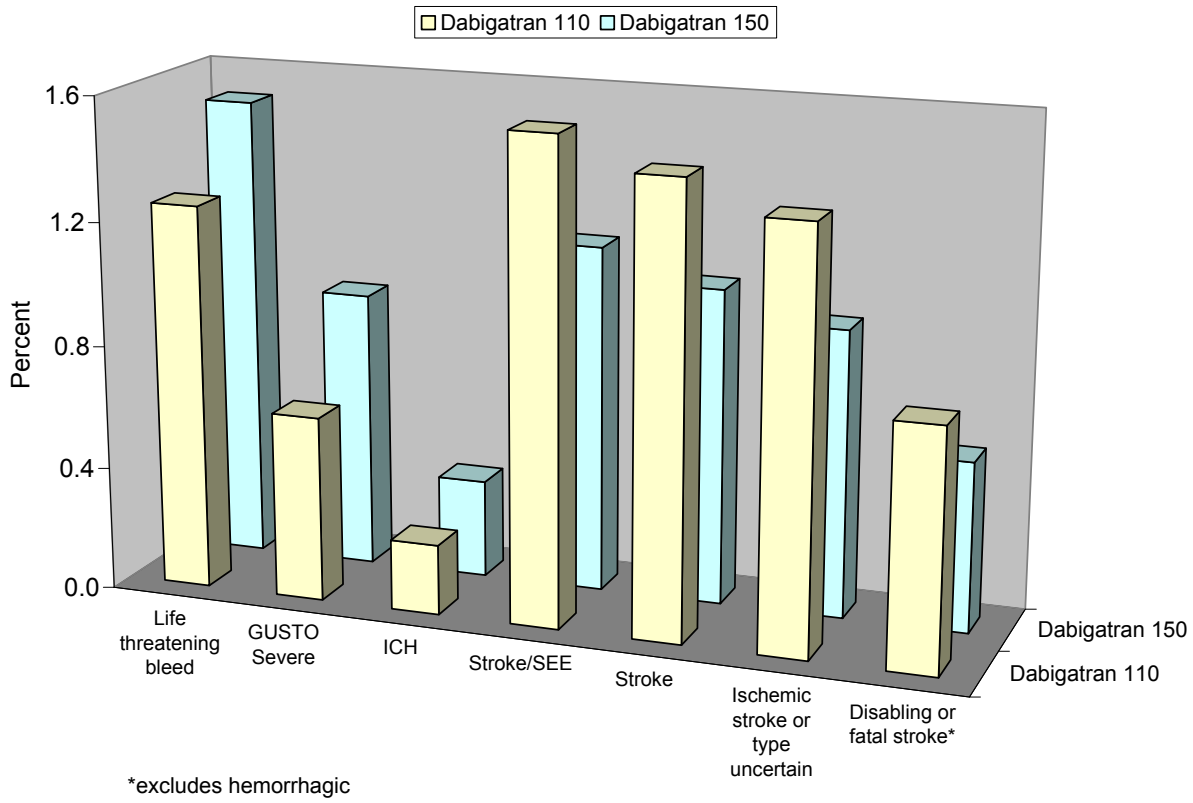


Table 4. Event rate per subject-year follow up in dabigatran treatment arms

	D110 (n=6015)		D150 (n=6076)	
Event	# events	%/yr	# events	%/yr
Life threatening bleed	147	1.2	179	1.5
GUSTO severe	74	0.6	106	0.9
ICH	27	0.2	38	0.3
Stroke/SEE	183	1.5	134	1.1
Stroke	171	1.4	122	1.0
Ischemic stroke	152	1.3	103	0.9
Ischemic stroke or type uncertain	159	1.4	111	0.9
Disabling/fatal strokes	103	0.9	76	0.6
Disabling /fatal strokes excluding hemorrhagic	92	0.8	66	0.6

Annual event rate calculated using sponsor's study termination date and randomization date for all randomized subjects.

In the proposed dabigatran label, the sponsor has approached the issue of dose by recommending the 150 mg dose, adding that "For patients with a potentially higher risk

of bleeding" a dose of 110 mg "may be considered". While this approach seems reasonable, it may be problematic.

- Though subjects with moderate renal impairment (CrCl 30 -50) had high rates of major bleeds in all treatment arms of RE-LY (high relative to the rates seen in the RE-LY population as a whole), there did not appear to be a difference in the risk of major bleeds in the 150 mg treatment arm compared to the 110 mg treatment arm. In contrast, there appeared to be a greater reduction in ischemic strokes at a dose of 150 mg than 110 mg, suggesting greater net benefit from the higher dose in this population.
- Subjects 75 years of age and older are another group perceived to be at increased risk of hemorrhage; yet, in analyses of net benefit (composites of various stroke and bleeding events), no clear advantage of the 110 mg dose over the 150 mg dose was seen.[3]

In light of these findings, the merits of adjusting dabigatran dose based on perceived bleeding risk is not immediately clear to us. While one could attempt to explore this issue by performing subgroup analyses of "net-benefit" in various RE-LY subpopulations, any findings generated by such analyses may be more reflective of chance than true dose-dependent drug effects. For this reason, we are wary of including recommendations on dose adjustment based on perceived bleeding risk in the dabigatran label and recommend that only the 150 mg dose be approved.

Efficacy vs. "Superiority": The efficacy and safety findings of dabigatran relative to warfarin are bolstered by a dose-response relationship for both bleeding and stroke events in the blinded portion of the trial (though why such a relationship should exist given the substantial overlap in exposure at the two doses is not entirely clear). The finding of a highly statistically significant reduction in the risk of stroke/SEE (p=0.0002) in the dabigatran 150 mg arm relative to warfarin is also notable but should be considered in light of RE-LY's open label design, as well as the lack of replication. In the ximelagatran experience, the stroke and systemic thromboembolism rate was numerically lower with ximelagatran in an open-label study and numerically higher in the blinded trial; according to an analysis based on risk reduction, the open label study supported the noninferiority of ximelagatran, but the blinded study did not. Whether the discrepant study findings in the ximelagatran program should serve as an example of the limitations of open-label studies, the importance of replication, or some other issue is debatable. It does raise questions, however, about granting a superiority claim based on the results of a single, open-label study. Moreover, consideration should be given to the late date at which the statistical analysis plan was finalized (essentially after all of the study data had been amassed), as well as the factors driving the highly statistically significant p-value/finding. As shown in the table below, much of the relative risk

3 This experience is perhaps not so dissimilar to the experience in BAFTA (Mant et al., 2007), a study comparing warfarin with aspirin in patients over the age of 75. In BAFTA, warfarin was superior to aspirin in the prevention of stroke (HR of 0.52, 95% CI of 0.33 to 0.80 warfarin vs. aspirin) and yet was not clearly associated with a greater incidence of major hemorrhage (HR of 0.96, 95% CI of 0.53 to 1.75 warfarin vs. aspirin).

reduction in stroke/SEE in the 150 mg arm vs. warfarin arm (and the associated p-value) is driven by subjects at sites with poorer INR control (as defined by a center-level INR below the median). Although the findings in subjects at centers achieving levels of INR control above the median are still supportive of efficacy, they are not supportive of superiority over warfarin.[4]

Table 4. Relative risk for stroke/SEE by center-level INR control

	Center-level INR control < Median		**Center-level INR control ≥ Median**	
	D110 vs. warfarin	D150 vs. warfarin	D110 vs. warfarin	D150 vs. warfarin
HR	0.86	0.57	0.96	0.77
95% CI	0.66, 1.12	0.42, 0.76	0.71, 1.30	0.56, 1.06
p-value	0.26	0.0002	0.78	0.10

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

The sponsor has proposed a REMS to mitigate the bleeding risk of dabigatran. The proposed REMS elements include a Medication Guide, Dear Health Care Professional Letter and Prescriber Brochure; these elements seem appropriate. In addition to a general discussion on the risk of bleeding, more specific topics that should be addressed in the REMS (Medication Guide, Dear Health Care Professional Letter and/or Prescriber Brochure) include:

- important issues impacted by dabigatran's short half life (relative to warfarin): the importance of patient compliance, what to do if a dose is missed, transitioning to and from dabigatran to warfarin/other anticoagulants, and the use/holding of medication in the peri-procedural/operative period;
- the effect of renal function on drug elimination (and how this impacts the use/holding of medication in the peri-procedural/operative period);
- the risk of gastrointestinal bleeding;
- use with antiplatelet agents;
- the performance of available assays in measuring the anticoagulant activity of dabigatran

The pharmacology-toxicology review has not yet been finalized. At this time, a concern has been raised for potential embryo toxicant effects in the clinical setting (based on findings in a rat study). This issue may also need to be addressed within the proposed REMS elements.

4 For further explanation of center-level based INR analyses as well as a discussion of the impact of center-level INR control on the treatment benefit of oral anticoagulant therapy, see the appendix.

1.4 Recommendations for Postmarket Requirements and Commitments

1. The mechanism behind the increased risk of gastrointestinal bleeding as well as measures that can mitigate this risk need further study.

2. In contrast to warfarin, effective interventions to stop dabigatran-related hemorrhage have not been established. Further studies should be done to determine the measures that physicians should take to stop bleeding in dabigatran treated subjects.

Postmarketing clinical studies may or may not be necessary to address the aforementioned concerns; if informative data can be obtained via *in vitro or* preclinical studies and/or post-hoc analyses of available clinical data, then this route should be pursued.

Finally, subjects with marked renal impairment (CrCl <30) were excluded from RE-LY. Whether or not further studies should be required in this populations (and if so, what types of studies) merits further discussion.

2 Introduction and Regulatory Background

2.1 Product Information

Dabigatran etexilate mesylate (proposed trade name Pradaxa) is an orally available, reversible, direct thrombin inhibitor and NME with a proposed indication for the prevention of stroke and systemic embolism in patients with atrial fibrillation. The chemical structure of dabigatran etexilate mesylate and an overview of key product attributes are provided below.

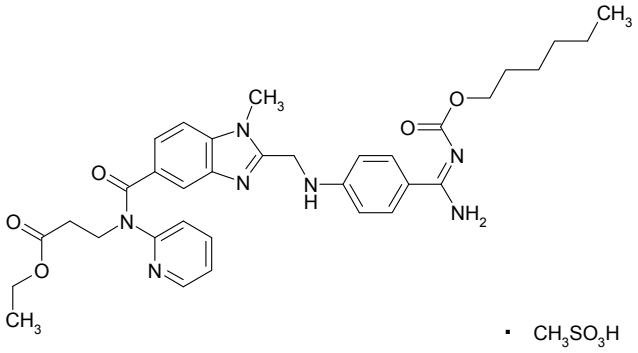


Figure 1. Chemical structure dabigatran etexilate mesylate

Table 5. Dabigatran etexilate mesylate product information

Attribute	Description
Chemical Name	β-Alanine, N-[[2-[[[(hexyloxy)carbonyl]4-amino] iminomethyl] phenyl]amino]methyl]-1-methyl-1H-benzimidazol-5-yl]carbonyl]-N-2-pyridinyl-,ethyl ester, methane-sulfonate
Appearance	Dabigatran etexilate mesylate is a yellow-white to yellow powder
Molecular Formula	$C_{35}H_{45}N_7O_8S$ [molecular weight: 723.86 (mesylate salt), 627.75 (free base)]
Dosing Regimen	150 mg taken orally, twice daily; for patients "with a potentially higher risk of bleeding," a dose of 110 mg taken orally, twice daily "may be considered"
Proposed Age Group	Adults

2.2 Tables of Currently Available Treatments for Proposed Indication

Atrial fibrillation is thought to affect approximately 2.3 million patients in North America and embolic events, primarily strokes, are an important complication of this condition. Warfarin, a vitamin K antagonist and antithrombotic agent, is approved in the United States for the prophylaxis and/or treatment of thromboembolic complications associated with atrial fibrillation. Six trials, five primary prevention and one secondary prevention, are widely referenced as establishing the efficacy of warfarin in preventing ischemic strokes in patients with atrial fibrillation (see appendix). A meta-analysis of these trials suggests that warfarin reduces the relative risk of ischemic stroke by 67% (95% CI, 54% to 77%). Though these trials clearly establish warfarin's efficacy, the safe and effective use of warfarin is limited by dietary and drug interactions and intersubject variability in exposure. Frequent blood test (INR) monitoring is needed and bleeding remains an important complication of therapy.

2.3 Availability of Proposed Active Ingredient in the United States

Dabigatran is not currently approved in the United States. Dabigatran was approved by the EMEA (EMA) in 2008 for the primary prevention of venous thromboembolic events in adults after elective total hip or knee replacement surgery.

2.4 Important Safety Issues with Consideration to Related Drugs

Dabigatran is a direct thrombin inhibitor. Approved direct thrombin inhibitors (all parenteral) include hirudin, argatroban, bivalirudin and desirudin. These agents are approved as anticoagulants for a variety of different conditions (e.g., bivalirudin for use in patients with unstable angina undergoing percutaneous intervention; desirudin as prophylaxis against deep venous thrombosis in hip replacement). Like other anticoagulants, an important safety concern with the use of these drugs is bleeding.

Ximelagatran, an oral member of this class, was also associated with hepatotoxicity, and a possible increased risk of serious coronary events, and was not approved in the United States. Bleeding and hepatotoxicity are discussed further in the review of safety.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

Table 6. Regulatory advice

Source (date of meeting or submission)	Advice from Agency
Meeting Minutes Type C Guidance Meeting (March 24, 2005)	• non-inferiority must be attained with optimal warfarin control • large safety database needed to address liver toxicity • single-dose strategy questioned (as opposed to having a parameter measurement and adjusting dose) • concern raised for ascertainment bias in identification of potential endpoint events given open-label nature of study
SPA response (July 11, 2005)	• double-blind trial preferred; more detail regarding why blinding was not feasible should be provided • warfarin control achieved in the proposed trial would need to be as good as that achieved in the historical warfarin trials; instructed to perform sensitivity analyses (for both efficacy and safety) including only warfarin patients for whom the monitoring and dosage adjustment matched “minimal specifications” • doses studied should be more widely spaced, and dose adjustment should be made based on renal function
Type C Guidance Meeting (August 18, 2008)	• late change to the SAP proposed by sponsor: testing for superiority in anticoagulant naïve patients and analysis pooling doses to test for superiority • Agency expressed significant concerns about the changes given the amount of information that was available to influence the decision to alter the statistical analysis plan • Agency reiterated that 1.38 was the recommended margin for non-inferiority
Type C Guidance Meeting (August 17, 2009)	• NDA should be submitted for rolling review; priority review was likely

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

Refuse to File
On December 15, 2009, the NDA for dabigatran was filed; on February 12, 2010, following several discussions with the sponsor regarding data integrity issues, the Agency issued a refuse to file letter. While the sponsor claimed an overall data error rate of 0.1% or less for primary outcome data and 0.25% or less for all other data, during the clinical review, a number of obvious and easily identified errors were found in data sets felt by the review team to be important for establishing dabigatran's efficacy and safety. The frequency and relative ease with which these errors were identified raised questions about the true error rate in the submitted data and undermined reviewer confidence in the data. These errors were found in two data sets examined early in the review: a data set containing information on INR and warfarin dosing and one containing information on blood transfusions (felt to be critical by the review team as the sponsor's definition of a "major bleed" was based in part on the number of units of blood transfused). With regard to the INR data, transcription, transposition and auditing errors were found in reported INR values and/or warfarin dose. The blood transfusion data set contained inaccurate data on the number of transfusions received. For example, the data set incorrectly reported that three subjects received 92 U, 82 U and 62 U, respectively, of a blood product in one day when these subjects had in fact received 2 U each. The errors were thought to stem in part from the use of optical character recognition (OCR) without a subsequent check of the scanned data (such errors occurred in both data sets). The second type of error (found in the INR data set) was a type of error that could have been detected by auditing/performing additional checks of the data. A transposition error had been made by the clinical site whereby the warfarin doses had clearly been transposed with the INR values.

As a result of the refuse to file letter and following agreement with the review team on a plan, the sponsor engaged in additional data quality checks to establish the integrity of the submitted data. These cross-checks focused on data critical for the establishment of efficacy and safety and included: cross-checks of different case report forms for possible inconsistencies in reporting outcome events; plausibility and range checks of particular CRFs; and sampling checks to evaluate the accuracy of the optical character recognition (OCR) process originally used to capture the data, including double-data entry of particular CRF pages. According to the sponsor, all SAE narratives were also reviewed for potential endpoint events.

According to the sponsor, these checks identified 3848 findings in 3054 subjects requiring further review. These events were reviewed by unblinded "Tier 1" reviewers who were instructed to look for evidence of an unreported outcome event in the materials provided (CRFs, narrative, adjudication documents of other events). If there was additional evidence of an outcome event, or if the reviewer suspected an event

based on the clinical course of the subject or some other evidence, the case was escalated as a possible outcome event. Unblinded Tier 2 reviewers, individuals involved with RE-LY or familiar with the trial, reviewed the escalated cases and decided whether or not the event should be pursued as a potential outcome event (i.e., sent to the data center for distribution to the site). Additional events were identified via unblinded Tier 2 reviewer over-reads of a subset of events not escalated by Tier 1 reviewers.

Reviewer's comment: How the subset of events were selected for over-read is not clear. According to the April 19, 2010 resubmission (page 33), "This over-read looked at a minimum of 10% of negative cases from each Tier 1 reviewer, trying to select representative cases. In addition, the Tier 2 reviewers examined additional negative cases from Tier 1 reviewers who, in their judgment, may not have been consistent in their application of the review guidelines."

Events of interest identified by Tier 2 reviewers were sent to the data center for verification that the event had not been previously reported. Cases that had not been previously reported were sent to the study site for review. Sites were to indicate if an event had occurred. Events confirmed by the study site (and also events at sites that did not respond to the inquiry) were sent for adjudication. The adjudication process was similar to that used in the original protocol- adjudication was to be conducted by two reviewers blinded to treatment assignment with a third reviewer used when the initial reviewers disagreed. An overview of the process implemented by the sponsor as well as the number of potential events identified/escalated at each stage of the review is shown in the figure and table below. Across the treatment arms, a similar proportion of events were escalated at each stage of the review.

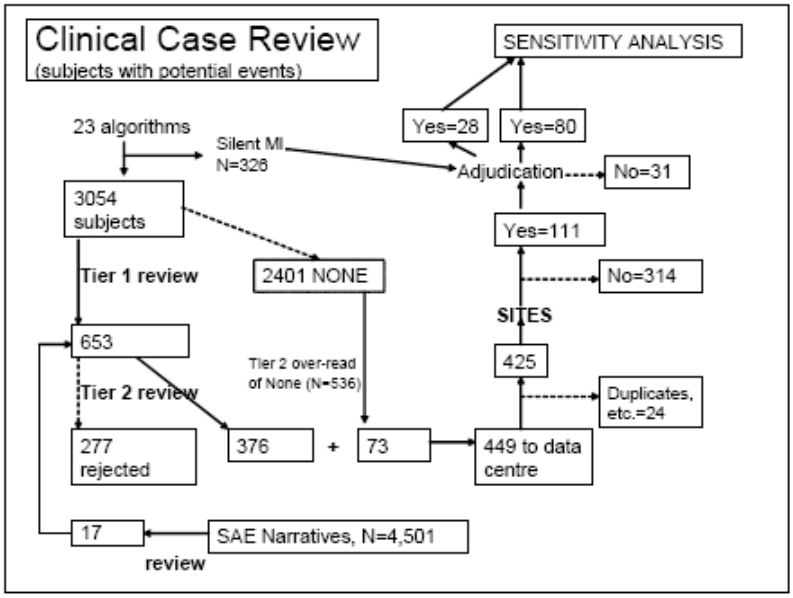


Figure 2. Overview of dataflow for subjects with potential events

[Source: Sponsor Information Amendment dated April 19, 2010, Figure 4.1.1]

Table 7. Numbers of subjects identified by quality checks

	DE 110mg bid N (%)	DE 150 mg bid N(%)	Warfarin N(%)	Total N(%)
Reviewed by Tier 1	986 (100.0)	1039 (100.0)	1029 (100.0)	3054 (100.0)
Reviewed by Tier 2	377 (38.2)	406 (39.1)	406 (39.5)	1189 (38.9)
Submitted to Data Center	147 (14.9)	158 (15.2)	144 (14.0)	449 (14.7)
Submitted to Site	135 (13.7)	153 (14.7)	137 (13.3)	425 (13.9)
Submitted to Adjudication	31 (3.1)	39 (3.8)	41 (4.0)	111 (3.6)
Adjudicated Subjects with Outcome Events	22 (2.2)	29 (2.8)	29 (2.8)	80(2.6)

[Source: Sponsor Information Amendment dated April 19, 2010, Table 4.1.7]

An overview of the adjudicated events by treatment arm is shown in the sponsor's table below. Few additional efficacy endpoint events were reported. Of the 68 newly identified adjudicated major bleeds, 32 were identified by programmed checks of hemoglobin drops of > 2 g/dL, 19 were identified by programmed checks of the blood transfusion data, 11 were identified by programmed checks comparing AE terms to potential outcome event terms, three were identified by a free text search of reported admission reasons, and three were identified by other checks.

Table 8. Additional outcome events identified by quality checks

	DE 110 N	DE 150 N(%)	Warfarin N(%)	Total N(%)
Stroke	0	0	1	1
SEE	0	0	1	1
Death	0	0	0	0
TIA	3	1	1	5
MI	1	0	3	4
PE	0	0	1	1
Major Bleed	18	28	22	68
Subtotal Subjects	**22**	**29**	**29**	**80**
Silent MI	11	8	9	28
Total Subjects	**33**	**37**	**38**	**108**

[Source: Sponsor Information Amendment dated April 19, 2010, Table 1.1]

With regard to the INR and warfarin dose data, these dose were manually reentered; the error rate in the originally submitted data was found to be ~2%. As a result of the manual re-entry process, a total of 3,743 of 174,773 dose values changed and 3,856 of 175,190 INR values changed. Forty-seven records were added and 59 records were removed.

Reviewer's comment: Tier 1 and 2 reviewers were unblinded to treatment assignment and some Tier 2 reviewers were "involved with RE-LY" and hence ascertainment bias is possible. Throughout the subsequent FDA Clinical Review, numerous checks were done, comparing the information reported in key resubmitted data sets to the CRF documents themselves. With the exception of errors in the disposition data (see Section

6.1.3), the data contained in the resubmitted data sets appear to match the data contained in the CRFs. Hence, at this time, we think the data are of sufficient quality to allow substantive review. Whether or not there were additional events that were not reported by investigators is an issue that the DSI audits will address.

3.2 Compliance with Good Clinical Practices

See also discussion under section 3.1.

Sites closed for cause by the sponsor
According to the sponsor, eight RE-LY study sites were closed for cause; these sites randomized a total of 166 subjects. At this time, DSI has inspected seven of these sites and recommended that data from a total of 43 subjects not be used to support the application. The inspection did not support the sponsor's allegation at one site (251). According to the TSAP events, events occurring at these sites prior to study site closure (defined as the date the site was notified of closure) are included in efficacy analyses (page 22 of TSAP). Subjects at sites closed for cause were not followed up for vital status.

Table 9. Sites closed for cause by sponsor

Site	Subjects (screened/ randomized)	DSI findings
108	41/31	OAI (letter/inspection findings pending)
128	8/6	Inspection confirmed sponsor's allegations; DSI recommended exclusion of subject 002 (no evidence AF on ECG)
146	10/4	NAI; Though site closed for lack of clinical investigator involvement in study, protocol violations and consent irregularities (IRB had withdrawn approval prior to sponsor site closure), inspection found that there had been substantial efforts to reconcile deficiencies and respond to queries
354	7/7	VAI: Investigator failed to maintain adequate case histories; data may be used to support application
251	68/52	VAI: Inspection did not support sponsor's allegations; data may be used to support application
265	60/37	OAI: Warning letter; data should not be used to support application
276	7/5	OAI: Warning letter; data should not be used to support application
6	27/24	Confirmed sponsor allegations for GCP violations, and resulting site closure

With regard to site 251, the sponsor alleged that their audit revealed missing or inconsistent study data and source documentation, protocol violations

(inclusion/exclusion criteria) and patient safety related issues including failure to report SAE and non-serious events to the sponsor, INR monitoring, patients bleeds and drug accountability issues (several subjects took drug beyond the expiration date). According to what was written in the EIR by the field investigators, the inspection found “no evidence to support the sponsor’s allegations,” despite inspection of documents for all 52 randomized subjects.

The table below shows the number of discontinuations, primary endpoint events, deaths and SAEs reported at site 251. The TTR reported at site 251 was 64.9%.

Table 10. Events at site 251

	Number (%) with event		
	Dabigatran 110 (N=17)	**Dabigatran 150 (N=17)**	**Warfarin (N=18)**
Discontinuations	4	6	7
Stroke or SEE	0	1	0
Death	1	0	0
SAE	14	0	4

Regarding "test article accountability," the DSI inspector at site 251 also commented that documentation left on site by the sponsor monitors was "inadequate, inaccurate and much of it was illegible." DSI plans to investigate the issue further with an audit of the sponsor/monitor and will also obtain additional data during their clinical investigator site audits.

Other sites for which DSI received complaints
In addition to the sites closed for cause by the sponsor, DSI received complaints for an additional three sites; information regarding two of these sites is provided in the table below. The third complaint was a notification from the sponsor: a Clinical Investigator had informed the sponsor that a study coordinator at his site had used a professional license and CV that belonged to somebody else.

Table 11. Sites for which DSI received complaints

Principle Investigator	**Site**	**Subjects (screened/ randomized)**	**DSI findings**
(b) (6)	(b) (6)	10/9	(b) (6)
Pilcher, George	232	44/43	VAI (data can be used in support of application)

Sites selected for audit following NDA submission
Six investigator sites were selected for audit; four foreign and three in the United States. A for-cause inspection was conducted at an additional site (Tonkin, site 351). No deficiencies were noted by the field investigator at the Ezekowitz site (site 32). A VAI was issued at the Tonkin site which had enrolled 5 subjects; it was concluded that the data could be used to support the application. At this time, no other inspection reports have been finalized. In addition to these sites, audits of the sponsor and academic research organization are also planned.

Reviewer's comment: The inspections have not yet been completed; however at this time, results of DSI audits suggest that there was compliance with good clinical practices and the trials were conducted in accordance with accepted ethical standards.

3.3 Financial Disclosures

Fourteen investigators enrolling subjects from 13 clinical sites were listed as holding financial interests requiring disclosure; all reported significant payments with a cumulative monetary value of $25,000 or more made by the sponsor to the investigator or investigator's institution exclusive of the costs of conducting the clinical study. Collectively, these sites enrolled 418 subjects (2.3% of subjects) and accounted for 2.5% of adjudicated primary endpoint events (stroke or SEE) and 3.5% of deaths. One of 13 sites at which investigators were reported to hold financial interests requiring disclosure was selected for audit.

Reviewer's comment: The applicant has adequately disclosed financial arrangements. These arrangements do not raise questions about the integrity of the data.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

Minor CMC issues have been communicated to the sponsor, however no significant efficacy or safety issues have been identified at this time. See section 2.1 for an overview of the drug substance/product.

4.2 Clinical Microbiology

Not applicable.

4.3 Preclinical Pharmacology/Toxicology

Dr. Harlow's draft review dated August 12, 2010, judged dabigatran approvable from a nonclinical perspective. Most of the observed toxicities were attributable to the pharmacodynamic effect of dabigatran or its active metabolite (e.g., decreases in hemoglobin, hematocrit and red blood cells). Other notable findings:

- In rat studies, dabigatran acted as an embryo toxicant. Dabigatran decreased the number of implantations, decreased the number of viable fetuses, increased the resorption rate, increased the post-implantation loss, and increased the number of dead offspring when given at doses of 70 mg/kg (about 2.3 times the MRHD of 300 mg/day on a mg/m^2 basis) to female rats prior to mating to implantation, from implantation to the end of organogenesis, and from implantation to weaning. Dr. Harlow has recommended specific language for describing these effects in the label.

- Dabigatran was not carcinogenic in mice and rats (doses were 3.2, and 6.5 times the MRHD) for up to two years, however an increased incidence of liver necrosis in all treated groups was observed in the rat carcinogenicity study. This was seen after a lifetime of treatment and without an accompanying increase in liver tests (AST/ALT). In contrast, no liver necrosis was observed in the 26- or 52-week monkey studies.

Reviewer's comment: The clinical significance of the liver findings in the rat carcinogenicity studies is unclear.

4.4 Clinical Pharmacology

No significant efficacy or safety issues have been identified at this time. Key pharmacodynamic and pharmacokinetic characteristics are described below. For a more comprehensive overview, see the Clinical Pharmacology Review.

4.4.1 Mechanism of Action

Dabigatran etexilate, a prodrug, is converted to dabigatran, the active metabolite. Dabigatran is a direct thrombin inhibitor that reversibly inhibits fibrin-bound thrombin, free circulating thrombin and thrombin-induced platelet aggregation.

4.4.2 Pharmacodynamics

The relationship between dabigatran plasma concentration and various pharmacodynamic markers in healthy subjects is shown in the sponsor's figure below. Of these tests, ecarin clotting time (ECT) values appear to correlate best with plasma concentrations; ECT appears to be linearly related to dabigatran concentration and

does not appear to reach a maximum/plateau at higher concentrations

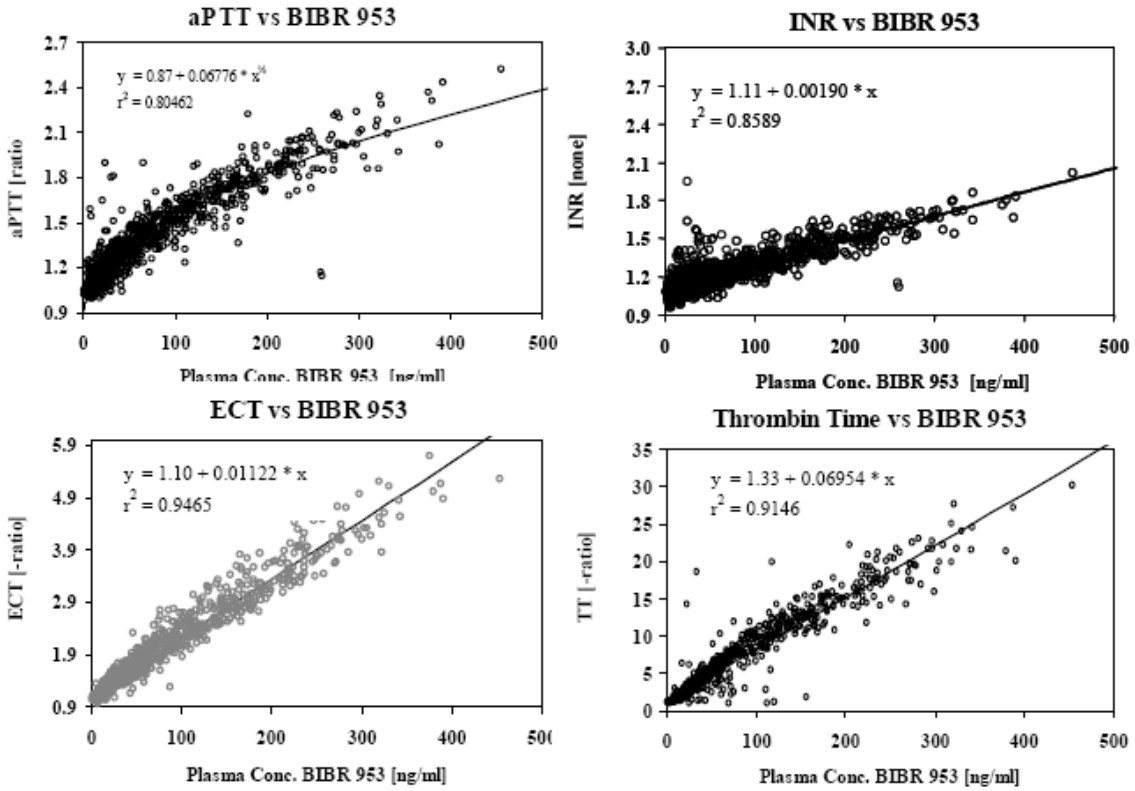


Figure 3. Relationship between dabigatran (BIBR 953) concentration and aPTT, ECT, Thrombin time, and INR

[Source: Sponsor's Clinical Overview (module 2): Figure 2.5.3.2:1]

APTT and ECT were measured in RE-LY at one month post randomization in dabigatran subjects. While both APTT and ECT were significant predictors of life-threatening bleeds (see next figure), ECT performed better overall.

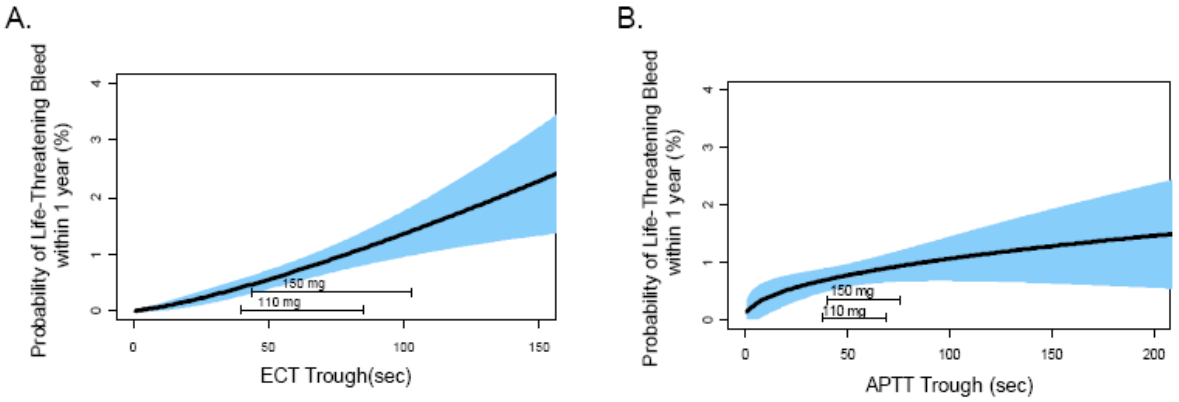


Figure 4. ECT and APTT and the probability of a life-threatening bleed within 1 year in RE-LY

[Source: Email correspondence from Dr. Krudys FDA Pharmacometrics Reviewer]
The shaded region represents the 95% CI; the bars on the bottom of the plot region represent the 10th to 90th percentiles of observed dabigatran predose concentrations in the RE-LY trial.

Reviewer's comment: Of the assays studied, ECT appears to be the best marker of bleeding risk and ECT should be recommended for monitoring the anticoagulant activity of dabigatran. Ecarin chromogenic assays (ECA) have also been developed and, based on a preliminary review of the literature, may also be suitable[5].

4.4.3 Pharmacokinetics

Renal function appears to be the most important parameter influencing the pharmacokinetics of dabigatran. In a Phase I study, exposure levels were ~3-fold higher in moderate renal impairment (CrCl 30 - < 50 mol/min) compared to normal renal function (> 80 mol/min). The difference between these two classes was ~2.3-fold in RE-LY. In subjects with severe renal impairment (CrCl <30 mol/min), the mean AUC of dabigatran was increased ~6.3 compared to normal renal function.

Key pharmacokinetic attributes are summarized in the next table.

5 An ecarin chromogenic assay, in which ecarin is added to a plasma sample and meizothrombin generation is measured using a chromagenic substrate, has been used to measure the anticoagulant activity of direct thrombin inhibitors and, according to some literature, may offer advantages over ECT (Lange et al., 2004).

Table 12. Key pharmacokinetic attributes

Parameter	Comments
Bioavailability	3 to 7%, pH dependent
Cmax and AUC	Cmax obtained 0.5 to 2.0 hours post administration; dose proportional increase in Cmax and AUC (after single oral doses from 10 to 400 mg); average ratio of accumulation of 150 mg dose with repeated dosing 1.4 and 1.3-fold for AUC and Cmax, respectively; after repeated dosing, steady state reached by Day 3 of treatment
High Fat Meal	No effect on bioavailability, delayed time to peak plasma concentration (~2 hrs)
Distribution	34-35% plasma protein binding; volume of distribution 60-70 L
Elimination	Primarily renal (85% urine), eliminated primarily unchanged at a rate of ~100 mol/min; ½ life ~10-11 hrs; ~15 and ~18 hours in mild and moderate renal impairment respectively; ½ life is independent of dose; 61 to 68% of systemic dabigatran removed by dialysis
Metabolism	Dabigatran etexilate rapidly converted to dabigatran (active form) by esterase catalyzed hydrolysis; neither dabigatran etexilate nor dabigatran are metabolized by the cytochrome P450 system. Dabigatran etexilate (but not dabigatran) is a substrate for the efflux transporter protein p-glycoprotein.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

According to the sponsor, dabigatran has been studied in 40 phase I studies, six completed phase 2 studies and four completed phase 3 trials. These studies were conducted either as part of the atrial fibrillation development program or for other indications. An overview of phase 2 studies conducted in patients with atrial fibrillation is provided in section 6.1.8. RE-LY, a phase 3 trial conducted in support of the proposed indication, is discussed in section 5.3. RE-LY-ABLE, a long term multi-center extension of dabigatran treatment in patients with atrial fibrillation who completed the RE-LY trial, is currently underway and is not described further in this review.

5.2 Review Strategy

The Clinical Review focused on the design and conduct of RE-LY and the resulting data. Efficacy was reviewed by Dr. Thompson; Safety was addressed by Dr. Beasley.

5.3 Discussion of Individual Studies/Clinical Trials

In support of the proposed indication, the sponsor conducted a single phase 3 trial titled "Randomized Evaluation of Long term anticoagulant therapy comparing the efficacy and safety of two blinded doses of dabigatran etexilate with open label warfarin for the prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation: prospective, multi-centre, parallel-group, non-inferiority trial (RE-LY)." An overview of the study protocol, as laid out in the sponsor's finalized protocol dated September 12, 2005 is provided below. Important revisions enacted by protocol amendments accompany the relevant sections of text; these amendments are also summarized at the end of this section.

RE-LY Overview

5.3.1 Study Design and Objectives

RE-LY was a randomized, active controlled, multi-center, non-inferiority study of open-label warfarin administration and blinded dabigatran administration at two doses (110 and 150 mg). RE-LY was an event-driven trial and the stated primary objective was to demonstrate the efficacy and safety of dabigatran in patients with non-valvular atrial fibrillation for the prevention of stroke and systemic embolism.

5.3.2 Study Duration/Dates

December 22, 2005 to March 15, 2009 (Final close out visit period- December 16, 2008 to March 15, 2009, visits 1-3 months earlier also accepted as normal study closeout)

5.3.3 Study Sample Size and Power Considerations

The study sample size was initially set at 15,000 subjects. Based on an assumed event rate of 1.6%/year (equal across treatment arms), with 5000 subjects per treatment group and a total of 450 events, each comparison would have ~90% power to conclude the non-inferiority of dabigatran to warfarin at a one-sided alpha=0.025 (without adjusting for multiple comparisons). The trial was expected to have ~84% power to declare non-inferiority for both dabigatran doses to warfarin. Protocol Amendment 2 dated 2007 increased the sample size to 18,000.
Reviewer's comment: The amendment noted faster than anticipated enrollment and cited the need to "maintain the statistical power in case of event rate < 1.6% within the original study time line." Correspondence between those conducting the trial and BI cite an opportunity to increase the power to determine whether both dabigatran doses are noninferior to warfarin. [6.]

[6] Letter to M. Haehl (BI) from S. Connolly, M. Ezekowitz, L. Wallentin and S. Yusef, dated April 19, 2007

5.3.4 Study Population

Key enrollment criteria included non-valvular atrial fibrillation and one of the following additional risk factors: previous ischemic stroke, TIA, or systemic embolism, left ventricular ejection fraction < 40, symptomatic heart failure (NYHA class II or greater), age ≥75 years, or age ≥65 with either diabetes mellitus, history of coronary artery disease, or hypertension.

A diagnosis of atrial fibrillation was established based on:

- ECG documented AF on the day of screening or randomization (protocol Amendment 1 expanded this criterion to include ECG documented AF within one week of screening);
- A symptomatic episode of paroxysmal or persistent AF documented by 12 lead ECG within six months prior to randomization;
- Documentation of symptomatic or asymptomatic paroxysmal or persistent AF (at least 30 seconds) on two separate occasions, at least one day apart, one of which within six months prior to randomization. Electrograms (not marker channels or mode switch episodes) from pacemakers and defibrillators could be used to document only one episode of paroxysmal or persistent AF.

Patients with active liver disease, anemia (defined as a hemoglobin <10 mg/dL), severe renal impairment (eGFR < 30 mol/min), contraindication to warfarin or conditions associated with an increased risk of bleeding were excluded. For a full listing of inclusion and exclusion criteria, see Appendix 9.5.1.

To better ensure enrollment of Vitamin K naïve patients, the protocol was amended (see Amendment 1) to specify that the proportion of Vitamin K naïve subjects would be monitored at randomization by IVRS; the Operations Committee could impose additional measures (e.g. a quota system) to ensure balanced enrollment.

5.3.5 Procedures

Patients were randomized by IVRS (1:1:1) without stratification for any baseline variables. Following randomization, telephone contact was made at 2 weeks and subjects were seen at 1, 3, 6, 9 and 12 months and then every 4 months thereafter. According to the original protocol, a final follow up visit was to be performed whenever a patient terminated the study, either prematurely or according to the protocol. Protocol Amendment 2 (May 24, 2007) clarified that the final follow-up visit would be performed in subjects who terminated prematurely via withdrawal of consent or according to the protocol. At this follow-up visit, adverse events, bleeding events, efficacy events and changes in concomitant medications since the last visit were to be assessed, in addition to other assessments (physical exam, laboratory, ECG, vital signs).

5.3.5.1 Liver monitoring

Liver tests (ALT, AST, Alk. phos, bilirubin) were evaluated monthly for the first 12 months of treatment and every 4 months thereafter. After liver test data were accrued on 6000 patients exposed for at least 6 months, the frequency of abnormalities was examined and a decision was made to reduce monitoring to every 3 months in subjects randomized after September 25, 2006 (see Protocol Amendment 3). See Appendix for details of specified follow-up for elevated liver tests.

5.3.5.2 Anticoagulation initiation, maintenance and monitoring

Anticoagulation was to be stopped on the day of randomization[7]. Subjects assigned to dabigatran therapy had their study medication started (if INR<2) or held (if INR ≥ 2) until their INR was < 2 (checked every 1-3 days). Subjects assigned to warfarin therapy started warfarin if their INR was less then 3.0, continued warfarin with dose adjustment based on their current INR or switched from other anticoagulant to warfarin therapy. Protocol Amendment 1 clarified that for subjects previously taking phenprocoumon, warfarin would be started when their INR was < 2.0.

During the course of the study, INR was to be monitored at least every 4 weeks in subjects assigned to warfarin or more frequently if needed, based on the clinical judgment of the investigator. Failure to measure the INR level was to be reported as a protocol violation[8]. All dose adjustments were to be done according to usual clinical practice; a nomogram containing recommended dose changes and INR re-testing times for different INR values was also provided to investigators to assist in dose adjustment. Copies of the initiation and maintenance nomograms are provided below.

7 Protocol amendment 1 added that the exact timing for stopping anticoagulation might be adjusted based on the subject's next possible clinic visit and last INR.
8 According to the sponsor, this practice (reporting the failure to measure INR as a protocol violation) was never implemented and this requirement was removed by protocol amendment 5.

Table 13. Nomogram for initiating warfarin

DAY	INR	WARFARIN DOSE (MG PER DAY)
1	-	5
2	-	5
3	<1.5 1.5-1.9 2.0-3.0 >3.0	10 5 2-3* 0
4	<1.5 1.5-1.9 2.0-3.0 >3.0	10 7-8* 5 0
5	<2.0 2.0-3.0 >3.0	10 5 0
6	<1.5 1.5-1.9 2.0-3.0 >3.0	12-13* 10 7-8* 0
*at discretion of physician		

Lower doses: age > 75 yrs, weight < 60 kg, interacting medications known to potentiate warfarin, hepatic dysfunction, hypoproteinemia, hyperthyroid, impaired nutritional intake, increased baseline INR.

Higher doses: hypothyroid, interacting medications known to inhibit warfarin, diet rich in vitamin K.

Table 14. Nomogram for warfarin maintenance

INR	ACTION
≤ 1.5	Increase weekly dose by 15%; repeat INR in 7 – 10 days.
1.51 – 1.99	If unexplained, increase weekly dose by 10%; repeat INR in 7 – 10 days.
2.00 – 3.00**	No change
3.01 – 4.99	If INR 3.01 – 3.99 do not hold warfarin. If high on two consecutive occasions, decrease weekly dose by 10%; If INR 4.00 – 4.99 hold for 1 day; repeat INR in 7 – 10 days.
5.00 – 8.99	Hold warfarin. Consider Vitamin K 2-4 mg PO if at increased risk of bleeding. If INR still high 24 hours later, consider giving 1-2mg additional Vitamin K PO and restart at lower dose (decrease weekly dose by 15%) when INR therapeutic. Check INR weekly until stable.
≥ 9.0	Hold warfarin and give Vitamin K 5.0-10 mg PO. Monitor more frequently and repeat Vitamin K if necessary.
Serious bleeding regardless of INR	Hold dose and give Vitamin K 10 mg IV and fresh frozen plasma, recombinant Factor VIIa, or prothrombin complex concentrates depending on urgency of situation.
**If INR between 1.80 – 2.00 or 3.00 – 3.20, consider no change in with repeat INR in 7 – 10 days, for first occurrence ONLY.	

5.3.5.3 Treatment of bleeds

Major bleeds: The protocol specified that study medication should be stopped and the treatment of major bleeds left to local practice. Bleeding in subjects on warfarin was to be reversed with Vitamin K and/or fresh frozen plasma (FFP) and consideration was to be given to prothrombin concentrates or recombinant factor VIIa (if used, guidance from a coagulation expert was recommended). For bleeding in the setting of dabigatran administration, the protocol originally noted that packed cells or FFP may be administered with consideration given to the use of prothrombin complex concentrates and recombinant factor VIIa, though their role in reversing the anticoagulant effect of dabigatran was unproven. If thrombocytopenia was present, consideration was also to be given to platelet concentrates. Protocol Amendment 5 (dated August 7, 2008, over 2.5 years after study initiation) indicated that it may be possible to remove dabigatran by hemodialysis and also added that though consideration may be given to the use of FFP

in subjects who are still anticoagulated at the time of surgery, there was no evidence that this would reverse dabigatran's anticoagulant effect. For subjects on warfarin or dabigatran, re-initiation of study medication after bleeding had resolved was left to the discretion of the local investigator.

Minor bleeds: Treatment of minor bleeds was left to the discretion of the investigator. Stopping medication was not required.

5.3.5.4 Emergency and elective surgery

For emergency and elective surgery, the following was specified:

- Warfarin Treatment Group, Preoperative Phase: Patients could be managed with or without bridging anticoagulant therapy. Warfarin should be stopped 5 days before the procedure and, if the physician considers the patient to be higher risk, replaced by either low molecular weight heparin or unfractionated heparin. If INR the day before surgery is >1.4, 1 mg of oral vitamin K can be prescribed. If the INR measurement repeated the day of surgery is >1.4, postponement of surgery should be considered.
- Warfarin Treatment Group, Post Procedural Period: Anticoagulation could be started as soon as clinically feasible with IV (unfractionated) or subcutaneous low molecular weight heparin and simultaneously with oral warfarin, if possible.
- Dabigatran Treatment Groups, Preoperative Phase: Dabigatran treatment could be continued until 24 hours before surgery.
- Dabigatran Treatment Groups, Post Procedural Period: Dabigatran could be initiated as soon as clinically indicated. If oral medication is not feasible, heparinization intravenously or subcutaneously should be considered.

In a protocol amendment dated August 7, 2008, a more detailed algorithm for holding dabigatran prior to surgery was added, with the discontinuation algorithm based in part on a subject's renal function, as indicated in the table below.

Table 15. Sponsor's algorithm for stopping dabigatran before surgery

Renal function (CrCl, mL/min)	Estimated half-life in hours	Stop dabigatran before surgery	
		High risk of bleeding*	Standard risk
≥50-80	~15 (12-18)	2-3 days before	24 h prior (2 doses)
≥30 to <50	~18 (18-24)	4 days	at least 2 days (48 h)
<30	~27 (>24)	> 5 days	2-5 days

5.3.5.5 Discontinuation of study medication and follow-up of subjects

Study medication could be temporarily discontinued for procedures, diseases or diagnoses that did not permit continued treatment with study medication, the need for a

concomitant medication excluded by the study protocol or intolerable adverse events. In subjects who temporarily discontinued therapy, attempts were to be made to re-start study medication if the investigator thought it was appropriate.

Subjects who experienced a "clear, persistent contraindication" to study medication (such as a major bleeding event or non-compliance with the dosing regimen or visit schedule) or who requested withdrawal of study drug were to have their study medication permanently discontinued and followed for the duration of the study. For subjects randomized to dabigatran, dabigatran was to be held if CrCl fell to <30 mol/min and was to be re-started if CrCl rose above 30 mol/min. If the CrCl fell below 30 mol/min for a second time, dabigatran was to be permanently discontinued and the subject was to be followed until trial completion. Of note, Amendment 2 to the RE-LY study protocol (dated May 24, 2007) changed how subjects who either permanently discontinued study drug or requested to be withdrawn from study drug treatment were followed. Amendment 2 allowed clinical investigator to "negotiate a revised visit schedule should the patient be unwilling to adhere to the regular schedule." Amendment 2 also specified that these follow-up visits could occur either be by telephone or in clinic.

Reviewer's comment: In addition to these protocol-specified measures, other steps were also taken to obtain vital status information. According to the sponsor, if "it became apparent" that a normal study completion visit could not be obtained within the closeout time window, information on vital status was sought in these subjects. Vital status was to be obtained in all study subjects with the exception of those subjects enrolled from sites that were closed for cause and subjects who had withdrawn consent and, as part of the consent withdrawal, had documented in writing that they would not attend study visits and were not to be contacted (based on local regulations concerning the meaning of withdrawal of consent). Sites were directed to contact the patient or primary care provider by phone and by letter; two contacts were required before a patient was considered lost to follow up. If a patient could come in for a final follow up visit within the close out window, a normal study completion visit was conducted and the patient was not categorized as vital status only (the patient was categorized as normal study termination). In some countries, where permitted by laws, an agency was hired to establish whether a subject was alive or dead.

5.3.6 Endpoints

The primary efficacy endpoint was the incidence of stroke (including hemorrhagic) and systemic embolism.

Secondary efficacy endpoints included the incidence of:

- stroke (including hemorrhagic), systemic embolism, or all-cause mortality
- stroke (including hemorrhagic), systemic embolism, pulmonary embolism, acute myocardial infarction, or vascular deaths (including deaths from bleeding)

Efficacy outcome events were defined as shown in the table below.

Table 16. Definitions of key efficacy outcome events

Efficacy outcome	Definition
Stroke	Acute onset of a focal neurological deficit of presumed vascular origin lasting for 24 hours or more or resulting in death. The stroke is categorized as ischemic or hemorrhagic or cause unknown (based on CT or MR scanning or autopsy). Fatal stroke is defined as death from any cause within 30 days of stroke. Severity of stroke will be assessed by modified Rankin score at discharge from hospital and at 3-6 months later.
Systemic embolism	Acute vascular occlusion of the extremities or any organ (kidneys, mesenteric arteries, spleen, retina or grafts), and must be documented by angiography, surgery, scintigraphy, or autopsy.
Myocardial infarction	Depending on whether or not PCI or CABG has been performed, a myocardial infarction (MI) was defined as**:** a. In subjects not undergoing PCI or CABG, at least 2 of the following 3 criteria had to be present: i. Typical prolonged severe chest pain or related symptoms or signs (e.g., ST-changes of T-wave inversion in the ECG) suggestive of MI. ii. Elevation of troponin or CK-MB to more than the upper level of normal (ULN) or, if CK-MB was elevated at baseline, re-elevation to more than 50% increase above the previous level. iii. New significant Q-waves in at least 2 adjacent ECG leads. b. After PCI (within 24 h): Elevation of troponin or CK-MB to more than 3xULN or, if CK-MB was elevated at baseline, re-elevation to more than 3xULN and a more than 50% increase above the previous level, and/or development of significant Q-waves in at least 2 adjacent ECG leads. c. After CABG (within 72 h): Elevation of CK-MB to more than 5xULN or, if CK-MB was elevated at baseline, re-elevation to more than 5xULN and a more than 50% increase above the previous level, and/or development of significant Q-waves in at least 2 adjacent ECG leads. d. Silent MI: retrospectively diagnosed by the appearance of significant new Q-waves between study visits. (In such cases, the date of the event was to be recorded as the midpoint between the 2 study visits) e. Demonstrated by autopsy
Deaths	Classified as vascular (including bleeding) or non-vascular, due to other specified causes (e.g., malignancy)], or of unknown etiology. [The definition of vascular death was expanded by the adjudication committee charter; see “Adjudication of Events” below]

Additional notes: Total CK could be used if CK-MB unavailable; significant Q-waves were defined as a duration of at least 0.04 seconds and a depth of more than a quarter of the amplitude of the corresponding R-wave, in at least 2 adjacent leads.

Prespecified safety endpoints included major and minor bleeds; life threatening bleeds were a subclassification of major bleeds (major bleed definitions presented in Table 1).

Additional safety endpoints included intracerebral hemorrhage, other ICH, elevations in liver transaminases, bilirubin and hepatic dysfunction, and other adverse events.

5.3.7 Statistical Analysis Plan

The protocol finalized on September 12, 2005 pre-specified one primary and two secondary endpoints (see "Endpoints" above) as well as an approach to their statistical analysis. On May 8, 2009, approximately two months after the study end date, a document entitled Trial Statistical Analysis Plan (TSAP) was finalized. The stated purpose of the TSAP was to specify the details of the statistical analyses described in the September 2005 protocol. The TSAP is described by the sponsor as a working document that could be amended as the trial progressed and was to be signed off at least 4 weeks prior to unblinding. The TSAP largely preserved the primary non-inferiority analysis specified in the 2005 protocol; the TSAP approach to the analysis of the secondary endpoints specified in the 2009 protocol also appears to mirror that specified in the 2005 protocol. In addition, the TSAP addresses analytic/endpoint changes made subsequent to the 2005 finalization of the protocol.

5.3.7.1 Primary endpoint analysis as specified in the 2005 protocol (and TSAP)

The primary efficacy variable was the time to first occurrence of stroke or systemic embolism and the study was designed to test the hypothesis that the hazard ratio of dabigatran vs. warfarin was larger than or equal to a non-inferiority margin of 1.46. The primary efficacy analysis was to be performed on all randomized subjects (full analysis set or FAS) using a Cox proportional hazard model that included treatment as a factor. All adjudicated and/or "un-refuted" [9] events were to be used. The protocol specified the Hochberg procedure to test each dose against warfarin separately. If the upper bound of the 95% CI for the less effective dose was < 1.46, then non-inferiority for both doses would be claimed. Otherwise, the upper bound of the 97.5% CI for the more effective dose had to be < 1.46 to claim non-inferiority for the more effective dose.

The non-inferiority margin was calculated using data from the historical placebo-controlled trials of warfarin (see appendix and sponsor's table below). To calculate the non-inferiority margin, the sponsor used 0.52 as the upper limit of the 95% CI of the hazard ratio of warfarin vs. placebo. There was a clinical decision to ensure that more than 50% of the effect was preserved giving a non-inferiority margin of 1.46.

9 Though no definition of this term could be found in the protocol, according to the sponsor (submission dated January 6, 2010), an un-refuted event is one that meets at least one of the following criteria: the adjudicator agrees with the investigator, the event has not been adjudicated (no events fell into this category in RE-LY) or no additional information can be checked (absent additional information, investigator judgment was acceptable).

Table 17. Meta-analyses of historical placebo-controlled trials

Meta-analysis	Hazard (Risk) ratio of warfarin vs. placebo (95% CI)
Hart et al of six-trial meta-analysis for strokes using summary statistics from each trial	0.38 (0.28, 0.52)
Meta-analysis for strokes/systemic embolisms of the five primary prevention trials, using pooled individual patient data	0.35 (0.23, 0.52)
Six-trial meta-analysis for strokes using constant hazard assumption	0.37(0.27, 0.50)
Meta-analysis for strokes of the five primary prevention trials for strokes, using constant hazard assumption	0.38(0.25, 0.57)

[Source: RE-LY protocol, Table 7.6.1:2]

5.3.7.2 Secondary endpoint analysis as specified in the 2005 protocol (and TSAP)

Secondary efficacy endpoints specified in the 2005 protocol included the incidence of:

- stroke (including hemorrhagic), systemic embolism, or all-cause mortality
- stroke (including hemorrhagic), systemic embolism, pulmonary embolism, acute myocardial infarction, or vascular deaths (including deaths from bleeding).

For these secondary efficacy endpoints, the same statistical model as that for the primary endpoint was to be applied. A FAS population was to be used and all "adjudicated and/or un-refuted" events were to be utilized. No approach to controlling the type 1 error rate was specified in the 2005 protocol for the analyses of secondary endpoints. The plan for analyzing these endpoints in the TSAP appeared to mirror that contained in the 2005 protocol.

5.3.8 Identification of potential endpoint events

(see appendix for relevant CRF pages):
According to the 2005 protocol, a patient's stroke status and bleeding events were to be evaluated at each visit by asking the patient a series of questions regarding the period of time since their last clinic visit.

Reviewer's comment: The CRF for scheduled study visits asked if the patient had experienced any of the study outcome events since the last visit (these individual events were listed with a check box next to each event for indicating yes/no).

In addition, the following measures were to be taken:

- Screening for signs and symptoms of stroke and bleeding: A questionnaire querying patients for signs and symptoms of stroke and bleeding was to be administered at each visit. All symptoms were to be evaluated and, if potentially consistent with a study event, were to be referred to the Adjudication Committee.

Reviewer's comment: According to the RE-LY Central Adjudication Core-Committee meeting February 2, 2009, PHRI created a CRF "to be completed by sites (applicable sites only) to document an 'Investigator verification' that the symptoms were not related to an event."

- Screening of hospitalizations: All hospitalizations were to be recorded with the reason for admission and all inter-current diagnoses. Any hospital diagnosis that included loss of neurological function, loss of organ function or need for surgical intervention, or reduction in hemoglobin was to trigger a request for more information from the centre and if potentially consistent with a study event was to be referred to the Adjudication Committee

Reviewer's comment: The measures implemented during the study appear to be more limited than those originally specified in the protocol. The CRF for hospitalizations captured data on the reason for admission (not all inter-current diagnoses) with possible answers including "outcome event" and other events falling into the following categories specified on the CRF: other cardiovascular, surgery, and other non-cardiovascular. Under some of these headings, there was an option for free text to specify the particular event that was the reason for hospitalization. According to the sponsor (Response to information request dated February 12, 20101), checks were performed on the hospitalization CRF page to confirm that events reported on this page as outcome events/ potential outcome events (those reported as "outcome event" or identified via a free text term match to a list of terms for outcome events) were captured as outcome events; if no event was reported by the site, the site was queried (for events indicated by free text search) or told to submit the appropriate outcome event CRF page (for events reported as "outcome event").

- Review of adverse events: Any adverse event indicating potential loss of neurological function, such as unilateral weakness, loss of vision or sensory disturbance was to trigger a request for more information from the centre for event adjudication if potentially consistent with a study event. Any decrease in hemoglobin of > 2 gm/dL was to be similarly investigated.

Reviewer's comment: According to the sponsor (response to information request dated February 12, 2010), adverse events were searched using a list of terms for the outcomes of stroke, MI, non-CNS systemic embolism, major bleed, death and TIA; minor bleeds were not cross checked. Hemoglobin drops of > 2, >4, or >5 g/dL between visits were identified and the results were also compared with the major or minor bleeding reports.

- Review of TIAs: All reported TIA events were to be referred to the Adjudication Committee for full adjudication of any possible strokes that may have been improperly reported.

- All reported major bleeding events, bleeds requiring discontinuation of study medication, hospitalizations or physician intervention, were to be forwarded for adjudication.

Reviewer's comment: In addition to these measures, additional steps were taken by PHRI/the sponsor. According to the sponsor, following database lock on June 17, 2009, additional outcome events were identified through two separate processes. In one process, the data coordinating center, PHRI, continued to query sites on outcome events for subjects lost to follow-up; this process continued until the finalization of the publication manuscript and was reported to be "part of PHRI's normal procedure." A separate process conducted by the sponsor after trial completion and database lock was routine site closeout visits. A total of 27 potential outcome events were identified via these processes of which 22 were adjudicated as meeting the criteria of an outcome event.

5.3.9 Protocol Amendments:

Global as well as region-specific protocol amendments were enacted over the course of the trial. Major revisions enacted by global protocol amendments are described in the table below.

Table 18. RE-LY protocol amendments

Amendment (date)	Key changes enacted
Amendment 1 (August 31, 2006)	To ensure balanced enrollment of Vitamin K antagonist (VKA) naïve and VKA-experienced subjects, the proportion of subjects falling into these categories was to be monitored at randomization by IVRS; if the proportion of subjects in these groups became "consistently disproportional," the Operations Committee could impose additional measures (e.g. a quota system) to ensure balanced enrollment. The definition of VKA naïve was also revised to include subjects treated with VK antagonist for two months or less (original definition= not previously treated with a VKA for 30 days or more).
Amendment 2 (May 24, 2007)	Increased subject number from 15,000 to 18,000. The stated rationale for the increase was that because of the faster enrollment, 15,000 patients will be randomized prior to the planned date. In order to maintain the statistical power in case of an event rate < 1.6% (the

	originally projected event rate), the enrollment should continue. Required that all subjects, including those that discontinued treatment, be followed until the end of the study. Patients who prematurely discontinue treatment were to be contacted at regular intervals (according to the regular visit schedule, an alternative reduced schedule negotiated with the subject either by clinic visits or phone in order to record endpoints (survival, stroke or embolic events or MI) and "other clinical status when feasible" Clarified that subjects terminating prematurely by withdrawal of consent would undergo a final follow-up visit.
Amendment 3 (September 11, 2007)	Decreased frequency of liver function test (LFT) monitoring (from monthly to ~every 3 months in the first year of the study) in subjects randomized after September 25, 2006. Change was based on a Data Safety Monitoring Board (DSMB) recommendation following a protocol specified review of LFT data accrued on 6000 subjects exposed for at least 6 months.
Amendment 4 (February 15, 2008)	Revised protocol to address new information regarding effect of p-gp inhibitors on dabigatran exposure: Contraindicated concomitant use of dabigatran and quinidine. Caution advised regarding use of dabigatran and moderate to strong p-glycoprotein (P-gp) inhibitors (e.g. verapamil and clarithromycin); physician to consider the use of a suitable alternative.
Amendment 5 (August 7, 2008)	Established a more detailed algorithm for holding dabigatran prior to surgery, with the discontinuation algorithm based in part on subject's renal function. Provided additional instruction on the treatment of major bleeds. Revised how the quality of INR control would be assessed (adopted Rosendale method and specified that the mean percentage of time of INR in range was to be calculated for each center and each country); also removed the failure to measure INR values per protocol as a protocol violation.

5.3.10 Adjudication process

[The submission contains a copy of the RE-LY Central Adjudication Manual Version 3 dated April 24, 2007 which serves as the source of the following information unless otherwise noted].

An Adjudication Committee adjudicated reported primary and secondary events including potential strokes, systemic embolism, pulmonary embolism, acute myocardial infarction (AMI), TIAs (to rule out strokes), major bleeding, life threatening bleeding and cause of death. The committee was comprised of experts in the field of neurology and cardiology; neurologists were to adjudicate potential strokes and other endpoints were to be "usually" adjudicated by cardiologists. A stroke subcommittee was also formed to review stroke, TIA and systemic embolism cases when the individual adjudicators could not reach consensus. Events were to be adjudicated using the definitions provided in the protocol with the exception of pulmonary embolism (no definition was provided in the protocol) and vascular death. In the charter, pulmonary embolism was defined as "clinical symptoms compatible" and at least one of the following:

a. High probability V/Q scan (one or more segmental or larger perfusion defects with normal ventilation
b. Positive CT angiogram showing an intraluminal filling defect
c. Positive pulmonary angiogram
d. Autopsy showing pulmonary embolism
e. Other objective imaging for DVT if investigations for pulmonary embolism not done, or non-diagnostic.

According to the adjudication committee charter, death was to be classified as vascular (including bleeding) or non-vascular, due to other specified causes (e.g., malignancy)], or of unknown etiology. Vascular death was considered to occur when no obvious nonvascular event to explain death was noted; sudden or unwitnessed deaths were considered vascular.

Reviewer's comment: While the adjudication form asked adjudicators to sub classify the major bleed, the second version of the adjudication charter (dated September 14, 2007) stated that the adjudication coordinator would identify the sub classification of major bleeds as life-threatening. Hence, it is unclear who did the adjudication.

All reported events were to be adjudicated independently and in a blinded manner by two members of the committee; if consensus was not achieved, the event was reviewed and the final decision was determined by a third adjudicator (in the case of potential endpoint events for stroke, TIA and systemic embolism events, a stroke subcommittee made the final decision if consensus was not achieved). Event information to be provided to members included event case report forms and supporting documentation. References to treatment arm, INRs and "other relevant clinical information" were to be removed from these documents. As a verification of blinding, the adjudication form asked adjudicators if they remained blinded to study treatment during the review of a

given event; if the adjudicator reported unblinding, the event was to be adjudicated by another member of the committee.

Reviewer's comments: Review of the meeting minutes of the Central Adjudication Core Committee revealed difficulty with blinding non-English documents and concern for inconsistencies in the adjudication of non-CNS embolic events. The latter concern resulted in a second review of these events: non-CNS embolic events were to be reviewed by one of two reviewers and the outcome of this second review was to be considered final and supersede previous documented decisions in the main clinical data base. Relevant excerpts from the February 2, 2009 Central Adjudication Core Committee Meeting Minutes are provided below:

- ***Verification of Blinding***

M. Robinson reported that an internal quality assurance review of Adjudicated Non-English events had been performed to verify the report by the Adjudicator of maintaining blinding during their review. A total of 30 adjudicated Non-English events that had been subsequently translated after adjudication, were randomly selected and reviewed by Marlene. The purpose of the review was to verify whether any evidence of potential unblinding was present and evaluate the declaration of the Adjudicator as to whether he/she was unblinded (note: a required question on each adjudication form).

M. Robinson reported that 6 (20%) of the 30 events reviewed potentially showed evidence of unblinding in the source documentation review by the adjudicator. In these instances, the report by the Adjudicator was that he/she was NOT unblinded.

M. Robinson reported samples of the phrases that had been identified as potential sources of unblinding;; *patient warfarinized; INR values visible, may need to speak with cardiologist regarding starting patient on an alternate anticoagulant such as Marveran at discharge*.

The group discussed the findings in detail and agreed upon the following points:

- The adjudicators generally review the documentation at a high level and apply the necessary criteria. Text embedded in documents may have been missed or overlooked the areas where unblinding may have occurred. (ie. for a stroke only reviewing the CT and discharge summary, and not reading the consults or progress notes).
- There are different levels of unblinding and revealing an INR of 5.0 may not necessarily unblind the Adjudicator to Coumadin (Warfarin), as it could also indicate Dabigatran effect.
- It is important to know the context within which the unblinding may have occurred, as it may not have been the case at all.
- It is important to take the word of the adjudicators.

Action:

- The committee agreed that another 30 events be reviewed and graded accordingly; true unblinding, and potentially unblinded. These events will be reviewed to determine blinding status with further discussion based on findings.

Reviewer's comment: While the minutes documented plans to review additional events with "further discussion based on findings," according to the sponsor (submission dated March 30, 2010), "The last meeting of the Adjudication Committee occurred on Feb 2, 2009 before data base lock in June. This item of reviewing 30 other events, was not pursued."

- ***Non-CNS Embolic Event Agreement Rate and Response***

M. Robinson noted the consistent low agreement rate of Non-CNS Embolic Event. The committee reviewed various considerations related to the interpretation, definitions and processing of this event and concluded the following:

- Nurses are completing the CRF for this event and may not be as familiar with the protocol definition and continue to capture venous events as opposed to 'systemic' arterial events
- The definitions are clearly outlined in the protocol.

M. Robinson reported that an internal quality assurance review of Adjudicated random selection of Non-CNS Embolic Events has been performed. A total of 30 events were randomly selected and reviewed by Marlene to review the supporting documents included and apply and verify the definitions and criteria for Non-CNS Embolic Events. The purpose of the review was to evaluate the Adjudicator application of the criteria of Non-CNS Embolic Event.

M. Robinson reported that 5 of the 30 (17%) Non-CNS Embolic selected were DVTs or Apical Thrombus.

The committee supported the initiatives and concluded that there is some evidence to suggest that there are inconsistencies in the adjudication of Non-CNS Embolic Events that need to be addressed. The committee unanimously agreed that all of the current

ELY-CA Update Meeting-: Teleconference Minutes Feb. 2, 2009 Page 2 of 4

adjudicated Non-CNS Embolic Events will require a second review. C. Joyner and H-C. Diener will each review 50% of the cases.

Action:

- M. Robinson will prepare and issue 50% of the Non-CNS Embolic Events to both C. Joyner and H-C. Diener. The additional review will be independent of the previous Adjudicator decision and without knowledge of this previous decision. The outcome of this second review will be considered final and supersede previous documented decisions in the main clinical data base.
- In the event that C. Joyner or H-C. Diener are uncertain about an event, they will forward the event to each other for comment and consensus.

Reviewer's comment: Though a description of this process was not otherwise noted in the submission, when asked about the readjudication, the sponsor confirmed that all but 3 of the 98 events were re-read as described above (sponsor submission dated February 11, 2010).

6 Review of Efficacy

Reviewer's comment: This section focuses on key analyses related to efficacy and addresses topics including the adequacy of anticoagulation in the warfarin arm, the PROBE design, and dabigatran's effect on mortality. For analyses addressing net benefit, as well as further discussion regarding a superiority claim, see Section 1 titled "Recommendations/Risk-Benefit Assessment".

Dabigatran etexilate is an orally available, reversible, direct thrombin inhibitor with a proposed indication for the prevention of stroke and systemic embolism and reduction of vascular mortality in patients with atrial fibrillation. In support of this indication, the sponsor conducted the RE-LY trial, a large (~18,000 subjects), randomized, non-inferiority study of open-label warfarin administration and blinded administration of two doses of dabigatran (110 and 150 mg). RE-LY's primary endpoint was a composite of stroke and systemic embolism. The sponsor's primary analysis, conducted on the ITT population, established efficacy. Compared to warfarin treated subjects, the HR in the dabigatran 150 arm was 0.66 (95% CI 0.53 to 0.82, $p<0.003$ for superiority) and in the 110 arm was 0.91 (95% CI 0.74 to 1.11, $p<0.0001$ for non-inferiority). Sensitivity analyses performed on "as treated" populations, as well as an analysis addressing a change in the protocol design (increase in sample size) were supportive of the ITT analysis. Importantly, efficacy findings for the 150 mg dose also appeared to be preserved across important subgroups of patients, including subjects previously treated with warfarin, those with a history of TIA/stroke and the subset of subjects enrolled from US sites. The efficacy of the 150 dose also appeared to be maintained in comparisons against the sub-population of warfarin-treated subjects who had achieved more optimal levels of INR control. The primary endpoint findings were further supported by a numerical imbalance in the number of disabling and fatal strokes in the dabigatran 150 compared to warfarin treatment arm, favoring subjects randomized to the 150 dose.

Adequacy of anticoagulation in the warfarin treatment arm: Dabigatran was studied against warfarin in RE-LY and hence to interpret the efficacy findings, one must understand the expected benefit of warfarin as it was given in this trial. Six randomized, placebo-controlled trials (five primary and one secondary prevention) are widely referenced as establishing the efficacy of warfarin for the prevention of ischemic stroke in patients with non-valvular atrial fibrillation (see appendix). According to a 2007 meta-analysis by Hart et al, in these studies warfarin reduced the risk of ischemic stroke by 67% (95% CI, 54% to 77%) and the risk of stroke (ischemic and hemorrhagic) by 64% (95% CI, 49% to 74%). There are certainly differences between these historical trials and RE-LY that affect the constancy assumption. Though the mean INR achieved in the historical studies was between 2 and 3, for the most part these studies targeted different INR values /prothrombin time ratios and a wider range of values than the 2-3 range currently recommended and used in RE-LY. The percentage of subjects with important risk markers for thromboembolic complications/strokes (e.g., heart failure, diabetes, and hypertension) was greater in RE-LY than in these historical trials (see table below). At

the same time, there have also been therapeutic advances in the treatment of at least some of these concomitant conditions that would be expected to lower the risk of stroke. For these reasons, it seems likely that the risk reduction associated with warfarin in RE-LY would be different than that seen in historical trials. Whether these differences, in balance, would translate into greater or lesser benefit from warfarin is not clear; either way, substantial benefit would still be expected.

Table 19. Demographics historical warfarin trials vs. RE-LY

	Historical trials of primary prevention	RE-LY
Year(s) published	1989-1992	2009
Mean Age (>75 years)	69 (20)	71 (40*)
Sex (%) Male	71	64
Prior stroke (%)	5	13
Hypertension (%)	45	79
CHF (%)	26	32
Diabetes (%)	13	23

[Sources: Historical trials- Jackson et al, 2008; RE-LY- Reviewer's analysis (Sponsor's dataset=basco; reviewer's filename=demographics]
*≥ 75 years

Several metrics can be used to assess the adequacy of anticoagulation in warfarin treated subjects in RE-LY a comparison with rates in other warfarin trials, the exposure to warfarin, time in therapeutic range, as well as the appropriateness of INR monitoring. Each measure has its limitations but as a whole, these measures suggested reasonable anticoagulation in subjects randomized to warfarin.

- In the warfarin arm of historical and more recently completed clinical trials, the absolute incidence of strokes was low (see table below). The incidence reported in RE-LY, as an absolute number, seems comparable. In comparison with the incidence of strokes in the placebo arm in the historical trials, the incidence of strokes in the warfarin treatment arm of RE-LY (both the absolute and relative incidence) is much lower.

Table 20. Stroke incidence per 100 subject-years in historical trials

	Year	Placebo	Warfarin/Vitamin K antagonist
Primary prevention			
AFASAK I	1989	4.8	2.2
SPAF I	1991	7.8	3.0
BAATAF	1990	3.0	0.6
CAFA	1991	3.7	2.5
SPINAF	1992	4.8	1.4

Overall	1989-1992	4.6	1.7
Secondary prevention			
EAFT	1993	12.3	3.9

[Calculations based on rates reported by Aguilar et al.]

Table 21. Demographics and stroke incidence in RE-LY, ACTIVE W and SPORTIF trials

	SPORTIF III	SPORTIF V	ACTIVE W	RE-LY
Year(s) published	2003	2005	2006	2009
Mean Age (% ≥75 years)	70 (34)	70 (42)	70 (NA)	71 (40)
Sex (%) Male	69	72	67	64
Prior stroke/TIA %	24	18	15	20
Hypertension %	72	81	83	79
CHF %	34**	39*	30	32
Diabetes %	22	NA	21	23
Strokes/100 subject-years (warfarin arm)	2.2	1.1	1.4	1.6
Hemorrhagic stroke/100 subject-years (warfarin arm)	0.4	0.1	0.4	0.4

*CHF/LV dysfunction; **LV dysfunction

- With regard to exposure to warfarin in RE-LY, 80.8% (4849) of subjects randomized to warfarin completed the study on study medication. Over 50% of subjects had at least one interruption of study medication over the course of the trial; overall, subjects in the warfarin arm were on study medication for ~91% of study days of follow up.

- The mean time in therapeutic range (2-3) was 64.4% (analyses excluding values obtained during treatment interruptions) and 63.4% (analyses including values obtained during treatment interruptions). The overall mean percent of reported INR measurements greater than 4 was ~2%; the overall mean percent of INR measurements <2.0 was ~22 to 23% and < 1.5 was ~5%.Compared to later months, during the first month of therapy, a greater percentage of INR measurements were greater than 4 (~5 vs. ~2%), less than 2 (32% vs. 23-24%) or less than 1.5 (~11% vs. ~5%). The results are not so dissimilar to those reported in recently reported controlled trials such as ACTIVE-W and SPORTIF III and V: 64-68% for an INR of 2 to 3 and ~20% for an INR<2; again suggesting reasonable control using these trials as benchmarks.

The PROBE design: RE-LY was open-label with respect to warfarin administration and to mitigate potential bias, several measures were implemented. Other means were used to identify potential events such as screening of adverse events, a questionnaire

querying patients for signs/symptoms of stroke, and a review of investigator-reported hospitalizations. The protocol specified that TIAs were to be adjudicated and events were to undergo blinded adjudication. Finally, the endpoints chosen were, for the most part, more objective endpoints.

Though warfarin administration was open-label, two doses of dabigatran, 110 and 150, were also studied and were administered in a blinded fashion. The inclusion of these two doses was perhaps one of the most important design aspects of RE-LY; while it cannot mitigate potential bias in comparisons of dabigatran against warfarin, it can allow establishment of efficacy via a dose-response relationship. In subjects treated with dabigatran 110 mg BID, 171 strokes were reported compared to 122 in subjects randomized to dabigatran 150 mg BID. Compared to the lower dose, the hazard ratio for the higher dose was 0.71 (95% CI 0.56 to 0.90, p-value=0.003). The finding of a dose response relationship changes the nature of the question surrounding dabigatran's efficacy. The question is no longer whether or not dabigatran at some dose is effective. The question is whether, in the setting of open-label warfarin administration, one can draw any conclusions about superiority over warfarin.

Bias can be introduced because of how events were ascertained or because of differential management or follow up of study subjects. As described above, several measures were implemented to minimize ascertainment bias and it is perhaps worthwhile to explore these measures and the results of these measures as implemented in RE-LY. Of investigator reported strokes, similar percentages were adjudicated as strokes in the three treatment arms of RE-LY. Similar percentages of investigator-reported TIAs were also upgraded to strokes by the adjudication committee across the treatment arms. Moreover, a sampling of investigator-reported events conducted by this reviewer suggested that the adjudications were, as a whole, reasonable. Such findings provide some reassurance; however, there were problematic aspects of the adjudication process, as well as limitations to the methods used to identify potential endpoint events in RE-LY:

- The adjudication documents often contained text that could potentially unblind reviewers. This was the case in 17% of documents reviewed by this reviewer, a figure not so dissimilar to the 20% noted by the Adjudication Core Committee in their review of non-English source documents reviewed by adjudicators. That said, on some occasions, adjudication documents with text indicating warfarin use were actually from subjects randomized to dabigatran who had discontinued study therapy.
- The screening of hospitalizations was a screening not of the hospitalization record itself, but of a CRF page completed by the investigator indicating that the patient had been hospitalized and containing the investigator reported reason for hospitalization. Hence, the screening of investigator-reported adverse events, investigator-reported reasons for hospitalization and questionnaire querying patients for signs/symptoms of stroke required that the investigator first report a suggestive event in order to capture additional events via this method; whether or not there were additional

events that were not reported by investigators is an issue that the DSI audits, some still pending, will address.

Even in the absence of any clear evidence of bias in the ascertainment of strokes/SEE, analysis of study findings suggests that knowledge of treatment arm may have led to important differences in the treatment of subjects. For example, if a subject experienced an ischemic stroke, TIA (a non-endpoint event) or minor bleed, she was more likely to have her study medication permanently discontinued in the dabigatran than the warfarin treatment arms (see Section 6.1.10). There were other treatment specific differences in management. According to the protocol, subjects whose CrCl fell and stayed below 30 mol/min (a sicker population) were to have their medication permanently discontinued in the dabigatran but not the warfarin-treatment arm. Because these subjects were to be followed until trial completion (assuming they were), these differences may not be so critical. Nonetheless, whether or not the management of subjects in the dabigatran and warfarin treatment arms differed in other important ways is uncertain. In light of the open-label design and these differences, one should perhaps be wary of attributing differences in patient outcomes solely to the study drug and also wary of granting dabigatran a superiority claim over warfarin.

Effects on mortality: Analyses conducted according to the finalized statistical analysis plan suggested favorable effects of the higher dose of dabigatran on all cause mortality (HR of 0.88, p-value 0.052 relative to warfarin) and vascular specific mortality (HR of 0.84, p-value of 0.04 relative to warfarin). While all-cause mortality and vascular mortality were specified as components of composite secondary endpoints, the RE-LY protocol did not pre-specify a plan for controlling the type-1 error rate in the analysis of secondary endpoints and neither endpoint was specified as an individual secondary endpoint. Moreover, RE-LY was an open label trial and the sponsor's statistical analysis plan was finalized late (essentially after all of the study data had been amassed). An analysis including deaths censored by the sponsor's statistical analysis plan, as well as an analysis excluding deaths identified by vital status queries in subjects who had prematurely discontinued from the trial shift the p-value for all-cause mortality higher (to 0.06 and 0.09, respectively). In addition, an analysis based on center-level INR control suggests that the imbalance in deaths (dabigatran relative to warfarin) is driven by subjects with poorly controlled INRs. Based on these findings, a mortality claim should not be given.

6.1 Indication

As previously stated, the proposed indication is for the prevention of stroke and systemic embolism. Though the sponsor requested an indication for the reduction of vascular mortality in the original NDA submission, in an amendment to the NDA dated July 27, 2010, the sponsor requested that the claim be removed from the proposed US indication statement; the letter cited "an effort to harmonize the indication statement for PRADAXA globally."

6.1.1 Methods

In the sponsor's efficacy analyses and in the efficacy analyses that follow, subjects without a reported endpoint event are censored at the last time vital status information was available. Subject-years of follow up are also calculated based on the last date vital status information was available.[10] For the primary efficacy endpoint, analyses were also conducted:

(1) censoring subjects without a reported endpoint event at the last time follow up information was available for the particular endpoint of interest, and
(2) censoring subjects without a reported endpoint event at the last clinic follow up visit at which a pulse was recorded.

These analyses produced similar findings as the analysis in which subjects were censored based on vital status information.

6.1.2 Demographics

Baseline demographics, including type of atrial fibrillation, history of stroke/TIA, risk factors for stroke and baseline use of warfarin and other anticoagulant medications, were similar across treatment arms. Baseline blood pressure and heart rate was 131/77 and 74, respectively, and was also similar across the treatment arms. Thirty-six percent of study subjects were enrolled from U.S. and Canadian sites. According to the sponsor, 70% of subjects were White, 16% Asian, 7% Hispanic or Latino and 1% were Black.

Table 22. Baseline demographics

Characteristic*	Dabigatran110 N=6015	Dabigatran150 N=6076	Warfarin N=6022
Male	3865(64.3)	3840(63.2)	3809(63.3)
Age			
Mean	71	71	72
65<= and <75	2668(44.4)	2580(42.5)	2646(43.9)
<65	998(16.6)	1030(17)	953(15.8)
>=75	2349(39.1)	2466(40.6)	2423(40.2)
AF type			
Paroxysmal	1929(32.1)	1978(32.6)	2036(33.8)
Permanent	2132(35.4)	2188(36)	2055(34.1)
Persistent	1950(32.4)	1909(31.4)	1930(32)
AF diagnosis			
<3 months	1844(30.7)	1854(30.5)	1929(32)

[10] Subject-years = sum(date of study termination – date of randomization +1) of all randomized subjects / 365.25

3 months to 2 years	1324(22)	1344(22.1)	1315(21.8)
>2 years	2843(47.3)	2876(47.3)	2776(46.1)
Characteristic*	**Dabigatran110 N=6015**	**Dabigatran150 N=6076**	**Warfarin N=6022**
VKA use			
VKA Naive	3005(50)	3028(49.8)	3093(51.4)
On VKA at randomization	3751(62.4)	3760(61.9)	3678(61.1)
Risk Factors			
History of stroke	761(12.7)	756(12.4)	756(12.6)
History of TIA	548(9.1)	587(9.7)	528(8.8)
History of stroke/TIA/SEE	1308(21.7)	1358(22.4)	1287(21.4)
History of hypertension	4738(78.8)	4795(78.9)	4750(78.9)
History of diabetes	1409(23.4)	1402(23.1)	1410(23.4)
History of HF	1937(32.2)	1934(31.8)	1922(31.9)
History of MI	1008(16.8)	1029(16.9)	968(16.1)
History of CAD	1661(27.6)	1710(28.1)	1663(27.6)
Smoker	440(7.3)	447(7.4)	448(7.4)
NYHA class			
NYHA I	295(4.9)	292(4.8)	297(4.9)
NYHA II	1225(20.4)	1198(19.7)	1222(20.3)
NYHA III	386(6.4)	401(6.6)	353(5.9)
NYHA IV	30(0.5)	41(0.7)	48(0.8)
CHADS2 score			
0	151(2.5)	146(2.4)	155(2.6)
1	1809(30.1)	1815(29.9)	1707(28.3)
2	2088(34.7)	2136(35.2)	2229(37)
3+	1966(32.7)	1979(32.6)	1931(32.1)
Creatinine clearance			
30<= and <50	1136(18.9)	1156(19)	1051(17.5)
50<= and <80	2714(45.1)	2777(45.7)	2806(46.6)
>=80	1899(31.6)	1882(31)	1877(31.2)

[Source: Reviewer's analysis (Sponsor's dataset=basco; reviewer filename=baseline_dm]
*Percentages may not add up to 100% because of missing data; a small number of subjects with a CrCl<30 were randomized (<0.05%).

Concomitant medications were also similar across the three treatment arms at baseline, as shown in the table below.

Table 23. Baseline medication use

Baseline medication	Dabigatran 110	Dabigatran 150	Warfarin
Beta blocker	3789(63)	3887(64)	3722(61.8)
Digoxin	1781(29.6)	1742(28.7)	1767(29.3)
Amiodarone	647(10.8)	672(11.1)	657(10.9)
Verapamil	352(5.9)	350(5.8)	369(6.1)
Diltiazem	564(9.4)	541(8.9)	581(9.6)
ACEI	2699(44.9)	2754(45.3)	2670(44.3)
ARB	1448(24.1)	1470(24.2)	1418(23.5)
Aspirin	2384(39.6)	2338(38.5)	2431(40.4)
Clopidogrel	338(5.6)	337(5.5)	345(5.7)
Aggrenox	16(0.3)	9(0.1)	16(0.3)
Statin	2702(44.9)	2682(44.1)	2673(44.4)
Proton Pump Inhibitor	847(14.1)	878(14.5)	842(14)
H2 receptor blocker	239(4)	257(4.2)	262(4.4)
NSAID	311(5.2)	294(4.8)	319(5.3)

[Source: Reviewer's analysis (Sponsor's dataset=basco; reviewer filename=subgroups]

6.1.3 Subject Disposition

Of 20,377 subjects screened, a total of 18,113 were randomized in RE-LY. Of the subjects that were screened but not randomized, approximately 70% did not meet study inclusion/exclusion criteria and another 18% withdrew consent. Over 99% of randomized subjects received at least one dose of study medication.

The disposition of subjects, as reported by the sponsor in an amendment dated August 4, 2010, is shown in the table below. The treatment groups do not appear to differ significantly in the number of subjects lost to follow up. Slightly more warfarin treated subjects were reported to have completed the study on study medication than dabigatran-treated subjects. The reasons for discontinuation of study medication are discussed further in section 6.1.10

Table 24. Disposition of subjects

	Dabigatran 110	Dabigatran 150	Warfarin
Randomized	6015	6076	6022
Treated	5983	6059	5998
Completed study	5765 (96.4)	5808 (95.9)	5748 (95.8)
Completed on study medication	4610 (77.1)	4625 (76.3)	4848 (80.8)
Completed follow up but stopped study medication prematurely	1155 (19.3)	1183 (19.5)	900 (15.0)
Premature discontinuation*	218 (3.6)	251 (4.1)	250 (4.2)

[Source: Sponsor submission dated August 4, 2010, Table 2.18.5.1]
*Included in this category: lost to follow up, withdrew consent, "Other", centers closed early for cause, and subjects with "no CRF pages 196, 126, 194 entered"

Reviewer's comment: Late in the review cycle, errors were found in the sponsor's disposition data. A few subjects who were initially counted by the sponsor as having a "normal study completion" were found to have prematurely discontinued from follow up. As a result, the sponsor performed additional checks of the data and identified 39 subjects in the database listed as having a "normal study termination status" who should have been counted as "early study termination". The disposition data shown above reflects the amended data.

The protocol allowed clinical investigators to "negotiate a revised visit schedule" for subjects who permanently discontinued study medication and follow up visits could occur by telephone. To further assess the adequacy of follow up, an analysis was conducted in which a subject's last day of follow up was defined as the last clinic visit at which a pulse was recorded. The number of days of follow up based on pulse data (shown below) appears similar across the treatment arms. Using the pulse data, subject years of follow up was ~8% less than that calculated using vital status information; the mean duration of follow up was ~ 1.5 months shorter.

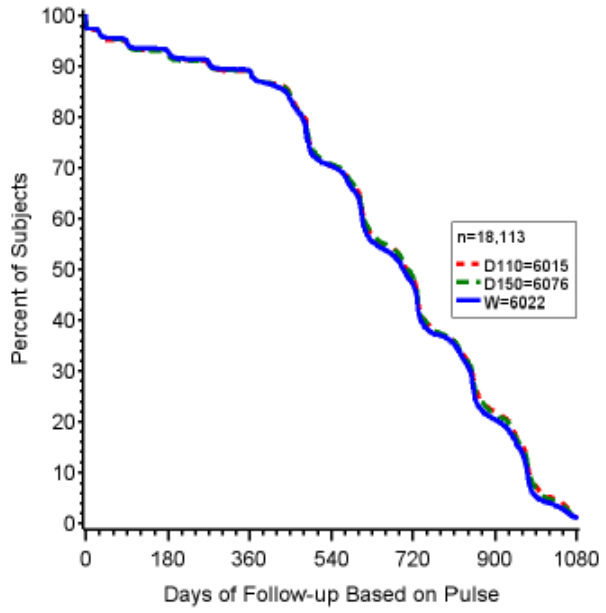


Figure 5. Days of follow- up based on pulse data

The mode of follow up (telephone vs. clinic visit) could impact the ascertainment of endpoint events, and in particular the ascertainment of non-disabling strokes. A total of 489, 499, and 469 subjects in the dabigatran 110, dabigatran 150 and warfarin treatment arms did not have a pulse reported within 6 months of the close out period.[11] These analyses, based on pulse data, suggest a greater loss of information (~8% across treatment arms) than the sponsor's analysis of "premature discontinuations" (~4% as shown in the table above).

Reviewer's comment: The missing data should be viewed in light of the efficacy findings. The number of additional events needed in the dabigatran treatment arms to reverse the efficacy findings is discussed in Section 6.1.4 below. It seems unlikely that this amount of missing information would reverse the efficacy findings, at least for non-inferiority.

6.1.4 Analysis of Primary Endpoint(s)

In the original NDA submission, it was reported that 182 subjects randomized to dabigatran 110 mg (1.5%), 133 subjects randomized to dabigatran 150 mg (1.1%) and 198 subjects randomized to warfarin (1.7%) experienced a stroke/SEE. A few additional events were identified following database lock as a result of queries to sites on outcome

11 For the purposes of this analysis, a subject was counted if no pulse was reported after 6/15/2008 (~6 months prior to study close out); subjects that died at any time prior to 12/15/2008 were excluded. The 6 month cut-off date was arbitrary.

events in subjects lost to follow up, routine site close out visits, and the data quality checks implemented in response to the Agency's refuse to file letter.

Table 25. Number of subjects with strokes/SEE

	Dabigatran 110 N	Dabigatran 150 N	Warfarin N
Original submission	182	133	198
Including events identified post Database lock	183	134	200
NDA resubmission	183	134	202

In addition to these events, two other strokes, one in the dabigatran 110 arm and one in the dabigatran 150 arm, were reported by investigators and adjudicated as stroke events but were not included in the sponsor's analysis of the primary endpoint. Both of these events occurred after the subject was reported to have had a "normal study termination" as indicated by the site investigator on the study termination CRF (CRF 196); according to the rules specified in the statistical analysis plan (finalized after the study was completed), events occurring after a "normal study termination" were not to be included in the primary endpoint analysis. Inclusion of these subjects did not alter the results of the primary endpoint analysis and in the analyses that follow, these subjects are excluded.

Table 26. Strokes excluded by the statistical analysis plan

Subject	Arm	Comments
1160-0026-00195011	Dabigatran 110	CRF 196 completed with visit date given as 12/17/2008, stroke on (b) (6)
1160-0026-01752009	Dabigatran 150	CRF 196 completed with visit date given as 2/11/2009, contact for this visit made by phone, stroke on (b) (6) stroke, death on (b) (6)

The primary endpoint, non-inferiority to warfarin for the time to the first occurrence of stroke/SEE, was established for both doses of dabigatran based on the margin recommended by the Agency, 1.38 ($p<0.0001$ for both comparisons) and the protocol-specified non-inferiority margin of 1.46 ($p<0.0001$ for both comparisons). The HR and 95% CI for the primary endpoint are shown below for both doses of dabigatran using the resubmitted data sets. The 150 mg dose was superior ($p<0.0001$) to warfarin for the primary endpoint. Analyses censoring subjects at the last clinic follow up visit at which a pulse was reported do not alter the findings. According to the FDA statistical reviewer, an additional 46 events (110 arm) and 97 events (150 arm) would be needed to reverse the non-inferiority findings (margin of 1.38) while an additional 33 events (150 arm) would be needed to reverse the superiority results. Hence, even in light of the missing disposition data, it seems unlikely that the efficacy findings (at least for noninferiority for the 150 dose) would be lost.

Table 27. Hazard ratios for stroke/SEE

	Dabigatran 110 vs. warfarin	Dabigatran 150 vs. warfarin
Hazard Ratio (95% CI)	0.90 (0.74, 1.10)	0.65 (0.52, 0.81)
P-value non-inferiority using 1.38	<0.0001	<0.0001
P-value non-inferiority using 1.46	<0.0001	<0.0001
P-value superiority	0.29	0.0001

[Source: Reviewer's analysis (Sponsor's datasets=adjrand; reviewer's filename= primary_endpoint)]
P-values for non-inferiority confirmed by Dr. Bai, FDA statistical reviewer.

The Kaplan-Meier estimate of time to first stroke/SEE by treatment arm is shown below.

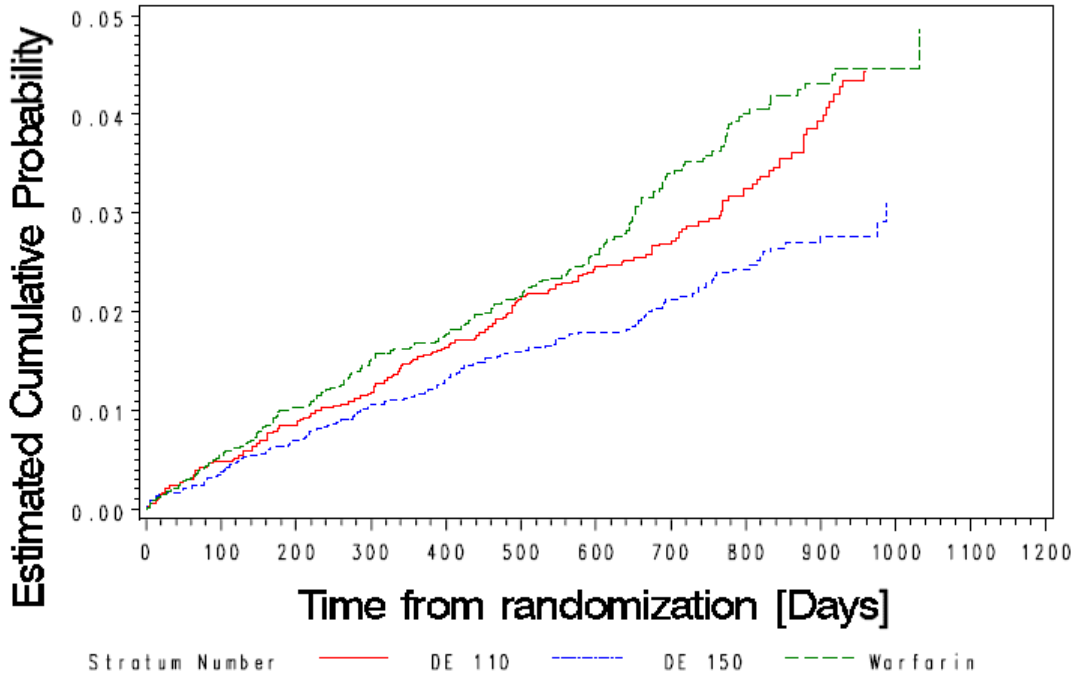


Figure 6. Kaplan Meier estimate of time to first stroke/SEE

[Source: FDA Statistical Reviewer]

Exclusion of sites/subjects recommended by DSI thus far (site 265 and 276 and subject 128002) do not alter the results of the primary endpoint analysis. A sensitivity analysis using the first 450th adjudicated events for data cut-off gives a HR of 0.94 (0.75, 1.16) for dabigatran 110 vs. warfarin, and a HR of 0.70 (0.56, 0.89) for dabigatran 150 vs. warfarin. "As treated" analyses censoring subjects 30 days after the time of first discontinuation of study medication (temporary or permanent), and 30 days after the last study medication date are also supportive of the ITT analysis (see table below). Analyses addressing effects in various subpopulations (baseline aspirin use, baseline

warfarin use, history of stroke/SEE/TIA) are presented in section 6.1.7. Analyses by center-level INR control are presented in section 6.10.

Table 28. "As treated" analysis of the primary endpoint

Time of censor	Dabigatran 110 vs. Warfarin		Dabigatran 150 vs. Warfarin	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Within 30 days of first discontinuation of study medication (temporary or permanent)	0.91 (0.70, 1.19)	0.50	0.67 (0.50, 0.89)	0.006
Within 30 days of last date of study medication usage	0.81 (0.65, 1.01.)	0.06	0.57 (0.45, 0.73)	<0.0001

[Source: Reviewer's analysis (Sponsor's datasets= lastmed, timev, timecens, adjrand; reviewer's filename= astreatedanalysis)]
P-values are for superiority; analyses are limited to subjects who were randomized and treated.

The yearly event rates (# of subjects with event/subject-years), HRs and 95% CIs for the individual components of the composite endpoint of stroke/SEE are shown in the tables below. The difference in the total number of stroke events in the dabigatran 150 mg versus warfarin treatment arms (65 events) is driven by a smaller number of both ischemic and hemorrhagic strokes. This contrasts with the findings in the dabigatran 110 mg arm where a smaller number of hemorrhagic strokes and numerically greater number of ischemic strokes are seen relative to warfarin.

Table 29. Yearly event rate for strokes and SEE

	Dabigatran 110 N (%)	Dabigatran 150 N (%)	Warfarin N (%)
Subject years of follow up	11899	12033	11794
Subjects with stroke/SEE	183 (1.5)	134 (1.1)	202 (1.7)
Subjects with stroke*	171 (1.4)	122 (1.0)	186 (1.6)
Ischemic	152 (1.3)	103 (0.9)	134 (1.1)
Hemorrhagic	14 (0.1)	12 (0.1)	45 (0.4)
SEE	15 (0.1)	13 (0.1)	21 (0.2)

[Source: Reviewer's analysis (Sponsor's datasets=adjrand; reviewer's filename=primary_ endpoint)] The numbers of ischemic and hemorrhagic strokes do not add up to the total strokes as some strokes were classified as "uncertain classification".

Table 30. Hazard ratios for components of primary endpoint

	Dabigatran 110 vs. warfarin		**Dabigatran 150 vs. warfarin**	
	HR (95% CI)	p-value superiority	HR (95% CI)	p-value superiority
Stroke	0.91 (0.74, 1.12)	0.38	0.64 (0.51,0.81)	.0001
Ischemic	1.13 (0.89,1.42)	0.31	0.75 (0.58,0.97)	0.030
Hemorrhagic	0.31 (0.17,0.56)	0.0001	0.26 (0.14,0.49)	<0.0001
SEE	0.71 (0.37,1.38)	0.31	0.61 (0.30,1.21)	0.16

[Source: Reviewer's analysis (Sponsor's datasets=adjrand; reviewer's filename=primary_ endpoint)]

Compared to warfarin treatment, treatment with Dabigatran 150 mg was associated with a smaller absolute number of strokes at each Rankin score, including fatal and disabling strokes.

Table 31. Investigator-reported Rankin scores at 3-6 months

Rankin Score 3-6 months	**Dabigatran 110**	**Dabigatran 150**	**Warfarin**
Missing	10	4	11
0	21	21	21
1	31	24	35
2	20	12	22
3	18	6	17
4	16	9	14
5	8	4	8
6	47	42	58

[Source: Reviewer's analysis (Sponsor's datasets=adjrand plt110n; reviewer's filename=primary_ endpoint)]
The Rankin scale runs from no symptoms (0) to death (6); a copy of the scale is provided in the appendix.

6.1.5 Analysis of Secondary Endpoints(s)

The results of secondary endpoint analyses as well as the yearly event rate of the individual components of these composites are shown below. The statistical analysis plan described in the 2005 protocol did not specify a strategy for controlling the type 1 error rate in testing these secondary endpoints and interpretation of their findings is limited. Mortality (all cause and vascular) appears to favor the dabigatran arms and is discussed further in section 6.1.6. The yearly event rate of PEs appears to be similar

across the three treatment arms. Finally, there is a numerical imbalance in the number of MI's that favors subjects randomized to warfarin.

Table 32. Hazard ratios for secondary endpoints

	Dabigatran 110 vs. warfarin		**Dabigatran 150 vs. warfarin**	
Secondary endpoints	HR (95% CI)	p-value for superiority	HR (95% CI)	p-value for superiority
Stroke (including hemorrhagic), systemic embolism, and all-cause mortality	0.93 (0.83,1.04)	0.22	0.83 (0.74,0.93)	0.0015
Stroke (including hemorrhagic), systemic embolism, pulmonary embolism, acute myocardial infarction, and vascular deaths (including deaths from bleeding)	0.98 (0.87, 1.11)	0.75	0.84 (0.74, 0.96)	0.009

[Source: Sponsor's April 19, 2010 submission; Tables 15.2.2.1:2 and 15.2.6.2:2]

Table 33. Yearly event rate (%) for stroke, SEE, PE, MI and vascular death

	Dabigatran 110 N (%)	**Dabigatran 150 N (%)**	**Warfarin N (%)**
Subject years of follow up	11899	12033	11794
Stroke	171 (1.4)	122 (1.0)	186 (1.6)
SEE	15 (0.1)	13 (0.1)	21 (0.2)
PE	14 (0.1)	18 (0.2)	12 (0.1)
MI	87 (0.7)	89 (0.7)	66 (0.6)
Silent MI	11 (0.1)	8 (0.1)	9 (0.1)
Vascular mortality	289 (2.4)	274 (2.3)	317 (2.7)
All cause morality	446 (3.7)	438 (3.6)	487 (4.1)

6.1.6 Mortality

The number of deaths in RE-LY, by treatment arm, is shown in the table below. Following database lock, two additional deaths were identified; one in the dabigatran 110 arm and one in the dabigatran 150 arm. In addition to these deaths, ten other deaths (six in the dabigatran 150 mg arm and four in the warfarin arm) were reported by investigators but were excluded from key analyses based on rules specified by the sponsor's statistical analysis plan.

Table 34. Number of deaths by treatment arm

Deaths	Dabigatran 110	Dabigatran 150	Warfarin
Original submission	445	437	486
Inclusive of events identified post database lock	446	438	487*
NDA resubmission	446	438	487
Inclusive of events excluded by sponsor's statistical analysis plan	446	444	491

*According to the sponsor (email correspondence dated 8.9.2010), one warfarin treated subject who died while in the study did not sign the Health Insurance Portability and Accountability Act form and was censored at the date of randomization in the original submission.

The events excluded by the sponsor's statistical analysis plan occurred after March 15, 2009, after the site was closed for cause, or after a patient was reported as having a "normal study termination" as indicated on the sponsor's study termination report ,CRF 196 (see table below). According to the statistical analysis plan (finalized on May 8 2009, after study completion), such events were not to be included "in the specified formal analysis."

Table 35. Deaths excluded by the sponsor's statistical analysis plan

Subject	Arm	Comments
1160-0026-00270004	Dabigatran 150	Death occurring after censor date/ (b) (6)
1160-0026-00715033	Dabigatran 150	Death occurring after censor date (b) (6)
1160-0026-00682034	Warfarin	Death occurring after censor date (b) (6)
1160-0026-00052015	Warfarin	Death occurring after censor date/ (b) (6)
1160-0026-00354003	Dabigatran 150	site closed for cause prior to death
1160-0026-00933035	Warfarin	CRF 196 completed with visit date given as 1/14/2009 (however investigator notes on form that patient didn't return for this visit given bad state of health), dies (b) (6)
1160-0026-01635006	Dabigatran 150	CRF 196 completed with visit date of (b) (6)
1160-0026-01677007	Dabigatran 150	CRF 196 completed with visit date given as (b) (6)

1160-0026-01752003	Warfarin	CRF 196 completed with visit date given as (b) (6) contact for this visit made by phone, admitted with fall on (b) (6)
1160-0026-01752009*	Dabigatran 150	CRF 196 completed with visit date given as (b) (6), contact for this visit made by phone, (b) (6)

*This subject is also presented in section 6.1.4

The yearly event rate for all cause mortality was 3.8, 3.6 and 4.1% in the dabigatran 110, dabigatran 150 and warfarin arms, respectively. The hazard ratios (relative to warfarin) are shown in the tables below. Conducting the analysis according to the finalized statistical analysis plan gives a p-value of 0.052 for the 150 dose; inclusion of the ten deaths described above shifts the p-value to 0.060. An analysis stratifying subjects by center-level INR control (subjects at centers with mean TTRs above the median and below the median) shows that the imbalance between treatment arms is driven by subjects at centers with less optimal levels of INR control (see the appendix for further explanation of center-level based analyses as well as a discussion of the impact of center-level INR control on the treatment benefit of warfarin).

Table 36. Hazard ratios for all cause mortality

	Dabigatran 110 vs. warfarin		**Dabigatran 150 vs. warfarin**	
	HR (95% CI)	p-value	HR (95% CI)	p-value
According to SAP	0.91 (0.80,1.03)	0.13	0.88 (0.77, 1.00)	0.052
Inclusive of deaths excluded by SAP	0.90 (0.88, 1.02)	0.10	0.88 (0.78,1.00)	0.060
According to center-level INR control				
Subjects at centers with mean TTR<67%	0.77 (0.65, 0.92)	0.005	0.78 (0.66, 0.93)	0.007
Subjects at center with mean TTR≥67%	1.08 (0.89, 1.30)	0.43	1.01 (0.84,1.23)	0.89

[Reviewer's analysis (sponsor's datasets=inrvis, adjrand timev, timecens; reviewer sas file=other_efficicacy_endpoints and inr)]; TTR=time in therapeutic range.

	Dabigatran 110 vs. warfarin		Dabigatran 150 vs. warfarin	
	HR (95% CI)	p-value	HR (95% CI)	p-value
According to SAP	0.91 (0.80,1.03)	0.13	0.88 (0.77, 1.00)	0.052
Inclusive of deaths excluded by SAP	0.90 (0.88, 1.02)	0.10	0.88 (0.78,1.00)	0.060
According to center-level INR control				
Subjects at centers with mean TTR<67%	0.77 (0.65, 0.92)	0.005	0.78 (0.66, 0.93)	0.007
Subjects at center with mean TTR≥67%	1.08 (0.89, 1.30)	0.43	1.01 (0.84,1.23)	0.89

[Reviewer's analysis (sponsor's datasets=inrvis, adjrand timev, timecens; reviewer sas file=other_efficicacy_endpoints and inr)]; TTR=time in therapeutic range.

The imbalance in all-cause mortality (relative to warfarin) was driven by an effect on adjudicated vascular specific mortality in the dabigatran 150 arm and by a numerically smaller number of adjudicated vascular and non vascular deaths in the dabigatran 110 arm[12]. The yearly event rate for adjudicated vascular mortality was 2.5, 2.3 and 2.7% in the dabigatran 110, dabigatran 150 and warfarin arms, respectively; the HR of dabigatran 150 relative to warfarin was 0.84 (p-value of 0.04).

In the CRF used to report deaths, investigators were to specify the cause of death. Relative to warfarin, a numerically smaller number of investigator reported fatal strokes were reported in the dabigatran arms (both doses); a slightly smaller number of deaths attributed to hemorrhage were also reported at the 110 dose. Other causes of death also contributed to the imbalance in all cause mortality in one or the other treatment arms (e.g. investigator-reported sudden/arrhythmic death, investigator reported non-vascular mortality "other").

Table 37. Adjudicated and investigator-reported cause of death

	Dabigatran 110	Dabigatran 150	Warfarin
	N=446	**N=438**	**N=487**
Adjudicated vascular mortality	289 (2.4)	274 (2.3)	317 (2.7)
Adjudicated non-vascular mortality	157 (1.3)	164 (1.4)	170 (1.5)
Inv-reported vascular mortality	266	244	284
Sudden/arrhythmic death	89	75	87
Pump failure death	71	76	69
Stroke	30	23	44

12 Deaths were adjudicated as vascular (including bleeding) or non-vascular. Vascular deaths were considered to occur when no obvious nonvascular event to explain death was noted; sudden or unwitnessed deaths were also considered vascular.

Pulmonary Embolism	2	1	4
Peripheral Embolus	2	1	2
Aortic dissection/rupture	4	1	3
Hemorrhage	11	14	18
Unknown Cause	46	41	46
Other	12	14	11
Inv-reported non-vascular mortality	163	173	177
Cancer	64	68	61
Respiratory Failure	33	29	31
Trauma	3	6	6
Infection	22	24	21
Other	41	47	59
Missing/Unknown	17	21	26

[Reviewer's analysis (sponsor's datasets=plt126n, adjrand; reviewer sas file=other_efficacy_endpoints)]

Reviewer's comments: The number of investigator reported stroke-related deaths differs from the number obtained using Investigator Rankin scores.

Vital status queries were made for subjects who prematurely discontinued from the study. A greater number of deaths were reported as part of these queries in the warfarin compared to dabigatran arms; when viewed as a proportion of the number of deaths reported in each treatment arm in the trial, the proportion was greatest in the warfarin arm. Analyses excluding this subpopulation give a HR for all cause mortality of 0.89 (95% CI 0.78 to 1.02, p= 0.09) for dabigatran 150 and 0.92 (95% CI 0.81 to 1.05, p= 0.20) for dabigatran 110.

Table 38. Results of vital status queries*

	Dabigatran 110	**Dabigatran 150**	**Warfarin**
All subjects reported by sponsor as prematurely discontinuing from study	203	235	242
Subjects who prematurely discontinued from study and vital status information sought	119 (58.6)	147 (62.6)	156 (63.7)
Alive	100 (84.0)	120 (81.0)*	126 (80.8)
Died	7 (5.9)	8 (5.4)*	17 (10.9)
Unknown	12 (10.1)	19 (12.9)	13 (8.3)
As a proportion of deaths reported for given treatment arm in the ITT population	1.6%	1.8%	3.5%

Because deaths occurring after 3.15.2009 were not included in efficacy analyses, one subject who died after 3.15.2009 is counted as being alive for the purposes of this table.
*These analyses were conducted prior to the submission of the corrected disposition data and hence the numbers of subjects prematurely discontinuing from the study differ from those shown in section 6.1.3.

Reviewer's comment: The results suggest possible bias in the ascertainment of vital status in subjects who prematurely discontinued from the study.

6.1.7 Subpopulations and concomitant medications

Effects on the primary endpoint, stroke and systemic embolic events were also explored across important subpopulations as shown in the sponsor's figure below. The efficacy of the 150 dose appeared to be preserved across these subpopulations (as defined by the sponsor) with no clear interaction seen; this was not consistently the case in subgroup analyses of the 110 dose (e.g., .subjects < 65, atrial fibrillation type, CHADS2 score). Few blacks were studied (167), limiting the ability to draw conclusions about efficacy/safety in this population; the point estimates were favorable, but the confidence intervals were wide (see FDA Statistical Reviewer's analysis). Analyses based on center-level INR control are discussed further in section 6.1.10.

Subgroup	Patients Total no.	DE110 % per year	DE150 % per year	Warfarin % per year	P-value Interaction
All patients	18113	1.54	1.11	1.71	
Age (years)					0.70
<65	2981	1.47	0.69	1.35	
65<= and <75	7894	1.26	0.98	1.45	
>=75	7238	1.89	1.43	2.15	
Gender					0.46
Male	11514	1.36	1.10	1.53	
Female	6598	1.86	1.14	2.03	
VKA use at entry					0.87
Naive	9126	1.57	1.07	1.69	
Experienced	8984	1.51	1.15	1.74	
BMI (kg/m2)					0.48
<25	4697	1.89	1.33	2.65	
25<= and <30	7111	1.54	1.16	1.49	
30<= and <35	4038	1.28	0.99	1.16	
>=35	2241	1.32	0.76	1.49	
CrCL (mL/min)					0.63
30<= and <50	3343	2.40	1.27	2.69	
50<= and <80	8297	1.69	1.21	1.87	
>=80	5658	0.86	0.73	1.03	
Region					0.64
USA, Canada	6533	1.19	1.11	1.51	
Central Europe	2119	1.31	0.96	0.96	
Western Europe	4651	1.45	1.11	1.46	
Latin America	956	1.82	0.91	1.68	
Asia	2782	2.50	1.39	3.06	
Other	1072	1.95	0.88	2.27	
ASA use at baseline					0.91
No	10960	1.45	1.01	1.57	
Yes	7153	1.67	1.29	1.93	
Stroke/SEE/TIA					0.75
No	14159	1.28	0.88	1.46	
Yes	3953	2.46	1.91	2.66	
Heart Failure					0.66
No	13203	1.41	1.00	1.64	
Yes	4904	1.90	1.44	1.92	
Diabetes and age>=65					0.49
No	14616	1.50	1.04	1.57	
Yes	3496	1.68	1.46	2.29	
Hypertension and age>=65					0.04
No	5922	1.70	0.83	1.39	
Yes	12190	1.46	1.26	1.87	
CHADS2 score					0.60
1	5331	1.12	0.68	1.09	
2	6453	1.45	0.84	1.38	
3+	5876	2.12	1.89	2.73	
AF type					0.16
Persistent	5789	1.72	1.14	1.80	
Paroxysmal	5943	1.07	1.09	1.77	
Permanent	6375	1.78	1.11	1.58	
Centre INR % time in range 2-3					0.41
<67%	9073	1.70	1.12	1.97	
>=67%	8951	1.38	1.11	1.45	

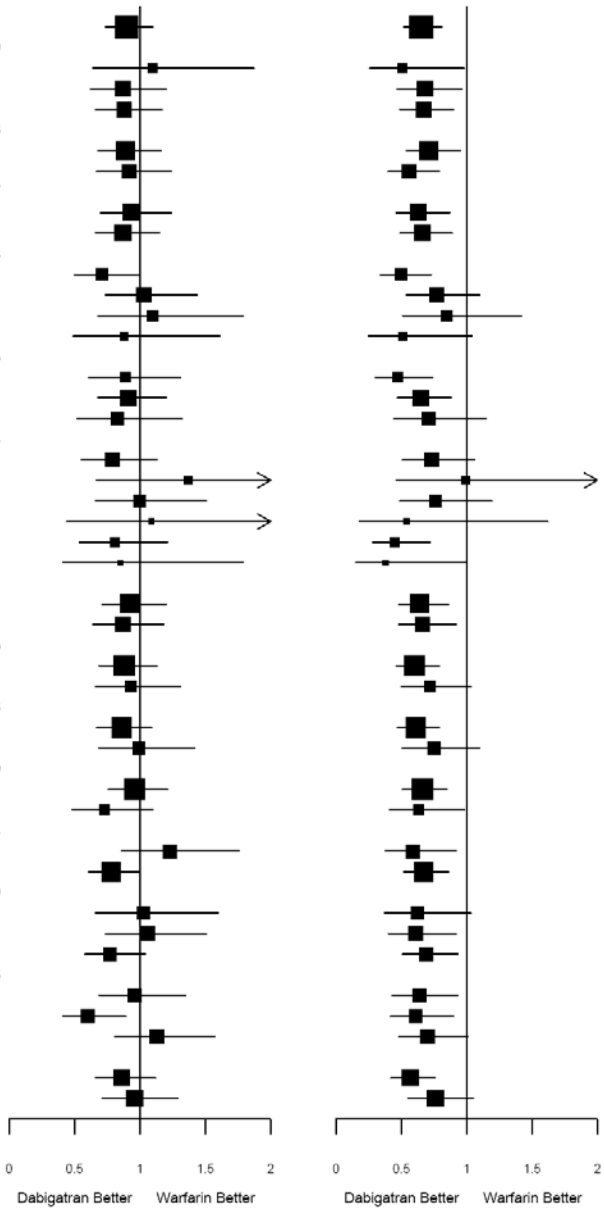


Figure 7. Stroke/SEE hazard ratios by baseline characteristics

[Source: Sponsor's proposed label dated May 27, 2010, Figure 3]

The FDA statistical reviewer also conducted sub-group analyses by history of stroke/SEE/TIA, age, gender, prior VKA use, country and aspirin use; these analyses were supportive of the findings shown above.

In light of the drug's pH dependent solubility and pharmacodynamic effects, additional sub-group analyses were also performed exploring the affect of concomitant

medications including aspirin, clopidogrel, proton pump inhibitors and H2 blockers on efficacy outcomes. As shown in Section 6.1.2, reported use of these medications was similar across treatment arms at baseline; whereas ~40% of subjects were on aspirin at baseline, use of clopidogrel and H2 blockers was uncommon (~5-6% and ~4%, respectively). Of subjects reported to be taking aspirin between randomization and study termination, the mean and median percent of time on aspirin was ~62-65% and 100%, respectively (incidence similar across treatment arms).

With the exception of the proton pump inhibitors, use of the aforementioned concomitant medications appeared to be comparable across treatment arms over time without any marked increase over the course of the study. In contrast, proton pump inhibitor use appeared to increase over the course of the trial and, over time, an imbalance was seen across the treatment arms, with greater use in dabigatran compared to warfarin-treated subjects (possibly secondary to the greater incidence of GI adverse events in the dabigatran arms). This change in use over time further complicates analyses addressing the effect of concomitant PPI usage on the incidence of efficacy outcome events.

Table 39. Changes in the use of proton pump inhibitor therapy during RE-LY

Proton Pump Inhibitor Use	Dabigatran 110	Dabigatran 150	Warfarin
Baseline	847(14.1)	878(14.5)	842(14)
anytime during year one	1279(21.3)	1315(21.6)	1108(18.4)
anytime during year two	1247(20.7)	1275(21)	1087(18.1)
anytime during year three	610(10.1)	614(10.1)	510(8.5)
anytime during study	1474(24.5)	1500(24.7)	1268(21.1)

As shown in the table below, the data from RE-LY do not suggest decreased efficacy in the setting of PPI use. The relationship between proton pump inhibitor use and the risk of ischemic stroke (relative to warfarin) was not consistent at the 110 and 150 dose and the confidence intervals encompassed the point estimates seen in the larger study population (HR of 1.12 and 0.75 for the 110 dose vs. warfarin and 150 dose vs. warfarin, respectively). There were few ischemic strokes reported in subjects on clopidogrel at baseline (29) or H2 blockers at baseline (19); point estimates were associated with very broad confidence intervals and hence interpretation was limited (results of analyses are not shown).

Table 40. Proton Pump Inhibitor use and the risk of ischemic stroke

	HR (95% CI)		
Proton Pump Inhibitor	D110 vs. warfarin	D150 vs. warfarin	D150 vs. D110
Never Used*	1.37 (1.04, 1.80)	0.75 (0.54, 1.03)	0.55 (0.41, 0.74)
Use at baseline	0.83 (0.45, 1.54)	1.12 (0.63, 1.97)	1.3 (0.74, 2.4)
100% Use	0.69 (0.35, 1.37)	1.10 (0.61, 2.01)	1.59 (0.82, 3.09)

[Reviewer's analysis (sponsor's datasets=bascocm, timecens and timev; reviewer sas file=ASA_PPI_analyses)]
*If subject had been on proton pump inhibitor, stop date was prior to date of first intake of study drug.

The HRs and 95% CIs for ischemic strokes by concomitant usage of aspirin is shown below. Though the confidence intervals of the hazard ratios are wide and cross one, the point estimates suggest that even in the setting of concomitant aspirin use, the 150 dose may provide greater benefit (ischemic stroke reduction) than the 110 dose.

Table 41. Aspirin use and the risk of ischemic stroke

	HR (95% CI)		
Aspirin	D110 vs. warfarin	D150 vs. warfarin	D150 vs. D110
Never Used*	1.0 (0.72, 1.39)	0.44 (0.29, 0.67)	0.44 (0.29, 0.67)
Use at baseline	1.30 (0.91, 1.85)	0.93 (0.63, 1.36)	0.72 (0.50, 1.03)
100% Use	1.38 (0.82, 2.32)	0.95 (0.53, 1.70)	0.69 (0.41, 1.18)

[Reviewer's analysis (sponsor's datasets=bascocm, timecens and timev; reviewer sas file=ASA_PPI_analyses)]
*If a subject had been on aspirin, stop date was prior to date of first intake of study drug.

6.1.8 Analysis of clinical information relevant to dosing recommendations

Three phase 2 dose-ranging studies were conducted in patients with atrial fibrillation. These studies, along with studies conducted as part of other indications, are cited by the sponsor as supporting the choice of dose selection in RE-LY. The phase 2 trials conducted in patients with atrial fibrillation studied doses ranging from 50 mg bid to 300 mg bid and are shown in the table below.

Table 42. Phase 2 studies in patients with atrial fibrillation

Study	Design	Doses (N)
1160.20 (PETRO)	Randomized, controlled, double-blind (dabigatran doses), open label (ASA and warfarin) 12-week study in patients with non-rheumatic atrial fibrillation and one stroke risk factor	*Dabigatran:* 50 mg bid (58) 50 mg bid + ASA 81 mg (20) 50 mg bid + ASA 325 mg (27) 150 mg bid (99) 150 mg bid + ASA 81 mg (34) 150 mg bid + ASA 325 mg (33) 300 mg bid (98) 300 mg bid + ASA 81 mg (33) 300 mg bid + ASA 325 mg (30) *Warfarin* to target INR 2-3 (70)
1160.42 (PETRO-EX)	Long-term (5 years), open-label, uncontrolled, non-randomized study of dabigatran (with ASA added at the investigator's discretion) in patients previously treated with dabigatran in Study 1160.2013	*Dabigatran*: 150 mg qd 150 mg bid 300 mg qd 300 mg bid
1160.49	Randomized, open label 12-week study in Japanese patients with moderate to high risk atrial fibrillation	*Dabigatran*: 110 mg bid (53) 150 mg bid (59) *Warfarin* to target INR 2-3, INR 1.6-2.6 in patients age ≥ 70 (62)

As a whole, the phase 2 studies suggest that over the dose range studied, increasing doses/exposures result in greater prolongation of aPTT and ECT. These studies also suggest that (at least at some dose levels of dabigatran) there may be a relationship between concomitant aspirin use and increased risk of bleeding; this issue is addressed further under safety. These studies do not, however, provide significant insight into the optimal dosing regimen for the prevention of thromboembolic events. Studies 1160.20 and 1160.49 were limited in size and study duration and few thromboembolic events were observed. In trial 1160.49, no thromboembolic events were seen during dabigatran treatment and in trial 1160.20, two thromboembolic events were reported (both in the 50 mg bid treatment arm). In study 1160.42, a long-term, open-label, non-randomized

13 Although treatment group assignment in study 1160.42 was based on treatment group assignment in study 1160.20, patients did not necessarily remain in the same treatment arm as in 1160.42. The doses administered in some treatment arms were also changed during the course of the study (with amendment 4, patients previously treated with dabigatran 150 mg QD or 300 mg BID were administered 150 mg BID). Down titration in dose also occurred in patients with both a low GFR and high corrected aPTT (but not below 150 mg QD).

study, a small number of strokes were reported (see table below). However, interpretation of the data from this trial is not straightforward. Patient-years of exposure is limited for doses other than 150 mg BID doses, some subjects were crossed-over to other treatment arms, the study was not randomized, nor was it blinded.

With respect to the lower end of the effective dose range, RE-LY itself provides the most informative data regarding thromboembolic prevention. In subjects randomized to dabigatran 110, 171 strokes were reported compared to 122 in subjects randomized to dabigatran 150. Compared to the lower dose, the hazard ratio for the higher dose was 0.71 (95% CI 0.56 to 0.90, p-value=0.003), suggesting a clinically important reduction in the risk of such events with the higher dose. RE-LY also provides important data that can speak to the upper end of the dose range likely to provide “net benefit;” an issue that is addressed in Section 1.2 on Risk-Benefit .

Table 43. Incidence of secondary efficacy endpoints in PETRO-EX (1160.42)

Event	50 mg QD	50 mg BID	150 mg QD	150 mg BID	300 mg QD	300 mg BID	Total Dabig.
Cumulative exposure (patient years)	0.05	24	60	842	242	82	1250
Any stroke							
N	0	1	3	9	4	0	17
Per 100 patient-years [1]	0.0	4.3	5.0	1.1	1.7	0.0	1.4
Ischaemic stroke							
N	0	1	3	4	4	0	12
Per 100 patient-years	0.0	4.3	5.0	0.5	1.7	0.0	1.0
Haemorrhagic stroke							
N	0	0	0	5	0	0	5
Per 100 patient-years	0.0	0.0	0.0	0.6	0.0	0.0	0.4
Any TIA							
N	0	0	0	2	1	0	3
Per 100 patient-years	0.0	0.0	0.0	0.2	0.4	0.0	0.2
Non-CNS systemic thromboembolism							
N	0	2	0	2	1	1	6
Per 100 patient-years	0.0	8.5	0.0	0.2	0.4	1.2	0.5
Myocardial infarction							
N	0	0	0	9	1	0	10
Per 100 patient-years	0.0	0.0	0.0	1.1	0.4	0.0	0.8
Other MACE							
N	0	2 [2]	0	9	2	1	14
Per 100 patient-years	0.0	8.5	0.0	1.1	0.8	1.2	1.1
All cause death							
N	0	0	0	23	5	0	28
Per 100 patient-years	0.0	0.0	0.0	2.7	2.1	0.0	2.2
Ischaemic stroke, TIA, non-CNS TE, MI, MACE, death							
N	0	4 [3]	3	46	11	2	66
Per 100 patient-years	0.0	17.0	5.0	5.5	4.5	2.4	5.3
Stroke, non-CNS TE							
N	0	2	3	11	5	1	22
Per 100 patient-years	0.0	8.5	5.0	1.3	2.1	1.2	1.8

[Source: Table 11.4.1.2:1]

In addition to the studies conducted in patients with atrial fibrillation, studies have also been conducted in other patient populations and indications, including primary and secondary prevention of venous thrombosis and as a treatment for acute coronary syndrome. From the standpoint of safety, these studies generally support the concept that higher doses are associated with increased risk of bleeding. With regard to efficacy, according to the sponsor, a dose dependent decrease in the frequency of venous thromboembolism events was seen with increasing dabigatran dose: 28.5%, 17.4%, 16.6%, 13.1%, of subjects assigned to dabigatran 50 BID, 150 BID, 300 QD, and 225 BID, respectively in a phase 2 study of primary venous thromboembolism prevention (study 1160.19). The sponsor noted that this effect was “more prominent” between the 50 and 150 BID dose and “less striking” at the higher doses. A relationship between increasing dabigatran dose and decreasing incidence of a composite endpoint of venous thromboembolism events and all-cause mortality is also cited by the sponsor (study 1160.50, another study of primary venous thromboembolism prevention). Differences in populations, concomitant medications, and indications limit the ability to extrapolate from the experience in these studies to the proposed indication and these studies were not reviewed further.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

The Kaplan-Meier curves of time to first stroke/SEE (see section 6.1.4) suggest no loss of efficacy over time.

6.1.10 Additional Efficacy Issues/Analyses

6.1.10.1 Warfarin administration and INR control

The following analyses address exposure to warfarin and the quality of INR control in subjects randomized to warfarin.

Exposure to warfarin
Of the 6,022 subjects randomized to warfarin in RE-LY, 80.8% (4849) completed the study on study medication. Over 50% of subjects had at least one interruption of study medication over the course of the trial; a similar percentage of subjects had interruptions in the dabigatran treatment arm (see section 7.2.1) As shown in the table below, most interruptions were for less than 30 days. Approximately 35% of temporary interruptions of study medication in the warfarin treatment arm were in the setting of a surgery or procedure; around 20% occurred in the context of an adverse event and 16% in the context of a hospitalization (source: sponsor’s table 15.1.1:4; subjects were counted in multiple categories when multiple reasons were given). Subjects in the warfarin arm were on study medication for 91.0% of study days of follow up (source; reviewer’s analysis using FDA censoring rules).

Table 44. Interruptions of study medication

	Subjects (%)
Randomized to warfarin	6022
Randomized and treated	5998
Number with interruptions	3120 (52.0)
Total temporary interruptions (days*)	
1 ≤ and < 8	1112 (18.5)
8 ≤ and <30	877 (14.6)
30 ≤ and <60	222 (3.7)
≥ 60	194 (3.2)
Permanently discontinued study medication	1073 (17.9)

[Source: adapted from sponsor's table 15.1.5:1, April 19, 2010 resubmission]
For subjects with more than one interruption, the cumulative days of interruptions were calculated. Subjects who had both temporary and permanent discontinuations were counted in both categories, hence these categories do not add up.

INR control
Of the 5998 subjects randomized and treated with warfarin, 134 subjects lacked follow up INR data (as reported in the CRF INR log). Of these, approximately 45% permanently discontinued study medication within one week of starting therapy; approximately 72% were on therapy for 30 days or less. Of those subjects with measurements that were taken and reported, approximately 32% of subjects had at least one INR measurement taken >60 days from the prior INR measurement and approximately 16% had at least one INR measurement taken > 90 days from the prior measurement.

To assess the adequacy of INR control, the percent of time reported INR values were within and outside the therapeutic range (2-3) were calculated using available data. Analyses of the percent of time values were in the therapeutic range (2-3) were initially performed by the sponsor excluding days in the first week after randomization and days while study warfarin was temporarily or permanently stopped. Because one reason given by investigators for holding warfarin was an elevated INR and because embolic strokes are likely to occur while anticoagulation is on hold, even if the reason for holding therapy is appropriate (e.g., bleed or procedure), an analysis was also performed in which available data during periods of medication interruption were included. The results of analyses excluding days while warfarin was temporarily or permanently stopped and including periods of medication interruption are shown in the tables below. The mean time in therapeutic range (2-3) was 64.4% (analyses excluding interruptions) and 63.4% (analyses including interruptions). The mean percent of time U.S. subjects were in an INR range of 2-3 was 66% (64.7% including available data during periods of medication interruption).

Table 45. Mean percent of time INR 2 to 3

	Percent of time INR 2 to 3 excluding data while study warfarin temporarily or permanently stopped			Percent of time INR 2 to 3 including available data during periods of medication interruption		
Months (cumulative)	N	MEAN	STD	N	MEAN	STD
1	4899	49.2	38.5	4956	48.7	38.2
3	5668	56.3	30.4	5711	55.6	30.2
6	5565	60.3	25.3	5624	59.4	25.4
12	5236	64.0	20.4	5301	63.0	20.7
Overall	5791	64.4	19.8	5812	63.4	19.9

[Reviewer's analysis (sponsor's dataset=inrvis); reviewer sas file=inr)]

The percent of INR measurements greater than 4, less than 2, and less than 1.5 (as determined using the Rosendale method) is shown in the tables below. The overall mean percent of reported INR measurements greater than 4 was ~2%; the overall mean percent of INR measurements < 2 and <1.5 was ~22-23% and ~5%, respectively. Compared to later months, during the first month of therapy, a greater percentage of INR measurements were greater than 4 or less than 1.5.

Table 46. Mean percent of time INR>4

	Percent of time INR >4 excluding data while study warfarin temporarily or permanently stopped			Percent of time INR> 4 including available data during periods of medication interruption		
Months (cumulative)	N	MEAN	STD	N	MEAN	STD
1	4899	5.2	16.4	4956	5.4	16.6
3	5668	3.1	9.7	5711	3.1	9.3
6	5565	2.3	6.3	5624	2.3	6.2
12	5236	1.9	4.2	5301	1.9	4.2
Overall	5791	2.2	6.0	5812	2.1	5.5

Table 47. Mean percent of time INR<2

	Percent of time INR <2.0 excluding data while study warfarin temporarily or permanently stopped			Percent of time INR< 2.0 including available data during periods of medication interruption		
Months (cumulative)	N	MEAN	STD	N	MEAN	STD
1	4899	31.6	38.7	4956	31.9	38.6
3	5668	29.0	30.7	5711	30.0	30.9
6	5565	26.2	25.5	5624	27.3	25.8
12	5236	22.8	19.9	5301	23.9	20.5
Overall	5791	22.2	19.1	5812	23.4	19.5

Table 48. Mean percent of time INR <1.5

	Percent of time INR <1.5 excluding data while study warfarin temporarily or permanently stopped			Percent of time INR< 1.5 including available data during periods of medication interruption		
Months (cumulative)	N	MEAN	STD	N	MEAN	STD
1	4899	10.6	26.2	4956	10.9	26.3
3	5668	8.4	20.2	5711	9.0	20.7
6	5565	6.6	15.7	5624	7.3	16.4
12	5236	4.7	10.8	5301	5.5	11.9
Overall	5791	4.8	11.3	5812	5.5	12.2

[Reviewer's analysis (sponsor's dataset=inrvis); reviewer sas file=inr)]

Reviewer's comment: These analyses suggest that, as a whole, reasonable INR control was achieved in warfarin-treated subjects in RE-LY. For further discussion, see the Efficacy Summary.

It has been shown that the time in therapeutic range measured at the center-level and country-level (determined by averaging the individual times in therapeutic range for all subjects randomized to oral anticoagulant therapy within a center or country to yield a value for that center or country), has an important impact on the treatment benefit of warfarin in intervention trials. The benefit of oral anticoagulants over antiplatelet agents has been shown to be dependent upon the quality of INR control as measured by the time in therapeutic range at the center and country level (Connolly et al. 2008; see also Appendix).

Analyses stratifying subjects by center-level INR control (stratifying centers into quartiles) are shown in the table below. These analyses do not show a clear graded

relationship between the center-level of INR control and the benefit of dabigatran relative to warfarin. For the primary efficacy endpoint, the point estimate of the HR for the 150 dose moves closer to one with broad confidence intervals that exceed one in the subset of subjects enrolled at sites achieving the highest quartile of INR control, suggesting that the benefit of the 150 dose of dabigatran (relative to warfarin) is somewhat dependent upon the level of INR control achieved in warfarin-treated subjects. With regard to bleeding, there appears to be a graded relationship between quartile of center-level INR control and the relative risk of adjudicated major bleeds, with much of the relative risk reduction in bleeding in the 110 arm driven by subjects at centers achieving lower levels of INR control. These results suggest that in patients with well controlled INRs, the 110 dose may not provide a significant reduction in the risk of bleeding relative to warfarin.

Table 49. Analyses by quartile of center-level INR control

Quartile of center-level INR control*		**1 <58.5**	**2 ≥58.5 and <66.8**	**3 ≥66.8 and <74.2**	**4 ≥74.2**
Number of subjects		N=4162	N=4662	N=4772	N=4428
Stroke/SEE					
Dabigatran 110 vs. warfarin	HR	0.95	0.79	0.97	0.92
	95% CI	0.64,1.40	0.54, 1.16	0.65,1.44	0.59,1.44
	p-value	0.79	0.23	0.87	0.72
Dabigatran 150 vs. warfarin	HR	0.60	0.53	0.65	0.90
	95% CI	0.39, 0.94	0.35,0.81	0.42,1.02	0.57,1.41
	p-value	0.02	0.003	0.06	0.63
Major Bleeds					
Dabigatran 110 vs. warfarin	HR	0.64	0.74	0.90	0.93
	95% CI	0.46, 0.88	0.57, .097	0.69, 1.17	0.68, 1.26
	p-value	0.005	0.03	0.43	0.62
Dabigatran 150 vs. warfarin	HR	0.68	0.90	1.00	1.20
	95% CI	0.50, 0.93	0.70, 1.16	0.77, 1.30	0.90, 1.60
	p-value	0.016	0.41	1.00	0.21

[Reviewer's analysis (sponsor's datasets= inrvis, adjrand); reviewer sas file=inr]
*Center-level INR control was determined by averaging the individual times in therapeutic range for all subjects randomized to warfarin within a center to yield a value for that center. Centers were than stratified into quartiles by center-level INR control.

The level of INR monitoring (as determined by the days on warfarin/the number of reported INR measurements) in subjects included in the sponsor's calculations of time in therapeutic range is shown in the figure below. As shown in the figure, the majority of subjects had at least one INR measurement for every 30 days of treatment, though some subjects had infrequent monitoring despite poor control. Some subjects with

reported optimal control (higher percent time in therapeutic range) also had infrequent monitoring.

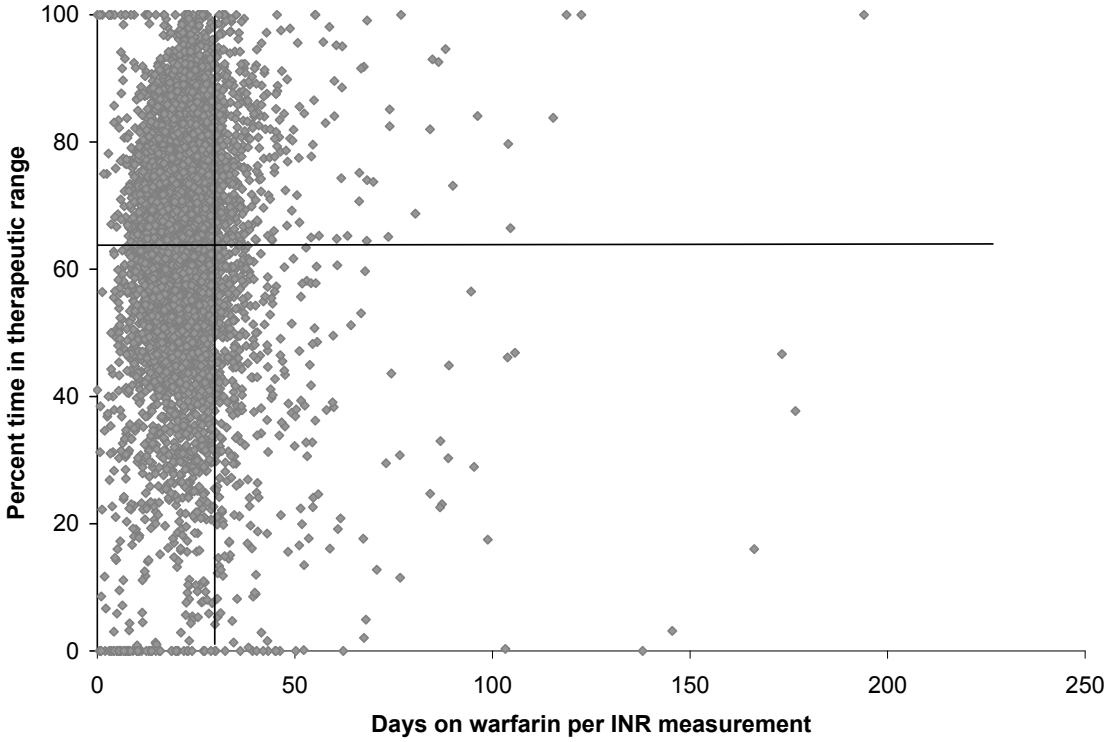
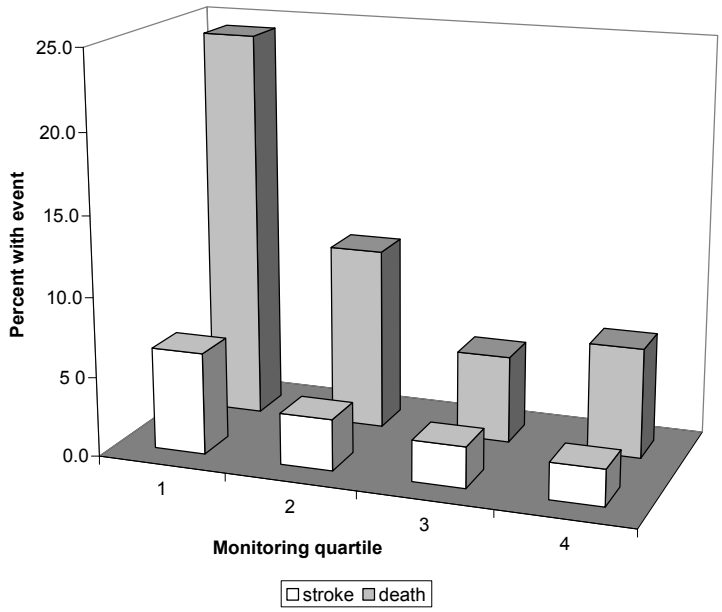


Figure 8. Percent time in therapeutic range vs. frequency of monitoring

[Reviewer's analysis (sponsor's datasets=offmed, inr2, inrvis); reviewer sas file=inr]
*Days on warfarin are cumulative and not necessarily consecutive. Vertical line drawn at 30 days; horizontal line drawn at 64% time in therapeutic range.

Analyses looking at adjudicated strokes and deaths in subjects by frequency of INR monitoring (broken into quartiles) and further stratified by the percentage of time a subject was in the therapeutic range (above and below the median value) did not suggest worse outcomes in those with less frequent INR monitoring. There did appear to be a numerical increase in the number of events (deaths and strokes) in subjects undergoing the most frequent monitoring, possibly representing the subset of subjects with more difficult to control or variable INRs.

A.



B.

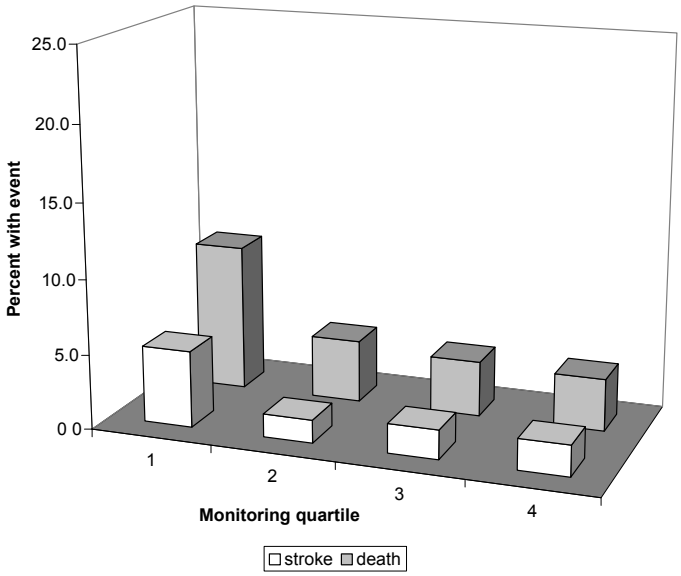


Figure 9. Events by frequency of monitoring and level of INR control

[Reviewer's analysis (sponsor's datasets=offmed, inr2, inrvis); reviewer sas file=inr]
A. Subjects with TTR >67%; B. Subjects with TTR≤67%
The frequency of monitoring decreases with increasing quartile.

6.1.10.2 Analyses pertaining to RE-LY's open-label design

RE-LY was an open-label study with respect to warfarin. The following analyses focus on the adjudication process. The differential treatment of subjects in the dabigatran vs. warfarin treatment arms is also addressed.

Investigator-reported vs. Adjudicated strokes, SEE and major bleeds
Of subjects with investigator reported strokes, similar percentages were adjudicated as having a stroke in the three treatment arms. Of subjects with investigator-reported TIAs, similar percentages were adjudicated as having a stroke. In contrast, a smaller percentage of subjects with investigator-reported systemic embolic events were adjudicated as having had systemic embolic events in the dabigatran compared to warfarin-treatment arms (discussed further below).

Table 50. Investigator-reported vs. adjudicated strokes, TIAs and SEE

	Dabigatran 110	**Dabigatran 150**	**Warfarin**
Subjects with investigator-reported strokes	183	143	205
Number (%) of subjects with adjudicated stroke	163 (89.1)	120 (83.9)	181 (88.3)
Subjects with investigator-reported TIAs	85	90	107
Number (%) of subjects with adjudicated stroke	16 (18.8)	12 (13.3)	17 (15.9)
Subjects with investigator-reported SEE	32	29	29
Number (%) of subjects with adjudicated SEE	15 (46.9)	13 (44.8)	21 (72)

[Reviewer's analysis (sponsor's datasets=timev; reviewer sas file=primary_endpoint)]

As a percentage of investigator reported major bleeds, the percentage of major bleeds adjudicated as "no event" was also similar across the treatment arms.

Table 51 Investigator-reported vs. adjudicated major bleeds

	Dabigatran 110	Dabigatran 150	Warfarin
Investigator reported major bleed	427	528	515
Total subjects (n)	355	427	449
Adjudicated bleeds			
Total Major bleed	404	492	478
Major bleed	248	296	250
Life threatening bleed	156	196	228
No Event	34	45	44

[Reviewer's analysis: (sponsor's datasets= adjud, adjud3, timev and plt122n; reviewer sas file= mj\adjud\original\adj and major) .Total major bleed + no event does not equal investigator reported because some major bleeds were not identified by the investigator

Identification of endpoint events and adjudication process

As previously noted in the review, the central adjudication committee had concluded that there were inconsistencies in the adjudication of Non-CNS embolic events and, as a result, non-CNS embolic events were re-adjudicated. The outcome of this second review was to be final and supersede previous documented decisions in the main clinical data base. A random sample of five events adjudicated as SEE in the warfarin arm and five investigator-reported events not adjudicated as SEE in the dabigatran arm were reviewed. In all of the warfarin cases, the re-adjudication was consistent with the original adjudication. In two of five dabigatran cases, the original adjudication was that an event had occurred. In both these cases, the re-adjudication appeared appropriate.

Table 52. Review of adjudicated SEE

Subject	Adjudication		FDA Reviewer	Comments
	Second	Original		
Warfarin				
00035039	yes	yes	yes	
00474008	yes	yes	yes	
01095010	yes	yes	yes	
01396006	yes	yes	yes	
01589031	NA	yes	yes	identified post database lock, not re-adjudicated
Dabigatran				
00226020	no	yes	no	DVT
00432016	no	no	no	DVT
00432019	no	no	no	DVT
00452014	no	no	no	DVT
01425011	no	yes	no	not documented via imaging, though history suggestive

To evaluate the adjudication process for stroke events, a random sample was taken of subjects with investigator reported strokes (59 events in 54 subjects). As suggested by the endpoint committee meeting minutes (see section 5.3), blinding, particularly of non-English documents, was not adequate. In 10 of 59 events reviewed (17%), the adjudication package contained information that could have unblinded adjudicators to treatment assignment (see table below). Unblinding was possible in 2 of 20 subjects (10%) from North American sites and in 8 of 34 subjects (24%) from non-North American sites; phrases found in these documents included the following:

- "recruited in RE-LY study…on Dabigatran"
- “atrial fibrillation being treated with warfarin”
- “on warfarin”
- "he is using an experimental blood thinner"
- “Sunday to check INR levels..consult with physician regarding the coumadin dose. Target INR 2.0”
- reference to antivitamin K being suspended
- "elevated INR blood test"
- "despite therapeutic anticoagulation"
- "Regular checks of INR"

Despite this text, many adjudicators reported that they remained blinded during their adjudication. With regard to the adjudication decisions themselves, although some cases were less clear cut than others, as a whole, the decisions reached by adjudicators seemed reasonable.

Reviewer's comment: The subject reported to be "on warfarin" was in the dabigatran treatment arm. A significant number of subjects who were randomized to dabigatran permanently discontinued study medication and some number of subjects with references to warfarin/INR in their adjudication documents may have been in the dabigatran treatment arms.

Discontinuation of study medication

Permanent discontinuations of study medication were more common in dabigatran compared to warfarin treated subjects. As a way to further explore the reason for permanent interruption of study medication, the sponsor performed an analysis of events occurring around the time of permanent interruptions of study medication. For the purposes of this analysis, when an outcome event was given as the reason for interruption, the exact event was identified using a 30 day window around the event. The results of this analysis are shown below (see appendix for timing of events). The numerically greater incidence of permanent study medication discontinuations for ischemic stroke, TIA (a non-endpoint event) or minor bleed in the dabigatran compared to warfarin treatment arms suggests that knowledge of treatment assignment in this open-label study may have led to differences in how subjects were treated. Though the sponsor reports reason for discontinuation of medication as "Death" for some subjects, such a categorization is nonsensical.

Table 52. Reasons for permanent discontinuation of study medication

	Dabigatran 110 N=1318	**Dabigatran 150 N=1382**	**Warfarin N=1073**
Serious AE not related to outcome event	162 (2.7)	170 (2.8)	119 (2.0)
Subject didn't want to take study drug	424 (7.1)	459 (7.6)	405 (6.8)
Outcome event	261 (4.4)	246 (4.1)	177 (3.0)
Stroke	53 (0.9)	42 (0.7)	26 (0.4)
Ischemic stroke	43 (0.7)	34 (0.6)	13 (0.2)
Hemorrhagic stroke	4 (0.1)	5 (0.1)	13 (0.2)
Stroke of uncertain classifications	6 (0.1)	4 (0.1)	0
SEE	10 (0.2)	1 (0.0)	2 (0.0)
PE	5 (0.1)	5 (0.1)	1 (0.0)
MI	9 (0.2)	8 (0.1)	8 (0.1)
Major Bleed	53 (0.9)	61 (1.0)	66 (1.1)
Life threatening major bleeds	20 (0.3)	37 (0.6)	47 (0.8)
Other major bleeds	33 (0.6)	24 (0.4)	19 (0.3)
Minor bleed	67 (1.1)	76 (1.3)	37 (0.6)
TIA	20 (0.3)	15 (0.2)	0
Death	18 (0.3)	17 (0.3)	18 (0.3)
Not matched with the algorithm	42 (0.7)	37 (0.6)	33 (0.6)
Other	471 (7.9)	507 (8.4)	372 (6.2)

Adverse Event	157 (2.6)	164 (2.7)	72 (1.2)
Lab changes	44 (0.7)	57 (0.9)	17 (0.3)
Procedure/hospitalization/surgery	30 (0.5)	35 (0.6)	46 (0.8)
Other	240 (4.0)	251 (4.1)	237 (4.0)

[Source: Sponsor; Modified from Table 15.1.1:3]
For the purposes of this analysis subjects who discontinued the study early without reason for discontinuation CRF were not included. A subject was counted in multiple categories when multiple reasons were given.

7 Review of Safety

7.1 Methods

In the sponsor's safety analyses and in the safety analyses that follow, subjects without a reported major bleed were censored at the last time vital status information was available. There were a few exceptions (noted in footnotes) where the reviewer's analyses did not use these censoring rule. As noted earlier, errors were found in the disposition data. These errors impact the censoring dates used for analyses, and in particular for those analyses in which subjects were to be censored based on the last date follow up information was available for the outcome of interest.[14] These errors, occurring in a small percentage of subjects, do not alter the results of key analyses and hence many analyses were not re-run using the corrected data sets submitted in August.

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The safety review focuses on the findings in RE-LY, and in particular, on the subset of subjects in RE-LY who received at least one dose of study medication (18,040 out of 18,113 randomized subjects). Though dabigatran has also been studied for VTE prevention (and has been approved outside the U.S. for the prevention of VTE post total hip/knee replacement), safety data from the VTE program were not, for the most part, analyzed. RE-LY provides more than 20,000 subject years of exposure and differences in populations, concomitant medications and the use of dabigatran (dose and duration) limit the ability to extrapolate from the safety experience in the VTE program to the proposed indication. However for rare events, such as drug induced liver injury (DILI) , the Periodic Safety Update Report (last dated March 2010) was used.

Reviewer's comment: A 4 month safety update was submitted on August 17, 2010; an addendum will be filed if the data contained in this submission significantly alter the safety findings/conclusions given in this review.

14 Datasets named adjrand2 and timecen2

7.1.2 Categorization of Adverse Events

The sponsor's coding of adverse events seemed, as a whole, appropriate. Adverse events (AE) were coded to MeDRA version 12.0.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

Data from different studies were not pooled.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

Exposure is adequate to describe safety in the intended population. There were over 20,000 subject years of dabigatran exposure in the RE-LY trial. Because more than 50% of subjects on dabigatran temporarily discontinued medication, exposure was calculated including and excluding periods of temporary discontinuation of study medication. In analyses excluding these periods, exposure was on average 9 days less than in analyses in which these periods were included. Subjects on dabigatran took study drug for approximately 1 month less than subjects on warfarin.

Table 53. Subject years of medication exposure

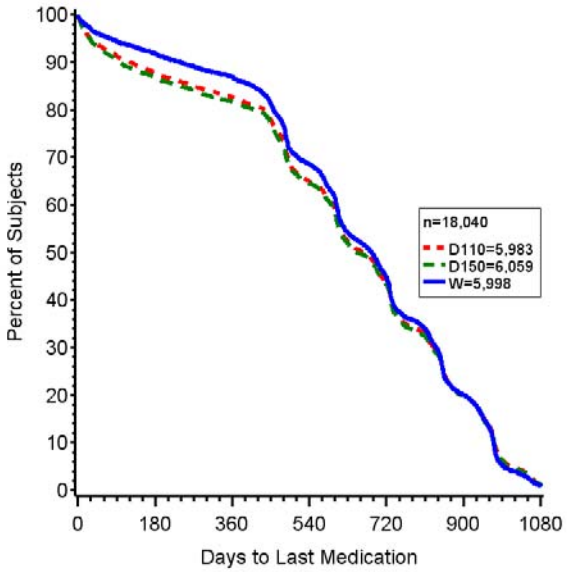
	D110 N=5983	**D150 N=6059**	**W N=5998**
Including periods of temporary medication discontinuation			
Subject years[1]	10242	10261	10659
Mean exposure (mo)	20.8	20.6	21.6
Excluding periods of temporary medication discontinuation			
Subject years	10089	10115	10508
Mean exposure (mo)	20.5	20.3	21.3

1. Subject years calculated as sum [(last med date – first med date) +1]; these calculations were used for the sponsor's safety analyses
[Source: reviewer's analysis file: ds\exposure; sponsor's data set: basco]

More subjects (4-5%) on dabigatran prematurely discontinued medication than on warfarin. The reasons for premature medication discontinuation have been presented in Section 6.1.10.2. The figure below shows the days to last medication in all subjects

treated in RE-LY. More subjects on dabigatran discontinue medication early as compared to warfarin, and the percent of subjects on treatment starts to coincide around 15 months.

Figure 10. Days to last medication



[Source: reviewer's analysis: Med dc perm days to; sponsor dataset:lastmed, popu, disco]

The demographics of the safety population mirror the demographics of the randomized population (see Section 6.1.2 for information). Exposure appears to be adequate in important patient subsets (e.g., age ≥ 75, CHADS2 score 3+, history of stroke/TIA/SEE), Mean exposure in subjects with and without prior VKA use was also explored. As shown in the table below, in VKA experienced subjects, mean exposure appeared to be greater in warfarin than dabigatran treated subjects, suggesting a greater tendency for VKA experienced subjects to discontinue from the dabigatran arms than the warfarin arms.

Table 54. Study drug exposure in VKA naïve and VKA experienced subjects

	VKA naïve				VKA Experienced			
	D110	**D150**	**W**	**Total**	**D110**	**D150**	**W**	**Total**
Total n	2990	3019	3082	9091	2991	3039	2916	8946
Mean (months)	19.4	19.2	19.7	19.4	21.7	21.5	23.0	22.1
Subject years	10242	10261	10659	14721	5411	5432	5595	16438

[Source: Sponsor's table 15.3.1:2 of QC report]

7.2.2 Explorations for Dose Response

There is a dose-response relationship for bleeding (see safety sections on bleeding and section 6.1.8).

7.2.3 Special Animal and/or In Vitro Testing

The nonclinical testing was adequate to explore potential adverse reactions of particular interest, including bleeding and liver toxicity.

7.2.4 Routine Clinical Testing

Routine clinical testing of clinical trial subjects, including the methods and tests used and the frequency of testing, was adequate. Information on outcome events (including stroke and bleeding questionnaires), adverse events, cardioversion, emergency/elective surgery, hospitalization, concomitant medications, INR evaluations, study medication, laboratory evaluation were assessed at each follow-up visit (every 3 months for the first year, then every 4 months until study end). ECGs were assessed at baseline, month 12, 24, 36 and at final follow-up.

7.2.5 Metabolic, Clearance, and Interaction Workup

Based on the draft Clinical Pharmacology Review dated August 4, 2010, the workup was sufficient to characterize the metabolism and excretion of dabigatran and important drug-drug interactions (see section 4.4)

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

The sponsor's evaluation for potential adverse events associated with other drugs in this class (thrombin inhibitors/anticoagulants) was adequate. Major adverse events of interest include bleeding and the potential for drug induced liver injury (DILI); these are discussed in detail. A discussion of serious cardiovascular events, including myocardial infarction, will be provided in an addendum to this review.

7.3 Major Safety Results

7.3.1 Deaths

An imbalance in deaths was seen across the three treatment arms, with a numerically smaller number of deaths reported in dabigatran treated subjects (relative to warfarin). The mortality findings are not a safety concern and are discussed under Efficacy (Section 6.1.6).

7.3.2 Nonfatal Serious Adverse Events

7.3.2.1. Major Bleeding

Overview of findings and conclusions

Bleeding was the most common and important safety concern identified in RE-LY. Major bleeds and life threatening bleeds (defined in the table below) were pre-specified, adjudicated safety endpoints in RE-LY. Relative to warfarin, there was no difference in major bleeds with dabigatran 150 mg (HR 0.93, 95% CI: 0.81, 1.07) whereas dabigatran 110 mg was associated with fewer major bleeds (HR 0.80, 95% CI: 0.68, 0.90, p<0.003). The risk reduction in major bleeds and life threatening bleeds (relative to warfarin) was influenced by the level of INR control. Subgroup analyses based on the level of INR control (center-level and subject- level) suggest that the risk reduction in major bleeds seen with dabigatran 110 mg is driven to some extent by the subset of warfarin treated subjects achieving lower levels of INR control.

Assessments of bleeding should take into consideration the severity/reversibility of the bleeding event. Important major bleeding has been defined in different ways in clinical trials; the definitions/categories used in RE-LY are shown in the table below. Of note, the ISTH, ESTEEM, and ISCOAT definitions[15] of major bleed are very similar to that used in RE-LY. The ISTH and ISCOAT criteria have also been used in patients receiving long-term anticoagulation.

Table 55. Various bleeding definitions used in RE-LY

Term	Definition
Adjudicated major bleed	Satisfying at least one: bleeding associated with a reduction in hemoglobin of at least 2 grams per deciliter or leading to a transfusion of at least 2 units of blood or packed cells; symptomatic bleeding in a critical area or organ (intraocular, intracranial, intraspinal or intramuscular with compartment syndrome, retroperitoneal bleeding, intra-articular bleeding or pericardial bleeding)
Adjudicated life-threatening bleed (sub classification of major bleed)	An adjudicated major bleed meeting at least one of the following criteria: fatal; symptomatic intracranial bleed; reduction in hemoglobin of at least 5 grams per deciliter; transfusion of at least 4 units of blood or packed cells, associated with hypotension requiring the use of intravenous inotropic agents; required surgical intervention
RE-LY's GUSTO	An adjudicated ICH event or an adjudicated major bleed with at

15 ISTH =International Society on Thrombosis & Haemostasis; ESTEEM =Efficacy and Safety of the Oral Direct Thrombin Inhibitor Ximelagatran in Patients with Recent Myocardial Damage; ISCOAT =Italian Study of Complications of Anticoagulant Therapy

severe	least one of the following criteria: associated with hypotension requiring use of intravenous inotropic agents; required surgical intervention to stop bleeding
Intracranial hemorrhage (ICH)	Includes adjudicated hemorrhagic stroke or adjudicated major bleed that was symptomatic intracranial

Compared to TIMI major or GUSTO severe, bleed categorizations used in well known intravenous thrombolytic trials, major bleeds, as defined in RE-LY, are not as severe. TIMI major bleeding includes ICH, overt bleeding with a 5 g/dL decrease in hemoglobin and GUSTO severe includes ICH or bleeding that causes hemodynamic compromise and requires intervention. In contrast, major bleeds in RE-LY included relatively small reductions in hemoglobin/transfusion requirements and hence more readily reversible bleeding events. In terms of the severity of the event, RE-LY's life-threatening bleeds and "GUSTO severe" bleeds[16] are perhaps more similar to the definitions of major bleeds used in past thrombolytic trials.

With regard to GUSTO-severe bleeding, dabigatran 110 mg was associated with a 52% reduction (HR 0.48, 95% CI: 0.37, 0.64, p-value <0.0001) relative to warfarin and dabigatran 150 mg was associated with a 31% reduction (HR 0.69, 95% CI: 0.54, 0.88, p-value 0.003) relative to warfarin. Compared to dabigatran 110 mg, dabigatran 150 mg was associated with a 42% greater risk of GUSTO-severe bleed (p=0.02). The reduction in ICH in comparison to warfarin was even greater. Dabigatran 110 mg was associated with a 70% reduction (HR 0.30, 95% CI: 0.19, 0.46, p-value <0.0001) in ICH relative to warfarin, and dabigatran 150 mg was associated with a 59% reduction (HR 0.41, 95% CI: 0.28, 0.60, p-value <0.0001) relative to warfarin. Thus, the findings in RE-LY support a relationship between dabigatran dose and major bleeding risk and suggest a favorable profile relative to warfarin.

Overview of major bleeds in RE-LY

The total number of adjudicated major bleeds is shown in the table below. While there were more adjudicated major bleeds in the warfarin arm, there were more subjects with multiple occurrences of major bleeds in the dabigatran arms.

Table 56. Total adjudicated major bleeds

	D110	%	D150	%	W	%	Total
Randomized	**6015**		**6076**		**6022**		
Subjects with major bleed	342	(5.7)	399	(6.6)	421	(7.0)	1162

16 RE-LY's "GUSTO severe" definition differs slightly from that used in the GUSTO trials. In the GUSTO trials, GUSTO severe was defined as ICH or bleeding that caused hemodynamic compromise **AND** required intervention.

	D110	%	D150	%	W	%	Total
Randomized	**6015**		**6076**		**6022**		
Number of major bleeds	406	(6.7)	489	(8.0)	483	(8.0)	1378
Number of subjects with occurrences							
1	291	(4.8)	335	(5.5)	367	(6.1)	
2	38	(0.6)	44	(0.7)	49	(0.8)	
≥ 3	13	(0.2)	20	(0.3)	5	(0.1)	
Total life threatening bleeds	159	(2.6)	193	(3.2)	233	(3.9)	

[source: Adapted from sponsor's table 15.3.5.4:11_New and reviewer's analysis: filename major, sponsor dataset timev]

The table below describes characteristics of the adjudicated major bleed that are not described elsewhere in the review. Deaths associated with major bleeds appeared to be more common in the warfarin arm than in the dabigatran arms.

Table 57. Characteristics of adjudicated major bleed not described elsewhere

Category	D110	%	D150	%	W	%
Total adjudicated major bleed*	397	(100)	486	(100)	476	(100)
Hg Drop of 2 gm/dL	266	(67.0)	330	(67.9)	282	(59.2)
Died	25	(6.3)	28	(5.8)	40	(8.4)
Hospitalization	286	(72.0)	368	(75.7)	364	(76.5)

[source: Reviewer's analysis: mj\tx\adj_plt122n, sponsor dataset plt122n,adjrand,popu]
*These descriptions were available for 1359 adjudicated bleeds.

Overall risk of bleeding

Compared to warfarin, the overall relative risk of major bleeding was 20% less for dabigatran 110 mg, and no different for dabigatran 150 mg. Compared to dabigatran 110 mg, dabigatran 150 mg was associated with a 16% greater risk of major bleeding. The relative risk of more severe bleeds (e.g., GUSTO severe, ICH) also appeared to be greater in the warfarin arm than in the dabigatran arms.

Table 58. Overall relative risk of serious bleeding

Type	D110 v. W HR (95%CI) p-value	D150 v. W HR (95%CI) p-value	D150 v. D110 HR (95%CI) p-value
Adjudicated major bleeding	0.80 (0.70, 0.93) 0.002	0.93 (0.81, 1.07) 0.31	1.16 (1.00, 1.34) 0.04
Life threatening bleed	0.67 (0.54, 0.81)	0.80 (0.66, 0.98)	1.21 (0.97, 1.50)
GUSTO severe	0.48 (0.37, 0.64)	0.69 (0.54, 0.88)	1.42 (1.05, 1.91)
ICH	0.30 (0.19, 0.46)	0.41 (0.28, 0.60)	1.39 (0.85, 2.28)
Adjudicated hemorrhagic strokes	0.31 (0.17, 0.56)	0.26 (0.14, 0.49)	0.85 (0.39, 1.83)
Reported symptomatic intracranial bleeds	0.29 (0.19, 0.44)	0.47 (0.33, 0.67)	1.61 (1.00, 2.61)

[Source: Reviewer's analysis, filename: timev\HR, sponsor's data;adjrand] Cox proportional regression, data shown are Hazard ratio (95% confidence interval)

The absolute event rates using various definitions of major bleeding are shown in the table below. As a whole, these data support a relationship between dabigatran dose and bleeding risk.

Table 59. Overall absolute risk of major bleeding

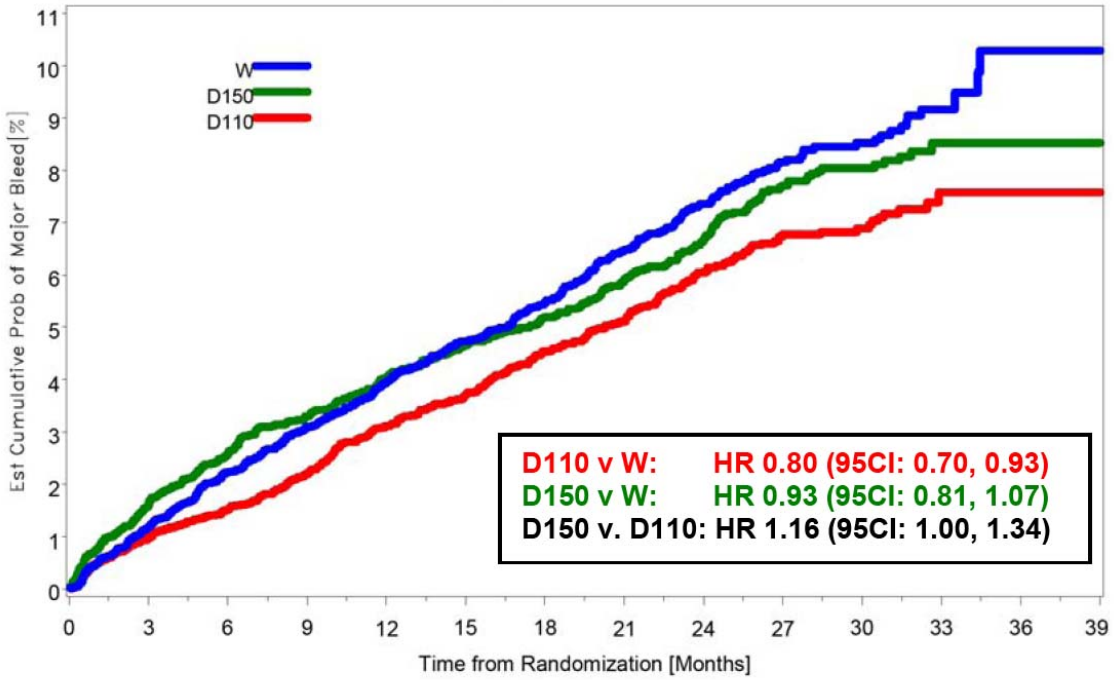
	D110 (n=6015)		D150 (n=6076)		W (n=6022)	
Type	**# events**	**%/yr**	**# events**	**%/yr**	**# events**	**%/yr**
Major bleed	342	2.87	399	3.32	421	3.57
Life threatening bleed	147	1.24	179	1.49	218	1.85
GUSTO severe	74	0.62	106	0.88	151	1.28
ICH	27	0.23	38	0.32	90	0.76[17]

[Source: reviewer's analysis, file: eventrate, sponsor's data: timev, adjrand]
Study duration=date of study termination-date of randomization +1
Subject years=sum (study duration for all subjects)/365.25
Yearly event rate (%/yr)=# subjects with event/subject years*100

The time to first major bleed is shown in the next figure. Throughout the period of follow up, the rates of major bleeding in the dabigatran 110 mg arm appear to be lower than the rates seen in the other treatment arms.[18]

17. It is noted that the rate of ICH in the warfarin arm seems high when compared to ACTIVE-W (annual rate 0.4% from Dr. U clinical review), despite the use of, what appears to be, similar definitions of ICH in the two trials. It is unclear what to make of this.

Figure 11. Time to first major bleed



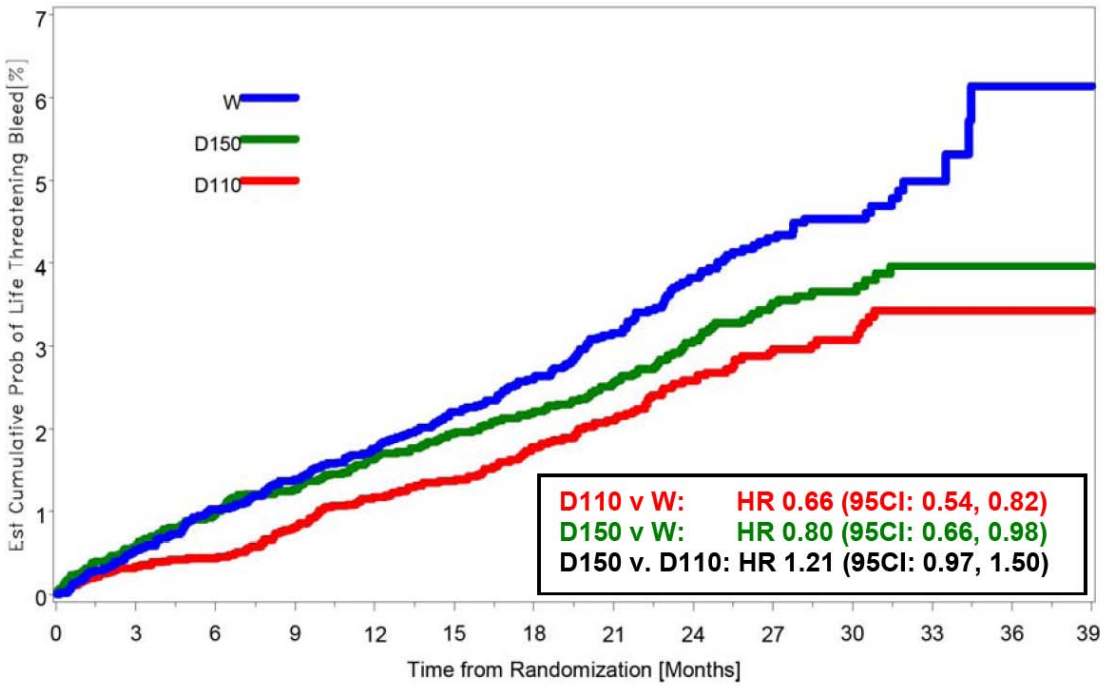
No. at risk													
D110	6015	5830	5738	5637	5527	5274	4409	3564	2972	2236	1365	447	75
D150	6076	5858	5731	5613	5519	5264	4450	3596	3022	2243	1367	450	82
W	6022	5822	5693	5567	5462	5138	4347	3444	2869	2160	1250	343	71

[Source: Reviewer's analysis, filename: time mjbleed, HR mjbleed; Kaplan Meier analysis, sponsor data: adjrand]

18. While there was no difference in major bleeding between dabigatran 150 mg and warfarin, it is noted that in the beginning of the trial the risk of bleeding appears higher with dabigatran 150 mg as compared to warfarin. After approximately 12-16 months, the slope of the curve decreases and runs below warfarin. Although completely speculative, the timing of the change in slope may be related to the permanent discontinuation of dabigatran (see Figure 9).

For life threatening bleeds, the curve for dabigatran 110 mg starts to separate from the curve for warfarin after about 3 months; the curve for dabigatran 150 mg starts to separate from warfarin after about 1 year.

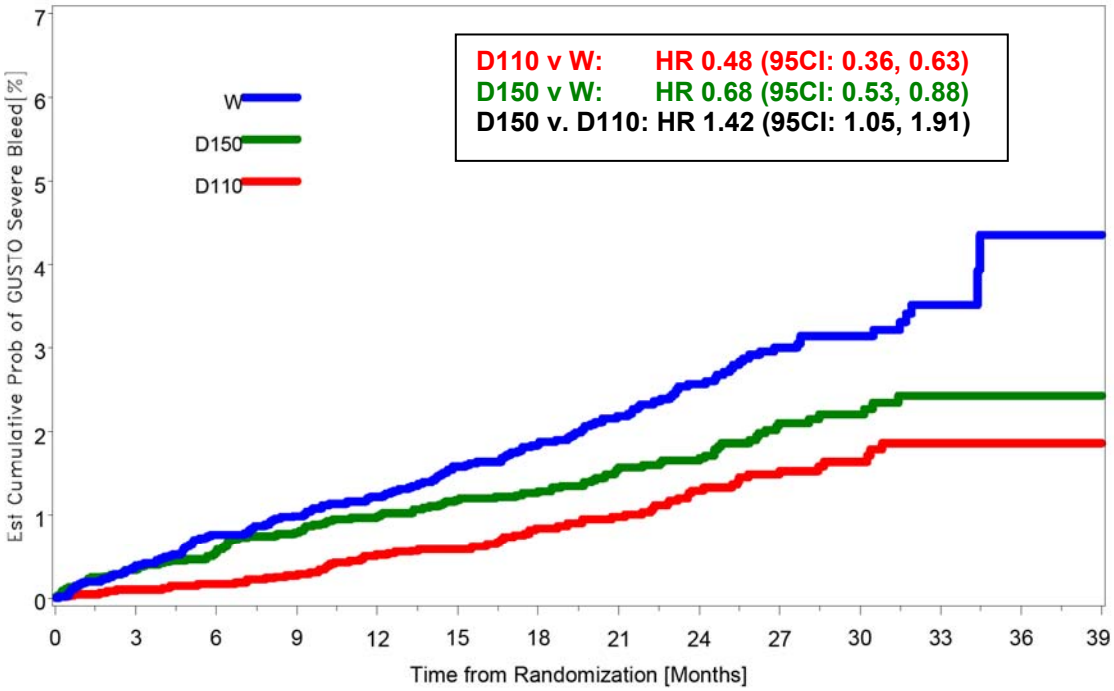
Figure 12. Time to first life threatening bleed



No. at risk													
D110	6015	5861	5791	5705	5622	5383	4519	3663	3064	2315	1409	461	79
D150	6076	5912	5816	5720	5642	5396	4570	3711	3128	2336	1427	471	86
W	6022	5857	5757	5657	5571	5253	4452	3541	2956	2235	1296	353	72

The next figure shows the time to first GUSTO severe bleed. The curves appear to separate earlier than for the other bleeding categories.

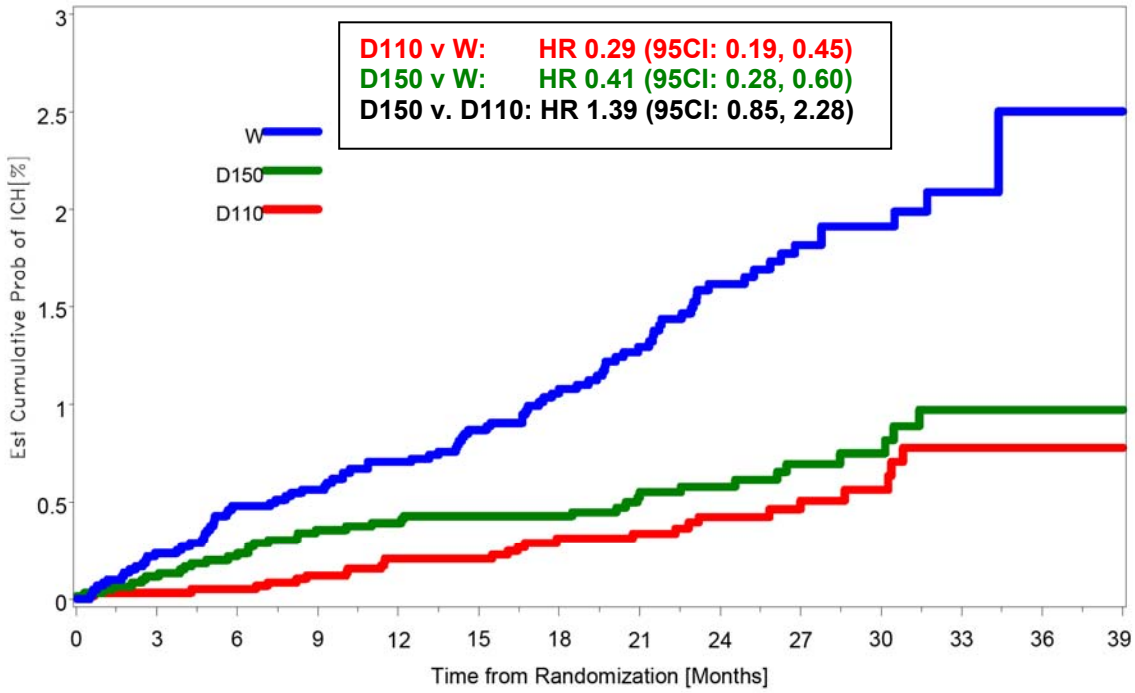
Figure 13. Time to first GUSTO severe bleed



No. at risk													
D110	6015	5872	5802	5729	5653	5418	4557	3697	3102	2344	1422	467	81
D150	6076	5923	5836	5741	5672	5427	4603	3737	3162	2362	1442	477	88
W	6022	5864	5767	5674	5595	5278	4478	3571	2987	2255	1306	355	72

The next figure shows the time to first ICH.

Figure 14. Time to first ICH



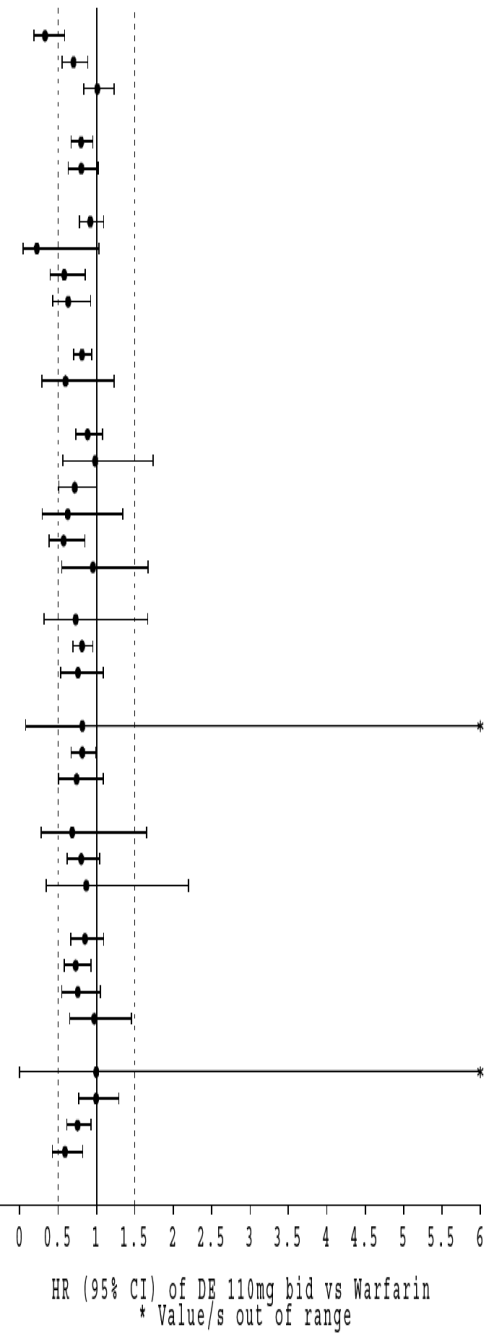
No. at risk													
D110	6015	5874	5806	5734	5665	5432	4575	3717	3123	2365	1437	476	81
D150	6076	5931	5847	5756	5694	5454	4626	3761	3182	2385	1456	480	88
W	6022	5871	5779	5694	5617	5306	4501	3594	3007	2279	1322	359	73

Subgroup analysis – baseline demographics

As a whole, subgroup analyses suggested no difference in major bleeding by gender, race, region, or weight compared to warfarin. In the Chinese, both the 110 and 150 mg doses of dabigatran were associated with a lower risk of major bleeding (relative to warfarin. Very few blacks were studied, limiting conclusions in this population. The effects of age and impaired renal function are discussed in sections 7.5.3 and 7.5.4, respectively.

Figure 15. Dabigatran 110 mg v. warfarin subgroup analysis

	DE 110mg bid #event/N	Warfarin #event/N	HR (95% CI)	Interaction p-value
Age (years)				<.0001
<65	16/ 998	45/ 953	0.33 (0.19, 0.59)	
65<= and <75	122/2668	170/2646	0.70 (0.56, 0.89)	
>=75	204/2349	206/2423	1.01 (0.83, 1.23)	
Gender				0.9978
Male	225/3865	273/3809	0.80 (0.67, 0.96)	
Female	117/2149	148/2213	0.80 (0.63, 1.03)	
Ethnicity class				0.0281
White	255/4208	275/4203	0.92 (0.78, 1.09)	
Black	2/ 52	10/ 67	0.23 (0.05, 1.03)	
Asian	41/ 955	68/ 955	0.58 (0.39, 0.86)	
Other	44/ 799	68/ 797	0.63 (0.43, 0.92)	
Hispanic or Latino				0.7128
No	330/5593	402/5615	0.81 (0.70, 0.94)	
Yes	12/ 421	19/ 407	0.60 (0.29, 1.23)	
Region				0.4212
USA, Canada	186/2166	209/2167	0.89 (0.73, 1.08)	
Central Europe	24/ 707	24/ 706	0.99 (0.56, 1.74)	
Western Europe	58/1544	80/1552	0.72 (0.51, 1.01)	
Latin America	11/ 320	17/ 316	0.63 (0.29, 1.34)	
Asia	39/ 923	66/ 926	0.57 (0.39, 0.85)	
Other	24/ 355	25/ 355	0.96 (0.55, 1.67)	
Weight (kg)				0.2765
<50	10/ 123	13/ 126	0.73 (0.32, 1.67)	
50<= and <100	278/4850	337/4848	0.81 (0.69, 0.95)	
>=100	54/1038	71/1044	0.76 (0.53, 1.09)	
Male: Weight (kg)				0.4465
<50	1/ 22	2/ 32	0.82 (0.07, 9.02)	
50<= and <100	178/2971	210/2912	0.82 (0.67, 1.00)	
>=100	46/ 871	61/ 864	0.74 (0.51, 1.09)	
Female: Weight (kg)				0.6565
<50	9/ 101	11/ 94	0.69 (0.28, 1.65)	
50<= and <100	100/1879	127/1936	0.80 (0.62, 1.05)	
>=100	8/ 167	10/ 180	0.87 (0.34, 2.20)	
BMI (kg/m2)				0.1825
<25	114/1575	130/1553	0.85 (0.66, 1.09)	
25<= and <30	117/2358	157/2338	0.73 (0.58, 0.93)	
30<= and <35	65/1316	86/1353	0.76 (0.55, 1.05)	
>=35	46/ 757	48/ 765	0.97 (0.65, 1.46)	
CrCL (mL/min)				0.3379
<30	0/ 15	0/ 30	1.00 (0.00,2E280)	
30<= and <50	120/1136	112/1051	1.00 (0.77, 1.29)	
50<= and <80	154/2714	206/2806	0.76 (0.61, 0.93)	
>=80	57/1899	94/1877	0.59 (0.43, 0.82)	

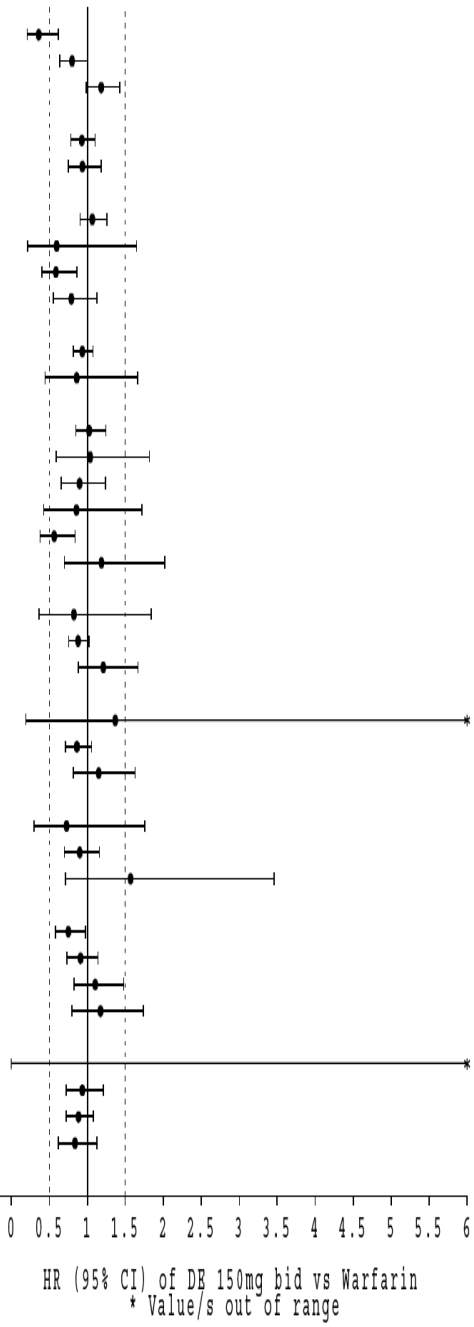


The hazard ratio and interaction p-values were calculated from Cox regression model with all three treatment groups and each specified subgroup variable in the model.

[Source: Sponsor Figure 15.3.2.2.2:1, 4.19.10 resubmission]

Figure 16. Dabigatran 150 v. warfarin subgroup analysis (baseline demographics)

	DE 150mg bid #event/N	Warfarin #event/N	HR (95% CI)	Interaction p-value
Age (years)				<.0001
<65	18/1030	45/ 953	0.36 (0.21, 0.62)	
65<= and <75	135/2580	170/2646	0.80 (0.64, 1.00)	
>=75	246/2466	206/2423	1.18 (0.98, 1.43)	
Gender				0.9978
Male	258/3840	273/3809	0.93 (0.78, 1.10)	
Female	141/2236	148/2213	0.94 (0.74, 1.18)	
Ethnicity class				0.0281
White	297/4268	275/4203	1.07 (0.91, 1.26)	
Black	6/ 57	10/ 67	0.60 (0.22, 1.65)	
Asian	42/ 965	68/ 955	0.59 (0.40, 0.86)	
Other	54/ 786	68/ 797	0.79 (0.55, 1.13)	
Hispanic or Latino				0.7128
No	382/5660	402/5615	0.94 (0.81, 1.08)	
Yes	17/ 416	19/ 407	0.86 (0.45, 1.66)	
Region				0.4212
USA, Canada	217/2200	209/2167	1.03 (0.85, 1.24)	
Central Europe	25/ 706	24/ 706	1.04 (0.59, 1.82)	
Western Europe	73/1555	80/1552	0.90 (0.66, 1.24)	
Latin America	15/ 320	17/ 316	0.86 (0.43, 1.72)	
Asia	39/ 933	66/ 926	0.57 (0.38, 0.84)	
Other	30/ 362	25/ 355	1.19 (0.70, 2.02)	
Weight (kg)				0.2765
<50	11/ 127	13/ 126	0.83 (0.37, 1.84)	
50<= and <100	305/4931	337/4848	0.88 (0.75, 1.03)	
>=100	83/1017	71/1044	1.21 (0.88, 1.66)	
Male: Weight (kg)				0.4465
<50	2/ 24	2/ 32	1.37 (0.19, 9.71)	
50<= and <100	189/2986	210/2912	0.87 (0.71, 1.05)	
>=100	67/ 829	61/ 864	1.15 (0.81, 1.63)	
Female: Weight (kg)				0.6565
<50	9/ 103	11/ 94	0.73 (0.30, 1.76)	
50<= and <100	116/1945	127/1936	0.90 (0.70, 1.16)	
>=100	16/ 188	10/ 180	1.57 (0.71, 3.46)	
BMI (kg/m2)				0.1825
<25	100/1569	130/1553	0.75 (0.58, 0.98)	
25<= and <30	150/2415	157/2338	0.91 (0.73, 1.14)	
30<= and <35	96/1369	86/1353	1.11 (0.83, 1.48)	
>=35	53/ 719	48/ 765	1.18 (0.80, 1.74)	
CrCL (mL/min)				0.3379
<30	7/ 32	0/ 30	285E3 (0.00,9E168)	
30<= and <50	116/1156	112/1051	0.94 (0.72, 1.21)	
50<= and <80	182/2777	206/2806	0.89 (0.73, 1.08)	
>=80	80/1882	94/1877	0.84 (0.62, 1.13)	



The hazard ratio and interaction p-values were calculated from Cox regression model with all three treatment groups and each specified subgroup variable in the model.

[Source: Sponsor Figure 15.3.2.2.2:2, 4.19.10 resubmission]

VKA use and INR control

Prior VKA use (as defined by the sponsor) did not clearly affect the relationship between risk of bleeding on dabigatran relative to warfarin.

Table 53. Relative and absolute risk by vitamin K antagonist use

Type	D110 v. W HR (95%CI)	D150 v. W HR (95%CI)	D110 %/yr	D150 %/yr	W %/yr
Adjudicated major bleeding	0.80 (0.70, 0.93)	0.93 (0.81, 1.07)	2.87	3.32	3.57
Naïve	0.87 (0.71, 1.07)	0.94 (0.77, 1.14)	3.11	3.33	3.57
Experienced	0.74 (0.60, 0.91)	0.93 (0.76,1.12)	2.66	3.30	3.57
Life threatening bleed	0.67 (0.54, 0.81)	0.80 (0.66, 0.98)	1.24	1.49	1.85
Naïve	0.75 (0.55, 1.01)	0.84 (0.62, 1.12)	1.27	1.42	1.71
Experienced	0.60 (0.45, 0.80)	0.78 (0.60, 1.02)	1.20	1.55	1.98
GUSTO severe	0.48 (0.37, 0.64)	0.69 (0.54, 0.88)	0.62	0.88	1.28
Naïve	0.47 (0.31, 0.72)	0.77 (0.53, 1.11)	0.55	0.89	1.17
Experienced	0.49 (0.34, 0.71)	0.62 (0.44, 0.88)	0.69	0.87	1.39
ICH	0.30 (0.19, 0.46)	0.41 (0.28, 0.60)	0.23	0.32	0.76
Naïve	0.27 (0.14, 0.51)	0.43 (0.25, 0.75)	0.19	0.32	0.73
Experienced	0.32 (0.18, 0.57)	0.40 (0.24, 0.67)	0.26	0.32	0.79

[source:reviewer's analysis: sub\vka, sponsor's file: adjrand, basco]

Relative risk: An analysis focusing on the subset of subjects known to be well controlled on warfarin at baseline is perhaps of greater interest. To this reviewer's knowledge, such information was not collected in the trial.

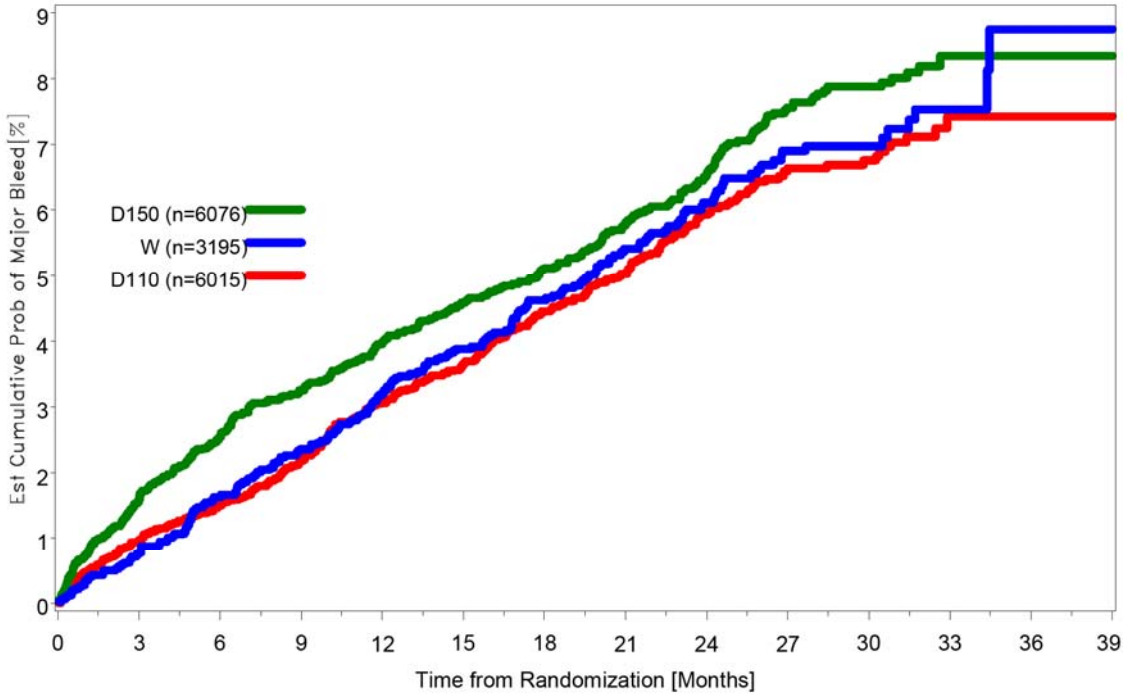
The risk reduction in major bleeds and life threatening bleeds (relative to warfarin) was influenced by the level of INR control; however such a relationship was not seen for GUSTO severe or ICH bleeding. Subgroup analyses based on the level of INR control (center-level and subject- level) suggest that the risk reduction in major bleeds seen with dabigatran 110 mg is driven to some extent by the subset of warfarin treated subjects achieving lower levels of INR control (see table below and section 6.1.10.1).

Table 54. Risk of bleeding compared to warfarin subjects with INR in range (2-3) ≥ 65% of the time

Type	D110 v. W HR (95%CI) p-value	D150 v. W HR (95%CI) p-value
Adjudicated major bleeding	0.95 (0.80, 1.13)	1.10 (0.93, 1.31)
Life threatening bleed	0.78 (0.61, 1.004)	0.94 (0.74, 1.20)
GUSTO severe	0.46 (0.34, 0.62)	0.65 (0.49, 0.86)
ICH	0.32 (0.21, 0.52)	0.45 (0.29, 0.70)

N=15,286 (3,195 on warfarin)[source: reviewer's analysis: inr\inr65, sponsor's data: adjrand, basco]

Figure 17. Time to first major bleed, warfarin subjects with INR 2-3 ≥ 65% of the time



No. at risk													
D110	6015	5904	5826	5739	5624	5379	4510	3674	3039	2304	1401	469	79
D150	6076	5936	5832	5731	5633	5387	4558	3701	3101	2309	1407	464	82
W	3195	3165	3126	3091	3050	2891	2477	1997	1682	1280	777	223	50

[source: reviewer's analysis: time mjb INR, sponsor data: adjrand, basco]

Concomitant medications

The yearly event rate of major bleeds based on baseline concomitant medication use and use during the study was higher for subjects on aspirin, clopidogrel or aspirin plus

clopidogrel across all treatment arms. This relationship didn't appear to be affected by whether or not a subject was treated with dabigatran or warfarin. Subjects that experienced significant bleeding were likely taken off of concomitant medications that also cause bleeding, which may explain the lower rates of bleeding in subjects reporting 100% use of these medications (relative to the other groupings of use).

Table 55. Yearly event rate of major bleeds by medication use during the study

	DE 110mg bid				DE 150mg bid				Warfarin			
% of time taking concomitant medication	# of subjects	Subject-years	Subjects with event	Yearly event rate (%)	# of subjects	Subject-years	Subjects with event	Yearly event rate (%)	# of subjects	Subject-years	Subjects with event	Yearly event rate (%)
Antithrombotic therapy												
ASA												
0% (never)	3615	7219	153	2.12	3687	7357	178	2.42	3616	7162	187	2.61
Used at least one time	2400	4681	189	4.04	2389	4676	221	4.73	2406	4632	234	5.05
0%< and <=50%	854	1680	76	4.52	907	1788	105	5.87	918	1762	92	5.22
50% <and < 100%	272	541	41	7.58	292	588	45	7.66	241	494	52	10.53
100% (always)	1274	2460	72	2.93	1190	2300	71	3.09	1247	2376	90	3.79
Clopidogrel												
0% (never)	5572	11044	295	2.67	5624	11109	344	3.10	5581	10930	363	3.32
Used at least one time	443	855	47	5.50	452	924	55	5.95	441	864	58	6.71
0%< and <=50%	218	428	26	6.08	248	509	35	6.88	225	462	29	6.28
50% <and < 100%	82	167	14	8.37	71	160	13	8.14	64	129	15	11.59
100% (always)	143	260	7	2.69	133	256	7	2.74	152	273	14	5.13
Dipyridamole												
0% (never)	5987	11841	339	2.86	6049	11981	397	3.31	5998	11743	420	3.58
Used at least one time	28	58	3	5.18	27	53	2	3.81	24	51	1	1.96
0%< and <=50%	12	25	2	8.03	7	14	0	0.00	11	23	0	0.00
50% <and < 100%	5	11	1	8.93	5	9	1	10.70	0	0	0	0.00
100% (always)	11	22	0	0.00	15	30	1	3.37	13	28	1	3.63

[sponsor table 15.3.2.2.3:3]

Dabigatran etexilate (but not dabigatran) is a substrate of p-gp, so a relationship between p-gp inhibitors and bleeding risk was also explored. No consistent pattern is seen with regard to the effect of these medications on the relative risk of bleeding on dabigatran (compared to warfarin). While the risk of bleeding was sometimes higher with concomitant p-gp inhibitors amiodarone, diltiazem, and verapamil, it also seemed higher in the warfarin arms. Since warfarin does not have an interaction with p-gp, it is difficult to draw conclusions from these analyses. There were too few subjects taking ketoconazole and p-gp inducers to make any definitive conclusions.

Table 56. Yearly event rate of major bleeds by concomitant p-gp inhibitor during treatment period safety set

	DE 110mg bid				DE 150mg bid				Warfarin			
% of time taking concomitant medication	# of subj	Subject-years	Subjects with event	Yearly event rate (%)	# of subj	Subject-years	Subjects with event	Yearly event rate (%)	# of subj	Subject-years	Subjects with event	Yearly event rate (%)
P-gp inhibitor												
Amiodarone												
0% (never)	5139	8855	241	2.72	5191	8792	295	3.36	5097	9118	321	3.52
Used at least once	844	1387	54	3.89	868	1469	55	3.74	901	1542	57	3.70
0%< and <=50%	209	379	19	5.01	200	360	21	5.84	209	387	19	4.91
50% <and < 100%	311	546	26	4.76	328	606	24	3.96	377	680	28	4.12
100% (always)	324	462	9	1.95	340	503	10	1.99	315	475	10	2.11
Diltiazem												
0% (never)	5310	9028	240	2.66	5384	9032	302	3.34	5298	9350	323	3.45
Used at least once	673	1214	55	4.53	675	1229	48	3.91	700	1309	55	4.20
0%< and <=50%	147	273	12	4.40	168	329	9	2.74	168	326	18	5.52
50% <and < 100%	260	513	31	6.04	268	526	27	5.14	287	571	29	5.08
100% (always)	266	428	12	2.80	239	374	12	3.20	245	412	8	1.94
Verapamil												
0% (never)	5574	9530	273	2.86	5650	9521	321	3.37	5553	9818	350	3.56
Used at least once	409	712	22	3.09	409	740	29	3.92	445	841	28	3.33
0%< and <=50%	83	158	7	4.44	95	178	6	3.38	103	200	7	3.50
50% <and < 100%	138	264	9	3.41	142	276	14	5.08	164	330	13	3.94
100% (always)	188	291	6	2.07	172	286	9	3.14	178	311	8	2.57

[sponsor's table 15.3.2.2.3:6]

Location of symptomatic major bleeds

The location of symptomatic adjudicated major bleeds is shown in the table below. Most of the symptomatic bleeding was gastrointestinal, followed by intracranial, and then intraocular bleeding. The risk of GI bleeding appears to be greater in the dabigatran arms compared to warfarin (discussed further below).

Table 57. Location of adjudicated major bleeds[19]

Location	D110	%	D150	%	W	%
Total adjudicated major bleeding	397	(100)	486	(100)	476	(100)
Symptomatic bleeding	225	(56.7)	285	(58.6)	237	(49.8)
Gastrointestinal	155	(39.0)	219	(45.1)	141	(29.6)
Symptomatic intracranial	27	(6.8)	33	(6.8)	82	(17.2)
Intraocular	16	(4.0)	11	(2.3)	16	(3.4)
Retroperitoneal	2	(0.5)	9	(1.9)	12	(2.5)
Intramuscular	8	(2.0)	8	(1.6)	19	(4.0)
Genito-urinary	16	(4.0)	7	(1.4)	10	(2.1)
ENT	4	(1.0)	7	(1.4)	7	(1.5)
Surgical	8	(2.0)	6	(1.2)	13	(2.7)
Intra-abdominal	3	(0.8)	5	(1.0)	2	(0.4)
Intra-thoracic	8	(2.0)	4	(0.8)	7	(1.5)
Intra-articular	5	(1.3)	4	(0.8)	7	(1.5)
Pericardial	2	(0.5)	3	(0.6)	3	(0.6)
Other area	1	(0.3)	2	(0.4)	7	(1.5)
Source unidentified	1	(0.3)	1	(0.2)	.	.
Intraspinal	.	.	.	.	1	(0.2)

[source: Reviewer's analysis: mj\tx\adj_plt122n, sponsor dataset plt122n,adjrand,popu] This description was available for 1359 adjudicated bleeds. Includes those subjects with an adjudicated major bleed for which CRF 122 or CRF 97 was completed.

GI Bleeds

There was a greater risk of a GI bleed with dabigatran 150 mg compared to warfarin (see table below). This effect persisted over time and was dose related (see figure). Relative to warfarin, the risk of a major GI bleed on dabigatran increased with age, with the greatest relative risk seen in subjects≥ 75 years treated with dabigatran 150 mg: HR 1.79 (95%CI: 1.32, 2.42). Across all treatment arms, subjects on aspirin, clopidogrel, or aspirin+clopidogrel at baseline had a greater absolute risk of a major GI bleed compared to subjects not on these medications at baseline (sponsor table 15.3.2.2.8:13).

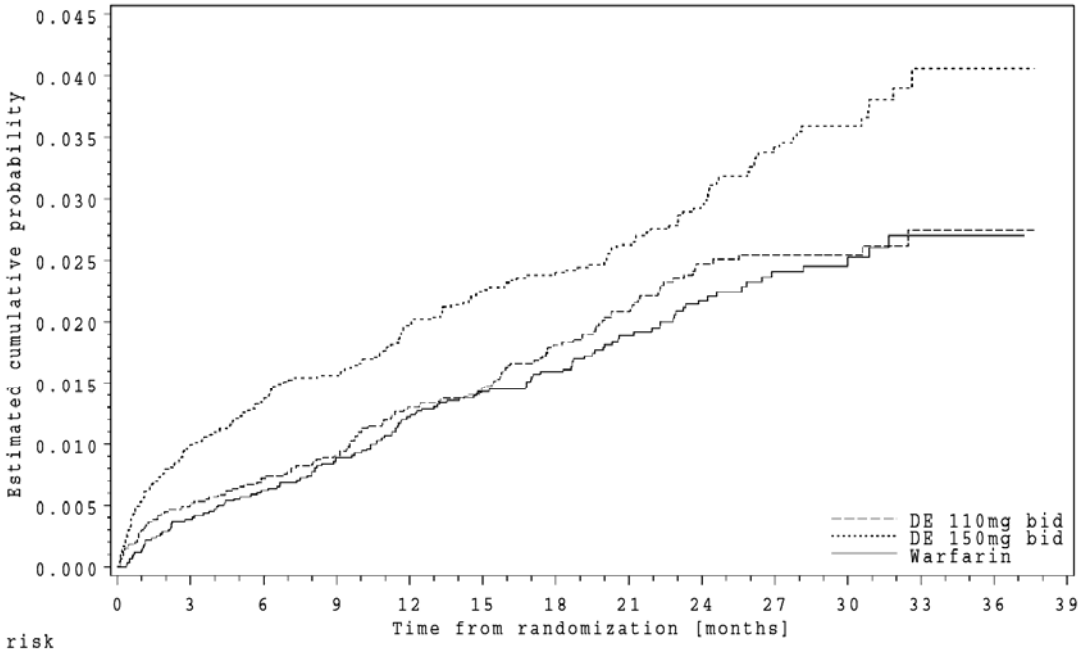
19 *Under the category, "Symptomatic bleeding in a critical area or organ", there was box left for "Other". PHRI recoded the "other" to an organ, if it could be, except for 15 of the major bleeds. These 15 were identified during the QC roadmap or during the close out period. For the purposes of this table, the reviewer categorized the 15 "Other"(if the event could be categorized), using a similar algorithm as that used by PHRI. The following "Other" were not categorized: Cancer of prostate, penile trauma, SAE anemia cancer treated with chemotherapy.*

Table 58. Risk of serious and any GI bleed

Type	D110 v. W HR (95%CI)	D150 v. W HR (95%CI)	D150 v. D110 HR (95%CI)	D110 %/yr	D150 %/yr	W %/yr
Adjudicated major bleeding, GI	1.07 (0.84, 1.36)	1.47 (1.17, 1.85)	1.38 (1.10, 1.72)	1.14	1.57	1.07
Life threatening, GI	1.17 (0.82, 1.67)	1.62 (1.17, 2.26)	1.39 (1.02, 1.90)	0.57	0.79	0.49
Any GI bleed	1.35 (1.19, 1.53)	1.52 (1.35, 1.72)	1.13 (1.01, 1.26)	5.41	6.13	4.02

[source: reviewer's analysis: hr\phreg_GI, sponsor dataset: timev]

Figure 18. Time to first major GI bleed



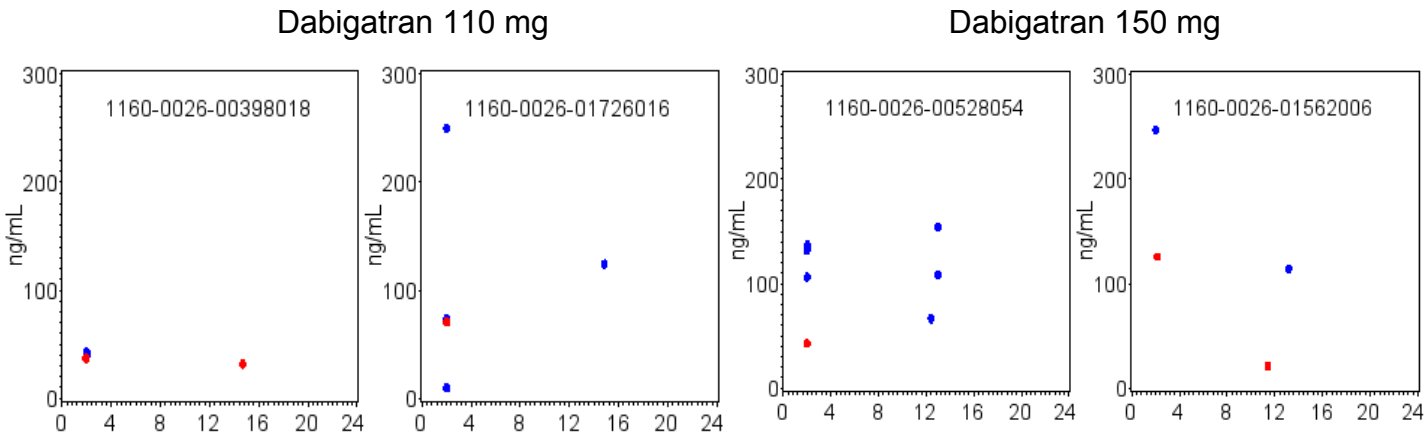
Subjects at risk													
DE 110mg bid	6015	5925	5863	5799	5710	5485	4615	3778	3133	2393	1457	496	86
DE 150mg bid	6076	5971	5894	5816	5732	5505	4663	3813	3204	2400	1461	487	89
Warfarin	6022	5938	5876	5790	5718	5443	4624	3709	3109	2353	1372	391	78

Figure 15.3.2.2.8: 1 Kaplan-Meier estimates of time to first gastrointestinal major bleeds randomized set

Dabigatran plasma concentrations

Four subjects were identified who had dabigatran concentration data at the time of an adjudicated major bleed who also had concentration data while not bleeding. Although the number of subjects is very small, it raises questions about the utility of using plasma concentrations to monitor individual subjects/adjust dose based on dabigatran concentrations.

Figure 19. Dabigatran concentrations in four subjects during a major bleed (red) and not during a major bleed (blue)



The x-axis is time in hours from last dose and the y-axis is the dabigatran plasma concentration in ng/mL. [Source: Reviewer's analysis: mj\conc\conc_2; sponsor datasets: timev, pk4p (5.3.10)]

7.3.2.2. Summary of non-bleeding SAEs

The total number of reported SAEs are shown by treatment arm in the table below, along with the reason given for reporting the event as "serious". The number of events reported as well as the reason given appears similar across the treatment arms.

Table 59. Reason given for reporting event as SAE

Category	D110 N=5983	%	D150 n=6059	%	W n=5998	%
SAE	1263	(21.2)	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/incapacitated	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)
Congenital anomaly	0	(0.0)	0	(0.0)	0	(0.0)
Other	1138	(19.0)	1243	(20.5)	939	(15.7)

[Source: Adapted from sponsor's table 15.3.2.6:1, sponsor resubmission 4.19.10. Subjects may be counted in more than one seriousness category]

There were no notable differences between treatment arms for any of the system organ classes (SOCs). The following table shows SAEs for selected SOC and associated SAEs of particular interest (i.e., cardiac, gastrointestinal). The SAE data do not markedly alter our understanding of the safety profile.

Table 16. SAE by system organ class (SOC)

SAE	D110 N=5983	%	D150 n=6059	%	W n=5998	%
SAE	1263	(21.2)	1290	(21.3)	1357	(22.6)
Cardiac disorders	310	(5.2)	291	(4.8)	321	(5.4)
Angina pectoris	29	(0.5)	30	(0.5)	22	(0.4)
Unstable angina	7	(0.1)	13	(0.2)	5	(0.1)
Gastrointestinal disorders	212	(3.5)	241	(4.0)	214	(3.6)
Abdominal pain	11	(0.2)	8	(0.1)	17	(0.3)
Dyspepsia	6	(0.1)	1	(0.0)	0	(0.0)
Pancreatitis (includes chronic)	1	(0.0)	5	(0.1)	8	(0.1)
Pancreatitis acute	3	(0.1)	1	(0.0)	0	(0.0)
Blood and lymphatic system disorders	68	(1.1)	69	(1.1)	71	(1.2)
Anemia	34	(0.6)	47	(0.8)	33	(0.6)
Renal and urinary disorders	104	(1.7)	94	(1.6)	113	(1.9)
Renal failure acute*	62	(1.0)	58	(1.0)	64	(1.1)
Renal impairment	3	(0.1)	5	(0.1)	2	(0.0)

[Source: Adapted from sponsor's table 15.3.2.6:2, sponsor resubmission 4.19.10. Subjects may be counted in more than one category] *includes acute, failure, renal tubular necrosis, azotemia, prerenal failure

7.3.3 Dropouts and/or Discontinuations

Adverse events leading to treatment discontinuation are shown in the table below. GI disorders were the most common adverse events leading to drug discontinuation in the dabigatran treatment arm. Other reasons for discontinuation of study medication are described in section 6.1.10.

Table 16. AE leading to treatment discontinuations

	D110 N=5983	%	D150 n=6059	%	W n=5998	%
Total subjects with AE leading to med d/c	1138	(19.0)	1243	(20.5)	939	(15.7)
Gastrointestinal disorders	387	(6.5)	422	(7.0)	232	(3.9)
Dyspepsia	57	(1.0)	57	(0.9)	2	(0.0)
GI hemorrhage	39	(0.7)	55	(0.9)	37	(0.6)
Cardiac disorders	144	(2.4)	140	(2.3)	120	(2.0)
Nervous system disorders	138	(2.3)	129	(2.1)	96	(1.6)
Renal and urinary disorders	129	(2.2)	119	(2.0)	85	(1.4)
Renal failure acute*	63	(1.1)	58	(1.0)	45	(0.8)

[source: Adapted from sponsor table 15.3.2.6:4, resubmission] *includes acute, failure, renal tubular necrosis, azotemia, prerenal failure

7.3.4 Significant Adverse Events

As noted under efficacy, there was a numerical imbalance in the number of MI's that favored subjects randomized to warfarin. This finding will be addressed further in a safety addendum.

7.3.5 Drug induced liver injury

Overview of findings and conclusions

Ximelagatran, an oral direct thrombin inhibitor, was associated with hepatotoxicity[20], raising concern for drug induced liver injury with dabigatran. To address this issue, the reviewer's comprehensive review included analyses of liver-related laboratory data and adverse event data, a review of cases of interest from the RE-LY trial, as well as an assessment of potential cases of DILI in the postmarketing setting. Drs. Senior and Seefe, from the Office of Surveillance and Epidemiology (OSE), reviewed the cases of interest and applied a scoring scale that assesses the severity (SEV) of liver injury and likelihood (LIK) of DILI,.[21]

Review of the laboratory data revealed 55 cases of interest in RE-LY: 16 occurring in subjects randomized to dabigatran 110, 16 in subjects randomized to dabigatran 150, and 23 in subjects randomized to warfarin. Among these cases, there were no definite

20. There were 14 cases of concern on ximelagatran (n=1960) in SPORTIF V; 1 very likely and 5 probable
21. This scoring system has been used in the past at FDA. It differs slightly from the Drug Induced Liver Injury Network (DILIN) scoring system and considerably from the NIH/NCI/CTEP/CTC (common toxicity criteria) manual.

or very likely DILI cases. One probable cause subject (51-75% likelihood, more likely than all other causes combined, only one other cause possible) was identified in the dabigatran 110 mg arm. There was not a greater frequency of more serious liver injury from dabigatran as compared to warfarin. While the review of postmarketing cases is not yet completed, to date, no definite DILI case has been identified in the postmarketing setting. Finally, no greater incidence of liver-related laboratory abnormalities or adverse events was seen in dabigatran treated subjects (compared to warfarin) in RE-LY.

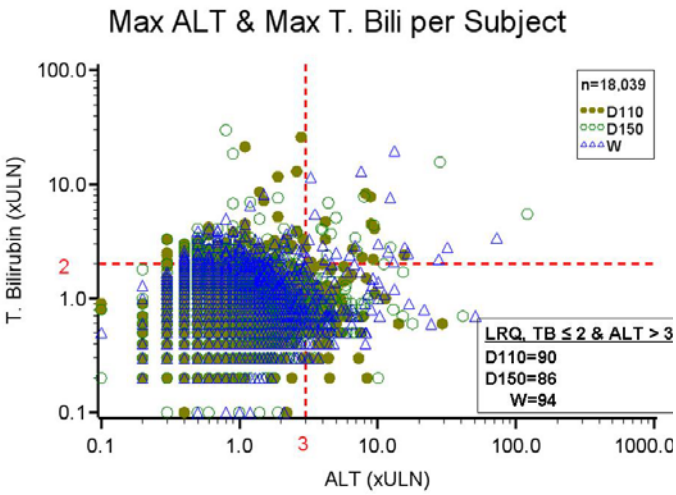
Based on these data, the risk of severe drug induced liver injury from dabigatran appears to be low. Because the perceived risk is low and frequent liver monitoring may not prevent serious cases from occurring (even if an association did exist), regular monitoring of liver tests is not recommended. A baseline assessment should perhaps be done for comparative purposes.

Assessments for DILI

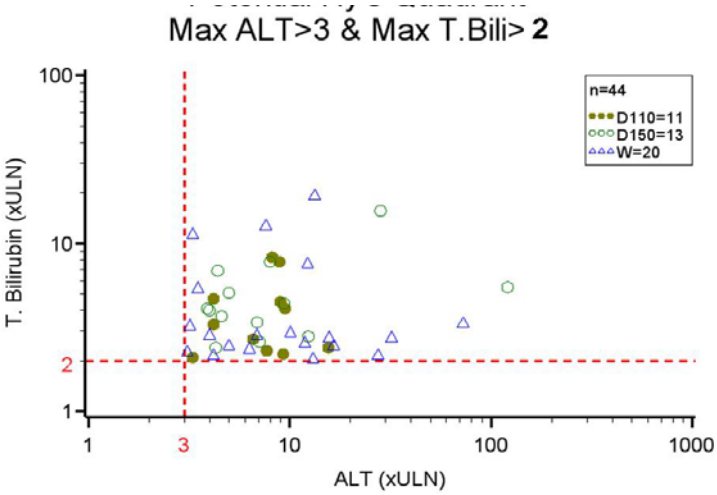
A total of 44 cases of interest were identified via a screen of peak ALT and peak total bilirubin(Tbili) values. The distribution of these values (taken as a ratio of the maximum ALT and maximum Tbili reported for a given subject) is shown below. Of the 44 subjects identified via this method, 11, 13, and 20 subjects were randomized to dabigatran 110 mg, dabigatran 150 mg and warfarin, respectively (Figure B).

Figure 20. Maximum ALT vs. maximum total bilirubin per subject

A. All subjects in safety database



B. Potential Hy's Quadrant



[Source: Reviewer's analysis: hep\figs\create ALT_TB.sas, sponsor's dataset: labdata]. Note that A. reflects only 18,039 subjects because one subject in the safety dataset did not have these labs done. This analysis was done without regard to the timing of the ALT and Tbili.

Eleven additional cases of interest (five dabigatran 110, three dabigatran 150, and three warfarin) were identified after including AST >3xULN, the results (line Cat 1) of which are shown in the table below.

For the analyses shown in the table below several bins of liver test abnormalities were created. For analyses not requiring a temporal relationship between the elevated aminotransferase (AT) and Tbili, the maximum liver test value was determined (Cat 1, 5, and 6-13 in table below). For analyses requiring a temporal relationship between the liver test findings (Cat 2, 3, and 4), the maximum AT value was determined and the maximum Tbili within 30 days after the maximum AT value was selected. For the potential Hy's Law cases (Cat 3), subjects with an ALKP ≥ 2 xULN within 30 days after the maximum AT were excluded.

Table 60. Liver test abnormalities in randomized population

Cat		D 110	%	D 150	%	W	%	Total
	Randomized (n)	6015		6076		6022		18113
1	ALT>3xULN &/or AST>3xULN and Tbili>2xULN	16	(0.3)	16	(0.3)	23	(0.4)	55
2	ALT>3xULN &/or AST>3xULN w/concurrent Tbili>2xULN*	12	(0.2)	14	(0.2)	18	(0.3)	44
3	ALT>3xULN &/or AST>3xULN w/concurrent Tbili>2xULN & ALKP<2xULN*	10	(0.2)	8	(0.1)	8	(0.1)	26
4	ALT>3xULN with concurrent Tbili>2xULN*	7	(0.1)	12	(0.2)	16	(0.3)	35
5	ALT>3xULN & Tbili>2xULN	11	(0.2)	13	(0.2)	20	(0.3)	44
6	ALT>3xULN	101	(1.7)	99	(1.6)	115	(1.9)	315
7	ALT>5xULN	29	(0.5)	37	(0.6)	45	(0.7)	111
8	ALT>10xULN	4	(0.1)	10	(0.2)	19	(0.3)	33
9	ALT>20xULN	1	(0.0)	3	(0.)	6	(0.1)	10
10	ALT>20xULN not in Cat 1	1		1		3		5
	Acute myocardial infarction					1		
	Elevation prior to randomized treatment			1		1		
	Normalized despite continued treatment					1		
	Likely due to amiodarone	1						
11	Tbili>2 xULN	114	(1.9)	114	(1.9)	121	(2.0)	349
12	ALT or AST > 3 xULN	125	(2.1)	118	(1.9)	136	(2.3)	379
13	ALKP>1.5xULN	773	(12.9)	393	(6.5)	869	(14.4)	2035

3 = Potential Hy's Cases
* = Concurrent defined as 30 days after max ALT or AST
Cat=category, Cat 4 is also a subset of Cat 5

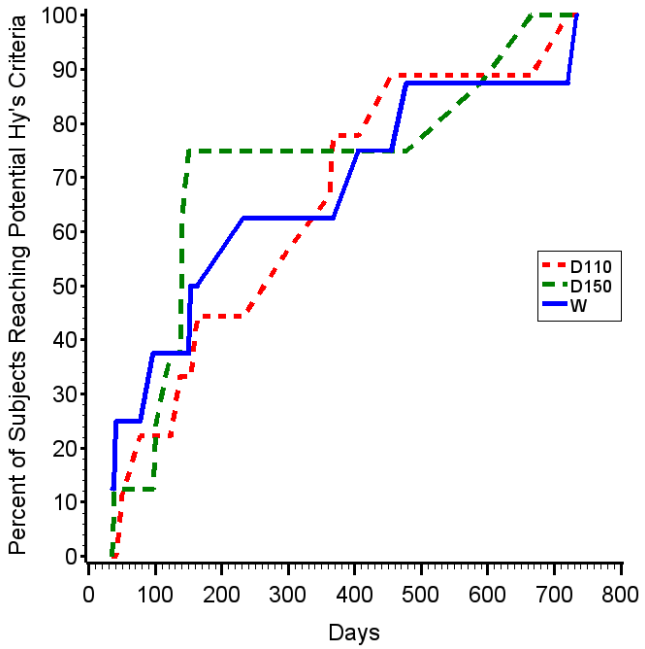
[Source: Reviewer's analysis: liver analysis time30.sas, liver analysis reviewer.sas, TA cats.xls, sponsor's dataset: labdata]

Regardless of how liver test elevations were defined (see table above), there did not appear to be a greater number of liver test abnormalities/Hy's Law cases in the dabigatran treatment arms relative to warfarin; if anything, there appeared to be more potential cases in the warfarin arm. No clear differences were seen in comparisons between the two dabigatran doses. Since hepatotoxic drugs with high rates of DILI have all caused an increased rate of AT elevations compared to control, categories 6-9 in the table shows results of various levels of ALT elevation since it might be a better indicator of the potential for severe DILI. Again, the data consistently show more subjects in the comparator arm. Lowering the degree of AT elevation to 2.5xULN and Tbili to 1.5xULN for categories 1-3 results in findings similar to above with more cases in the warfarin arm.

The time from the start of study medication to the development of liver abnormalities meeting Hy's Law criteria (Cat 3 in the table above) is shown in the figure below. The

time ranged from 35 to 734 days. With regard to onset, no clear differences were seen among the treatment arms.

Figure 21. Days to reach potential Hy's criteria (n=25)



[Source: Reviewer's analysis: hep2\time freq, sponsor's dataset, timeL]
Figure shows 25 subjects with potential Hy's criteria
Days are from the start of study medication. One subject (on dabigatran 110 mg) was removed because he met Hy's Law criteria at baseline.

Scoring results for 55 cases reviewed by OSE

Dr. Senior's review has not yet been finalized, but Drs. Senior and Seefe have evaluated and scored the 55 cases of interest. These cases were evaluated using a scoring scale that assesses both the severity (SEV) of liver injury and likelihood (LIK) of DILI.[22] The cases were also scored for completeness of information (CMP) and informative use of the data (INF).[23]

In terms of the clinical severity of the liver injury in RE-LY, one subject on dabigatran 150 mg received a score of 5 (death results from liver failure or liver transplant required because of liver failure) and 3 subjects on warfarin received a score of 4 (acute liver failure with secondary failure of brain or kidney function due to liver injury). The one death on dabigatran that was scored a 5 was a 57 year-old obese woman in the US with other valvular heart disease, hypertension, and heart failure who after approximately 4

22. This scoring system has been used in the past at FDA. It differs slightly from the Drug Induced Liver Injury Network (DILIN) scoring system and considerably from the NIH/NCI/CTEP/CTC (common toxicity criteria) manual.
23. For further discussion of CMP and INF, see the Appendix, section 9.7.

months on treatment developed significant AT elevations, endocarditis, septicemia, anemia, renal failure, and respiratory distress. Dabigatran was stopped and six days later she acutely decompensated and had an embolic stroke. She died nine days after drug was stopped. Though she was given a severity score of 5, the event was scored as being very unlikely to be DILI (LIK 0). Her CMP score was 2 (several items) and her INF score was 4 (very good basis for causal decision).

Table 61. Summary of severity (SEV) of DILI injury scores

SEV	Definition	D110	D150	W
1	ALT or AST >3xULN, usually transient and reversible by adaptation = mild	5	1	1
2	Also TBL >2xULN, after or concurrent, indicating early functional loss = Hy's Law case	2	4	8
3	Serious, meaning disabling, requiring or prolonging hospitalization because of liver dysfunction	9	10	11
4	Acute liver failure, with secondary failure of brain or kidney function due to liver injury	0	0	3
5	Fatal, or requiring liver transplantation due to liver failure	0	1	0

Of the 55 cases reviewed[24], no definite or very likely DILI case was seen. One probable case (51-75% likelihood, more likely than all other causes combined, only one other cause possible) was identified in the dabigatran 110 mg arm (see table below).

Table 62. Summary of likelihood (LIK) of DILI injury scores

LIK	Definition	D110	D150	W
0	Very unlikely, >5%, relatively rare cause for DILI	5	9	7
1	Unlikely, 5-25%, no other cause very likely or definite	9	7	13
2	Possible, 26-50% likely, up to three possible alternative causes	1	0	3
3	Probable, 51-75%, more likely than all other causes combined, only one other possible	1	0	0
4	Very likely, 76-95% likely, no other cause even rated as possible	0	0	0
5	Definite, >95% likely, no other cause even unlikely	0	0	0

The probable cause subject was a 67 year-old South Korean male with a history of hypertension, diabetes, heart failure, and benign prostatic hypertrophy. He did not have a known history of pancreatitis, cholecystitis or viral hepatitis. His symptoms began after 77 days of drug exposure and lasted until he was hospitalized for persistent pain. Dabigatran was stopped at the time of hospitalization (~3 days after the onset of

24 Of the 55 cases reviewed, the most probable cause of liver injury was heart failure with or without hypotension or shock.

symptoms). His liver tests were normal prior to his symptoms and were elevated upon hospital admission (see table below).

Table 63. Liver test ratios in probable DILI subject

Date	ALTx	ASTx	TBilix	ALKPx	Central lab
07-JUL-2006	0.6	0.8	1.1	0.6	0
26-JUL-2006*	9.0	10.0	4.5	1.0	1

Central lab indicated by a 1, local lab=0
*This lab was the one taken upon hospital admission

During his hospitalizations, the following laboratory abnormalities were also noted: lipase 128 (0-6 U/L), indirect bilirubin 55 (17-21 umol/L), and ceruloplasmin 350 (20-50 mg/L). Notably, the following laboratory tests were unremarkable/negative: AMA, ANA, ASMA, LKM-1, alpha-1 antitrypsin, Anti-HCV, and HBsAG screen w/ confirmation. An abdominal (liver, gall bladder, pancreas) ultrasound showed peripheral ductal dilatations without an abnormal mass in the liver and a mildly enlarged spleen. Coarse and prominent echogenicity of the liver was seen and was read as being suggestive of a diffuse hepatocellular process, but not cholecystitis. A CT scan reported no liver lesion.

It was reported that the patient drank "some amount" of concentrates of red ginseng (2 pack, about 80 mol/pack) for 1 year. Concomitant medications are as shown below.

Medication: provide generic name	Start Date Year/month/day	Stop Date Year/month/day
Antibiotics : Unknown	2006/07/25	2006/07/25
NSAIDs	2006/07/25	2006/07/25
KERLONE(selective b-blocker)	2004/03/21	Ongoing
COZAAR(Angiotensin 2 recepterAntagonist	2005/12/06	Ongoing
CADIL(alpha blocker)	2005/12/06	Ongoing
LASIX(Loop diuretics)	2005/12/06	Ongoing

The site investigator diagnosed him with DILI. He was switched to warfarin and discharged after 8 days in the hospital. His liver abnormalities normalized 13 days after hospital admission and remained normal while on warfarin for 30 months.

While his likelihood score was a 3, heart failure was also considered a possible cause (though he was not treated for heart failure during the hospitalization). His other scores were SEV 3 (serious, disabling, requiring or prolonging hospitalization), CMP 3 (most of the key items provided) and INF 3 (very well supported conclusion).

For summary of CMP and INF scores see the Appendix.

Adverse event data

As another way to identify potential cases of DILI, the adverse event data set (aeads18.xpt) was searched for terms suggestive of drug induced liver injury. Because of the high incidence of abdominal pain and the poor specificity of this term, "jaundice" was used as a High Level Term to identify subjects with potential liver-related adverse events. The subjects identified had the following lower level terms: cholestasis, cholestatic jaundice, hyperbilirubinaemia/hyperbilirubinemia, icterus, jaundice, liver cholestasis, and obstructive jaundice. Subjects who were rechallenged with drug and had normal liver function tests following rechallenge were removed. This search identified an additional 36 subjects (beyond the 55 initially identified). These subjects were randomized as follows: 9, 8, and 19 on dabigatran 110, dabigatran 150, and warfarin, respectively. The adverse event data do not raise concerns of potential DILI.

Discontinuations

The table below shows subjects whose reason for discontinuation of study medication was given by the investigator as "elevated LFT". As shown in the table below, a greater number of subjects on dabigatran (relative to warfarin) were discontinued from study medication for reason of elevated LFT.

The table also looks at the last AT prior to discontinuation in subjects who either permanently discontinued study or prematurely discontinued from the trial. This analysis was done to evaluate subjects who might have been developing liver injury. The AT cut-off ratios (1.5x and 2x) were arbitrarily chosen. There was no clear indication based on last AT value that more subjects on dabigatran compared to warfarin might have been at risk for potential liver injury. Additionally, there were more subjects on warfarin who discontinued medication and had a last AT >3xULN, an elevation more clinically meaningful than the arbitrarily chosen cut-offs.

Table 64. Premature discontinuations with elevated aminotransaminases

	D1101	**D150**	**W**
Treated	**N=5983**	**N=6059**	**N=5998**
Completed follow-up but stopped med prematurely[1]	1170	1197	907
Elevated LFT result given by investigator as reason for discontinuation[1]	25	16	11
Last AT > 1.5 xULN (not in Cat 1)[2]	49	32	34
Last AT > 1.5 xULN (subjects that are not included in sponsor's elevated LFT result)[2]	48	33	37
Last AT > 3xULN	9	6	14
Premature d/c from trial[1]	203	235	242
Premature d/c with last AT > 1.5xULN[3]	4	7	6
Premature d/c w/ last AT > 2.0 xULN*,[3]	1	3	2

AT=ALT or AST, d/c=discontinue, LFT=liver function test
Cat 1 = 55 identified subjects of interest to evaluate for potential drug induced liver injury
1. Adapted from sponsor's table 15.1.1:1.

2. Reveiwer's analysis: last lft dcmed, sponsor's data: disco, labdata
3. Reviewer's analysis: last lft dcmed dcstud

Postmarketing data

Three cases of interest have been reported in the postmarketing experience: one death (2009-RA-00265RA), one hospitalization (2010-CN-00363CN), and a case of elevated liver enzymes associated with jaundice, skin rash and pruritis (2010-AP-00222AP). These cases are currently being review by OSE at FDA. An addendum will be filed for these cases if their review affects the conclusions of the hepatic safety analysis presented in this review.

Table 65. Three postmarketing cases under review

2009-RA-00265RA: This is a death in a 72 year old Hispanic man taking dabigatran 220 mg for superficial venous thrombosis (also on paracetamol). One day after starting dabigatran, he experienced non-serious diarrhea and abdominal pain. Dabigatran was stopped 2 days later. His symptoms subsided and warfarin was started. Two days after dabigatran was stopped he developed severe liver failure and died two weeks later. The investigator's causation was "not reasonably possible".
2010-CN-00363CN: This was a male from Canada taking dabigatran 150 mg BID for atrial fibrillation who experienced "Hy's elevation" 12 weeks after starting drug and requiring hospitalization. Dabigatran was stopped and the investigator's assessment was likely DILI; alcohol and autoimmune etiologies were considered unlikely. According to the sponsor, because of privacy laws in Canada, further information could not be obtained.
2010-AP-00222AP: This is a 79 year old female with diabetes, hypertension, hyperlipidemia, hyperuricemia and prior cholecystectomy who was taking dabigatran 150 mg following elective knee replacement. She presented with generalized pruritis and significant elevations in AT, GGT, ALKP and TBili 1-2 weeks after completing a 49 day course of dabigatran. Liver biopsy showed severe hepatic steatosis and the investigator could not exclude dabigatran. She subsequently recovered and liver tests returned to normal.

Incidence of liver test abnormalities on warfarin

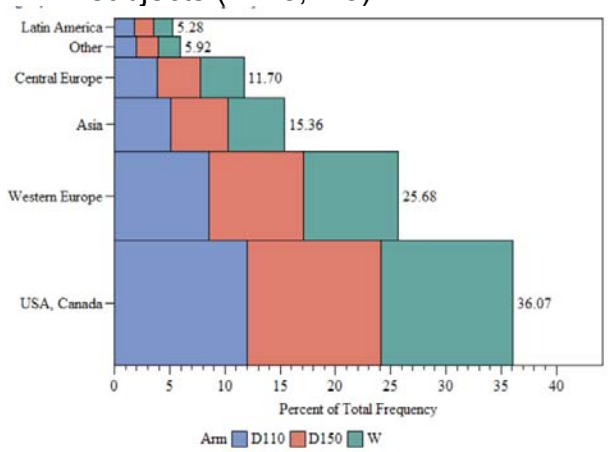
The incidence of cases of interest in the warfarin treatment arm of RE-LY was ~6.5-fold greater than that seen in SPORTIF V, a randomized controlled trial comparing ximelagatran against warfarin for stroke prevention in atrial fibrillation (20 cases in 6021 subjects in RE-LY vs. 1 case in 1922 subjects in SPORTIF V). The reason for this difference is not clear. Monitoring of liver tests did not appear to be markedly different between the two studies[25]; nor did there appear to be clear differences between the studies in the incidence of background diseases[26] that might provide some explanation. It is possible that the difference in incidence may be attributable in part to the longer

25 SPORTIF V liver tests were drawn monthly for 6 months, then bimonthly for the first year, and then quarterly
26 SPORTIF V population had 40% with heart failure versus 32% in RE-LY

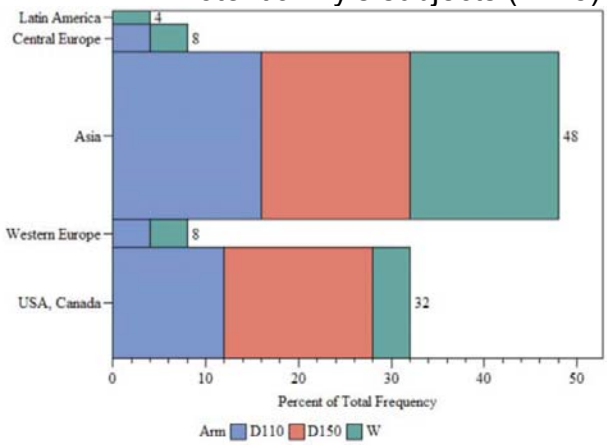
duration and larger size of RE-LY and the geographic locations where these studies were conducted. Whereas SPORTIF V was conducted in the US and Canada, RE-LY was an international study. As shown in the figure below, approximately ½ of the 25 potential Hy's cases were from sites in Asia and Latin America.

Figure 22. Regional population in RE-LY

A. All subjects (n=18,113)



B. Potential Hy's subjects (n=25)



[source: reviewer's analysis:hep\region, sponsor datast: basco]

If laboratory measurements were drawn more frequently in the warfarin arm, it may help explain the greater number of cases of interest compared to dabigatran. However, laboratory monitoring of each liver test was equally distributed (33%) between the treatment arms (ALT monitoring shown in next table).

Table 66. Frequency of ALT monitoring in treated subjects, n (%)

	Dabigatran 110	**Dabigatran 150**	**Warfarin**
Entire study duration	78,362 (33)	78,735 (33)	78,709 (33)
Central lab	66,902 (85)	67,357 (86)	66,951 (85)
Prior to September 25, 2006[1]	27,576 (34)	26,801(33)	26,652 (33)
Central lab	22,983 (83)	22,401 (84)	22,218 (83)

1 This is based on treatment starting (not randomization) prior to September 25, 2006
[Source: Reviewer's analysis: liver lab freq, sponsor dataset=labdata]

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Bleeding and GI adverse events were among the most common adverse events reported in RE-LY. Dyspepsia/gastritis was reported at a greater frequency in dabigatran compared to warfarin-treated subjects, as shown in the table below. Study medication discontinuation because of dyspepsia/gastritis was also more common in dabigatran treated subjects. Approximately 2% of dabigatran treated subjects discontinued study medication because of dyspepsia. In contrast, 0.6% of warfarin treated subjects discontinued study medication for this reason. Study medication discontinuation as a result of gastritis was 0.6% and 0.3% in the dabigatran and warfarin treatment arms, respectively.

Table 67. Frequency of dyspepsia and gastritis

Table 15.3.2.8: 1 Frequency (%) of subjects with dyspepsia/gastritis ++ by treatment

User-defined AE category/ Preferred term	DE 110mg bid N (%)	DE 150mg bid N (%)	Warfarin N (%)
Number of patients	5983 (100.0)	6059 (100.0)	5998 (100.0)
Total with dyspepsia/gastritis++	983 (16.4)	940 (15.5)	470 (7.8)
Dyspepsia+	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+	297 (5.0)	257 (4.2)	142 (2.4)
Gastritis	147 (2.5)	127 (2.1)	87 (1.5)
Gastrooesophageal reflux disease	117 (2.0)	99 (1.6)	46 (0.8)
Oesophagitis	32 (0.5)	27 (0.4)	8 (0.1)
Gastritis erosive	21 (0.4)	19 (0.3)	3 (0.1)
Gastric haemorrhage	0 (0.0)	4 (0.1)	3 (0.1)
Gastritis haemorrhagic	5 (0.1)	4 (0.1)	3 (0.1)
Haemorrhagic erosive gastritis	2 (0.0)	0 (0.0)	0 (0.0)

In the dabigatran and warfarin treatment groups, the yearly event rate for dyspepsia and gastritis was slightly higher in subjects taking aspirin (no aspirin use vs. use at least once).

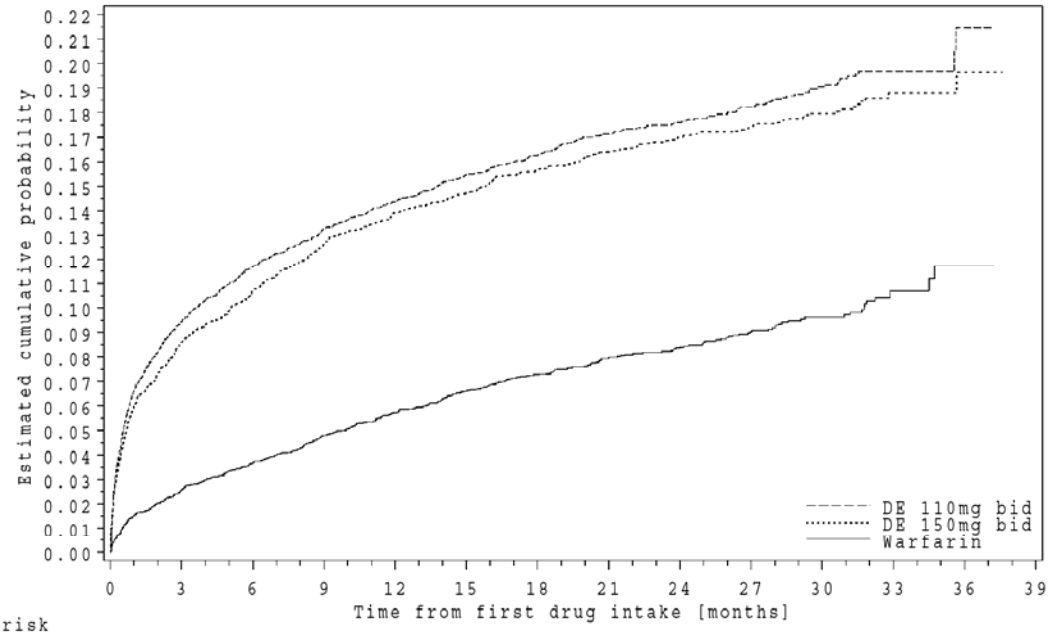
Table 68. Frequency of dyspepsia and gastritis by aspirin use

Table 15.3.2.8: 4 Yearly event rate of dyspepsia/gastritis ++ by ASA use during treatment period
safety set

	DE 110mg bid				DE 150mg bid				Warfarin			
	# of subjects	Subject-years	Subjects with event	Yearly event rate (%)	# of subjects	Subject-years	Subjects with event	Yearly event rate (%)	# of subjects	Subject-years	Subjects with event	Yearly event rate (%)
Dyspepsia+	5983	10242	761	7.43	6059	10261	738	7.19	5998	10659	354	3.32
No ASA	3779	6551	452	6.90	3880	6615	446	6.74	3780	6814	198	2.91
Use ASA at least once	2204	3691	309	8.37	2179	3646	292	8.01	2218	3846	156	4.06
Gastritis+	5983	10242	297	2.90	6059	10261	257	2.50	5998	10659	142	1.33
No ASA	3779	6551	181	2.76	3880	6615	136	2.06	3780	6814	74	1.09
Use ASA at least once	2204	3691	116	3.14	2179	3646	121	3.32	2218	3846	68	1.77
Dyspepsia/gastritis ++	5983	10242	983	9.60	6059	10261	940	9.16	5998	10659	470	4.41
No ASA	3779	6551	592	9.04	3880	6615	553	8.36	3780	6814	262	3.85
Use ASA at least once	2204	3691	391	10.59	2179	3646	387	10.61	2218	3846	208	5.41

A Kaplan-Meier estimate of the time to first dyspepsia/gastritis event suggests that this adverse event manifests soon after the start of therapy with dabigatran.

Figure 23. Time to first dyspepsia/gastritis



Subjects at risk													
DE 110mg bid	5983	5034	4736	4511	4342	4054	3348	2688	2217	1664	996	335	54
DE 150mg bid	6059	5107	4800	4565	4383	4097	3399	2702	2237	1662	997	313	71
Warfarin	5998	5546	5336	5121	4954	4608	3857	3019	2498	1882	1100	291	57

Figure 15.3.2.8: 2 Kaplan-Meier estimates of time to first dyspepsia/gastritis ++
safety set

Source data: Appendix 16.1.9.2, Statdoc 7.3.5.2 scs26\sf_kaplan_ad.sas 03APR2010

7.4.2 Laboratory Findings

The significant laboratory findings related to liver tests are discussed in section 7.3.5.1.

7.4.3 Vital Signs

No clear differences were seen across treatment arms in terms of changes in blood pressure over the course of the study. Approximately 66-67% of subjects were in atrial fibrillation at study end; the incidence was similar in the dabigatran and warfarin treatment arms.

7.4.4 Electrocardiograms (ECGs)

The Interdisciplinary QT Team reviewed the thorough QT study (placebo and moxifloxacin controlled) and found no significant QT prolonging effect with a single dabigatran dose of 150 mg and 600 mg. Assay sensitivity was established via the moxifloxacin control. The largest upper bounds of the 2-sided 90% CI for the mean difference between dabigatran and placebo were below 10 ms, the threshold for regulatory concern. However, there was concern that the QT study did not explore a high enough dose to cover a potential worse case scenario. In RE-LY, no cases of torsade de pointe on dabigatran were noted and there was not an increased incidence of sudden/arrhythmic deaths in dabigatran compared to warfarin treated subjects (1.5% on dabigatran 110 mg, 1.2% on dabigatran 150 mg and 1.4 % on warfarin).

7.4.5 Special Safety Studies/Clinical Trials

No special safety studies were conducted other than a thorough QT study.

7.4.6 Immunogenicity

Not applicable. Dabigatran is not a therapeutic protein.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

A dose dependent relationship was seen for major bleeding events.

7.5.2 Time Dependency for Adverse Events

This is discussed within each SAE.

7.5.3 Drug-Demographic Interactions: Eldery

Subjects 75 years of age and older are perceived to be at increased risk of hemorrhage and also have impaired renal function which would result in increased exposure to dabigatran. Relative to warfarin, rates of major bleeds appeared similar if not greater in dabigatran treated subjects ≥ 75 years of age. In contrast, rates appeared lower (relative to warfarin) in those less than 75.

Table 69. Frequency and yearly event rate of major bleed in elderly (age ≥ 75 years)

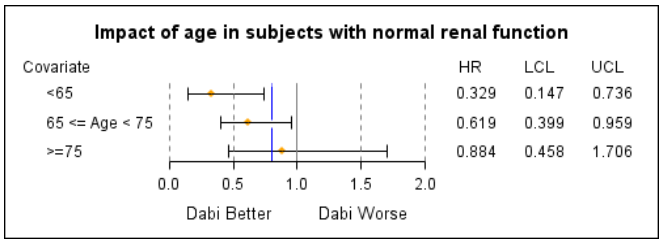
	DE 110		DE 150		Warfarin	
	#of subjects	Yearly event rate (%)	# of subjects	Yearly event rate (%)	# of subjects	Yearly event rate (%)
Age (years)						
<65	998	0.71	1030	0.79	953	2.26
65<= and <75	2668	2.10	2580	2.45	2646	3.07
>=75	2349	4.18	2466	4.82	2423	4.11

[Source: Sponsor, Original submission, Table 12.2.2.5:1]

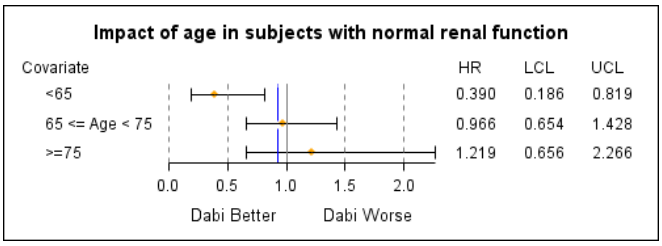
Reviewer's comment: Though renal function plays an important role in this relationship, analyses suggest that increasing age, independent of renal function, may be associated with a greater risk (relative to warfarin) of a major bleed on dabigatran. (see figure)

Figure 24. Impact of age on major bleeding in subjects with normal renal function

A. D110 v. W



B. D150 v. W



[source: reviewer's analysis, sponsor's data: adjrand2]

While subjects ≥ 75 years of age may be at greater risk for bleeding, analyses of net benefit (composites of bleeding and stroke/SEE), do not suggest a clear benefit of the 110 mg dose over the 150 mg dose in this population. These data as a whole indicate that there is no reason to dose adjust in the elderly.

Table 70. Net benefit comparison of dabigatran doses in elderly

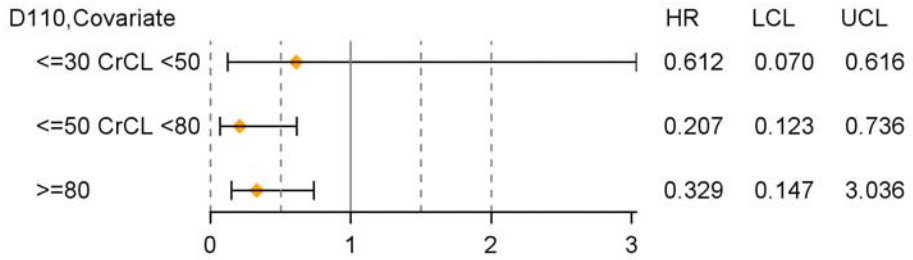
Net benefit	D150vD110 HR	95% LL	95% UL	p-value
Adjudicated life threatening bleed or stroke/SEE	0.98	0.79	1.22	0.87
Adjudicated life threatening bleed or disabling or fatal stroke	0.96	0.76	1.21	0.72
ICH or stroke/SEE	0.82	0.61	1.11	0.20
ICH or disabling or fatal stroke	0.77	0.54	1.09	0.13
GUSTO-severe or disabling or fatal stroke	0.98	0.74	1.30	0.88
Major bleed or stroke/SEE	1.07	0.91	1.26	0.42

[source: reviewer's analysis: net\age, sponsor's data adjrand, timev, timecens]

7.5.4 Drug-Disease Interactions: Renal impairment

Dabigatran is primarily renally cleared with an ~2-3-fold increase in exposure seen in subjects with moderate renal impairment (creatinine clearance of 30 to 50 mol/min). Despite an expected increase in exposure, no greater risk of bleeding was seen in dabigatran compared to warfarin treated subjects with baseline renal clearance between 30 and 50 mol/min (see figure).

Figure 25. Impact of renal function on major bleeding in subjects less than 65 years old



[source: reviewer's analysis, sponsor dataset adjrand2]. Since there is a relationship with bleeding and age, this analysis looks at an age subpopulation.

Relative to the dabigatran 110 mg dose, the incidence of bleeding was not greater at the 150 mg dose, though a dose-response relationship still existed for stroke/SEE. Why bleeding rates were not greater in subjects receiving dabigatran 150 mg is not clear. The results suggest that a dose of 150 mg should be used in patients with moderate renal impairment.

Table 71. Frequency and yearly event rate for major bleeds by baseline renal function

	DE 110		DE 150		Warfarin	
	#of subjects	Yearly event rate (%)	# of subjects	Yearly event rate (%)	# of subjects	Yearly event rate (%)
CrCL (ml/min)						
<30	15	0.00	32	13.31	30	0.00
30<= and <50	1136	5.42	1157	5.08	1050	5.28
50<= and <80	2714	2.59	2777	3.17	2807	3.63
>=80	1899	1.40	1882	1.86	1877	2.27

[Source: Sponsor, Original submission, Table 12.2.2.5:1]

Table 72. Frequency and yearly event rate for stroke/SEE by baseline renal function

	DE 110		DE 150		Warfarin	
	# of subject	Event rate	# of subject	Event rate	# of subject	Event rate
CrCL (ml/Min)						
30<= and <50	1136	2.36	1157	1.23	1050	2.64
50<= and <80	2714	1.69	2777	1.21	2807	1.82
>=80	1899	0.86	1882	0.73	1877	1.03

[Source: Sponsor, Original submission, Table 11.4.1.4.1:1]

7.5.5 Drug-Drug Interactions

Drug-Drug interactions are discussed under concomitant medications (Section 7.3.2.1).

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

Preclinical data were not suggestive of carcinogenicity and no imbalance was seen across treatment arms in the incidence of neoplasms.

7.6.2 Human Reproduction and Pregnancy Data

There is no information on drug exposure in pregnant or lactating women.

7.6.3 Pediatrics and Assessment of Effects on Growth

Studies were not conducted in children.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

An overdose would be expected to result in hemorrhagic complications. There is no established antidote to dabigatran-induced hemorrhage and in RE-LY, investigator were told to give consideration to the following therapies in subjects with major bleeding on dabigatran: packed cells, FFP, prothrombin complex concentrates, and recombinant factor VIIa. Hemodialysis could also be considered. The measures taken by investigators are shown in the tables below for all subjects with adjudicated major bleeds and by whether or not the subject lived or died. Subjects were not randomized to the intervention that they received and interpretation of the data is limited.

Table 73. Corrective therapies used in subjects with adjudicated major bleed

	D110	%	D150	%	W	%
Total subjects	397	(100)	486	(100)	476	(100)
Required Transfusion	234	(58.9)	315	(64.8)	246	(51.7)
Associated with Hypotension requiring pressors	18	(4.5)	34	(7.0)	22	(4.6)
Required surgical intervention	36	(9.1)	57	(11.7)	65	(13.7)
Other corrective treatment for bleed	132	(33.2)	170	(35.0)	244	(51.3)
FFP	73	(18.4)	107	(22.0)	144	(30.3)
VitaminK	37	(9.3)	53	(10.9)	124	(26.1)
Other	56	(14.1)	50	(10.3)	56	(11.8)
Platelets	13	(3.3)	18	(3.7)	24	(5.0)
Cryoprecipitate	3	(0.8)	5	(1.0)	7	(1.5)
Recombinant Factor VIIa	1	(0.3)	7	(1.4)	3	(0.6)
Coagulation Factor	1	(0.3)	3	(0.6)	5	(1.1)
Prothrombin Complex Conc	3	(0.8)	2	(0.4)	5	(1.1)

[Source: reviewer's analysis: adj_plt122n, sponsor's data plt122n, timev,adjrand].

Table 74. Corrective therapies used for adjudicated major bleeds in subjects that died

Corrective therapy	D110	D150	W
Subject died	25	28	40
Required Transfusion	8	11	10
Associated with Hypotension requiring pressors	6	11	8
Required surgical intervention	1	8	8
Other corrective treatment for bleed	10	14	18
FFP	7	9	11
VitaminK	5	4	10
Other	2	3	4
Platelets	2	3	2
Cryoprecipitate	1	3	.
Recombinant Factor VIIa	1	4	1
Coagulation Factor	1	2	1
Prothrombin Complex Conc	2	.	.

[source: reviewer's analysis, filename: Tx\Dead v alive corrective, sponsor data plt122n, timev]

Table 75. Corrective therapies used for adjudicated major bleeds in subjects that did not die

Corrective therapy	D110	D150	W
Subject alive	369	456	435
Required Transfusion	225	304	236
Associated with Hypotension requiring pressors	12	23	14
Required surgical intervention	35	49	57
Other corrective treatment for bleed	120	156	226
FFP	65	98	133
VitaminK	32	49	114
Other	53	47	52
Platelets	11	15	22
Cryoprecipitate	2	2	7
Recombinant Factor VIIa	.	3	2
Coagulation Factor	.	1	4
Prothrombin Complex Conc	1	2	5

[source: reviewer's analysis, filename: Tx\Dead v alive corrective, sponsor data plt122n, timev]

7.7 Interruptions for elective surgeries/procedures

The RE-LY protocol provided guidance on the use of warfarin and dabigatran around the time of emergency and elective surgeries/procedures (see section 5.3.5.4). Overall, 4623 subjects (25.6%) had interruptions of anticoagulant therapy for a surgery/procedure; the numbers/percents were similar across the three treatment arms. A minority of subjects (525) had interruptions for an emergency surgery/procedure.

In upwards of 70% of subjects on dabigatran who had interruptions for a procedure/surgery, bridging therapy was not used, as shown in the table below.

Table 76. Summary of bridging therapy for subjects with interruptions of anticoagulant for surgery/procedure

	Dabigatran 110	Dabigatran 150	Warfarin
Subject with interruptions for procedure/surgery	1501	1554	1568
Subjects with no bridging therapy	1190 (79.3)	1203 (77.4)	1030 (65.7)

Subjects with bridging therapy*	311 (20.7)	351 (22.6)	538 (34.3)
Pre-procedural bridging	203 (13.5)	210 (13.5)	394 (25.1)
Post-procedural bridging	262 (17.5)	293 (18.9)	447 (28.5)
Pre- and Post procedural bridging	154 (10.3)	152 (9.8)	303 (19.3)

*subjects counted in more than one category if multiple interruptions for surgery/procedure occurred. [Source: taken from sponsor's table 17.2, appendix-3, 7.30.10 submission]

The nature of the procedures, medication used for bridging and timing of procedures since previous dose of anticoagulation therapy is shown below for subjects undergoing pre-procedural bridging therapy. The majority of dabigatran subjects receiving a bridge had been off of therapy for more than 2 days.

Table 77. Summary of surgery/procedures for subjects used pre-procedural bridging therapy

	Dabigatran 110	**Dabigatran 150**	**Warfarin**
Day procedure or hospital admission			
Day procedure	104	122	246
Hospital admission	273	265	452
Type of procedure			
Pacemaker/ICD	36	37	56
Surgery	215	215	356
Dental procedure	11	21	59
Diagnostic procedure	72	73	140
Other	43	41	87
Emergency or elective			
Emergency	51	36	58
Elective	326	351	639
Time of procedure since previous dose (days)			
<= 2	99	89	50
2< and <= 5	98	91	169
> 5	53	58	204
Medication used for bridging			
Subcutaneous LMWH	175	172	421
Unfractionated heparin	74	70	107
Study medication restarted after procedure			
No	51	42	68
Yes	326	344	630
Blood transfusion required			

No	344	369	653
Yes	31	18	44

[Source: taken from sponsor's table 17.3, appendix-3, 7.30.10 submission]

Of the subjects who did not use a bridge, the number/percent experiencing an important outcome event (stroke/SEE, major bleed) around the time of surgery appeared similar in the dabigatran compared to warfarin treatment arms. This also appeared to be the case in subjects who used a bridge.

Table 78. Summary of outcome events for subjects without bridging therapy for surgery/procedure

	Dabigatran 110	**Dabigatran 150**	**Warfarin**
Subjects with interruptions for procedure/surgery and no bridging therapy	1190	1203	1030
Subjects with outcome events occurred within 7 days prior to surgery/procedure	43 (3.6)	51 (4.2)	38 (3.7)
Stroke/SEE	0 (0.0)	0 (0.0)	2 (0.2)
Major bleed	23 (1.9)	17 (1.4)	13 (1.3)
Minor bleed	23 (1.9)	34 (2.8)	25 (2.4)
Death	0 (0.0)	0 (0.0)	0 (0.0)
Subjects with outcome events occurring within 30 days post surgery/procedure	135 (11.3)	155 (12.9)	115 (11.2)
Stroke/SEE	2 (0.2)	3 (0.2)	6 (0.6)
Major bleed	29 (2.4)	45 (3.7)	25 (2.4)
Minor bleed	106 (8.9)	114 (9.5)	92 (8.9)
Death	5 (0.4)	2 (0.2)	2 (0.2)

[Source: taken from sponsor's table 17.8, appendix-3, 7.30.10 submission]

In subjects undergoing interruptions for emergency surgery/procedure, outcomes were not worse in dabigatran compared to warfarin treated subjects.

Table 79. Summary of outcome events for subjects using emergency procedure for surgery/procedure

	Dabigatran 110	**Dabigatran 150**	**Warfarin**
Subjects with interruptions for emergency surgery/procedure	167	196	162
Subjects with outcome events occurring within 7 days prior to surgery/procedure	26 (15.6)	26 (13.3)	24 (14.8)

Stroke/SEE	2 (1.2)	1 (0.5)	3 (1.9)
Major bleed	17 (10.2)	13 (6.6)	15 (9.3)
Minor bleed	10 (6.0)	12 (6.1)	11 (6.8)
Death	0 (0.0)	0 (0.0)	0 (0.0)
Subjects with outcome events occurring within 30 days post surgery/procedure	40 (24.0)	42 (21.4)	44 (27.2)
Stroke/SEE	5 (3.0)	1 (0.5)	5 (3.1)
Major bleed	17 (10.2)	26 (13.3)	24 (14.8)
Minor bleed	20 (12.0)	20 (10.2)	23 (14.2)
Death	4 (2.4)	3 (1.5)	1 (0.6)

[Source: taken from sponsor's table 17.10, appendix-3, 7.30.10 submission]

9 Appendices

9.1 Literature Review/References

Aguilar MI, Hart R. Oral anticoagulants for preventing stroke in patients with non-valvular atrial fibrillation and no previous history of stroke or transient ischemic attacks. *Cochrane Database of Systematic Reviews* 2005, Issue 3. Art. No.: CD001927. DOI: 10.1002/14651858.CD001927.pub2.

Connolly et al. Benefit of Oral Anticoagulants over Antiplatelet Therapy in Atrial Fibrillation Depends on the Quality of International Normalized Ratio Control Achieved by Centers and Countries as Measured by Time in Therapeutic Range. Circulation. 1008; 118: 2029-2037.

Fuster et al. ACC/AHA/ESC 2006 Guidelines for the Management of Patients with Atrial Fibrillation. Circulation. 2006; 114:700-752.

Hart et al. Antithrombotic Therapy to Prevent Stroke in Patients with Atrial Fibrillation: A Meta-Analysis. Ann Intern Med. 1999; 131: 492-501.

Hart et al. Meta-analysis: Antithrombotic Therapy to Prevent Stroke in Patients Who Have Nonvalvular Atrial Fibrillation. Ann Intern Med. 2007; 146: 857-867.

Hirsh et al. American Heart Association/American College of Cardiology Foundation Guide to Warfarin Therapy. Circulation. 2003; 107: 1692-1711.

Jackson et al. Antithrombotic drug development for atrial fibrillation: Proceedings, Washington, DC, July 25-27, 2005. Am Heart J. 2008; 155: 829-840.

Jones M et al. Evaluation of the pattern of treatment, level of anticoagulation control, and outcome of treatment with warfarin in patients with non-valvular atrial fibrillation: a record linkage study in a large British population. Heart 2005; 91:472–477.

Lange U, Nowak G, Bucha E. Ecarin Chromogenic Assay- A New Method for Quantitative Determination of Direct Thrombin Inhibitors Like Hirudin. Pahtophysiol Haemost Thromb. 2003/04; 33:184-191.

Mant J et al. Warfarin versus aspirin for stroke prevention in an elderly community population with atrial fibrillation (the Birmingham Atrial Fibrillation Treatment of the Aged Study, BAFTA): a randomized controlled trial. Lancet 2007; 370: 493-503.

Secondary prevention in non-rheumatic atrial fibrillation after transient ischaemic attack or minor stroke. EAFT (European Atrial Fibrillation Trial) Study Group. Lancet. 1993; 342(8882):1255-62.

White HD et al. Comparison of Outcomes among Patients Randomized to Warfarin Therapy according to Anticoagulant Control. Arch Intern Med. 2007; 167: 239-245.

9.2 Labeling Recommendations

The labeling review will be provided as an addendum.

9.3 Advisory Committee Meeting

An advisory committee meeting has been scheduled for September 20, 2010. We believe that the advisory committee meeting should focus on dose selection for anticoagulant therapies and how to weigh the benefits of these therapies against their risks (specifically when the risk of bleeding events balances the risk of stroke). We think that the advisory committee should be asked to opine on the dose(s) of dabigatran that should be approved and the particular population(s) in which the dose(s) should be used. In particular, we think that there needs to be discussion about whether or not it makes sense to recommend a lower dose of dabigatran in patients at increased risk of bleeding, and, if so, how one defines this population.

9.4 Efficacy of Warfarin

The clinical trial experience supporting the efficacy of warfarin in the treatment of atrial fibrillation is discussed below. Topics addressed include the nature of the benefit of warfarin (effect on stroke and magnitude of effect) and how warfarin was used and in whom it was used in the referenced clinical trials. This section also reviews the data

supporting time in therapeutic range (TTR) as a measure of the quality/adequacy of anticoagulation in warfarin treated subjects in clinical trials.

The nature of the benefit of warfarin: Five randomized, placebo-controlled primary prevention trials are widely referenced as establishing the efficacy of warfarin for the primary prevention of ischemic stroke in patients with non-valvular atrial fibrillation: Copenhagen Atrial Fibrillation, Aspirin, Anticoagulation (AFASAK I), Boston Area Anticoagulation Trial for Atrial Fibrillation (BAATAF), Canadian Atrial Fibrillation Anticoagulation (CAFA), Stroke Prevention in Atrial Fibrillation (SPAF I), Stroke Prevention in Nonrheumatic Atrial Fibrillation (SPINAF). A sixth study, European Atrial Fibrillation Trial (EAFT), addressed the efficacy of warfarin for the prevention of stroke in patients with atrial fibrillation and a history of nondisabling stroke or TIA within 3 months (trial of secondary prevention). As shown in the table below, the primary endpoint varied somewhat across the studies. Four of the five primary prevention trials were terminated early for reasons of efficacy; a fifth (CAFA) was terminated in light of the efficacy findings in the other studies.

Study	Participants (follow up)	Target INR	Mean INR	Primary Endpoint
Open Label				
AFASAK I	Denmark, chronic AF, median age 74.2, 54% male (~1.2 years/subject)	2.8-4.2	~ 2.5	TIA, stroke, systemic embolism
SPAF I	U.S., constant or intermittent chronic AF, mean age 67, 71% male (~2.2 years/subject)	2-4.5	~2.6	Ischemic stroke, systemic embolism
BAATAF†	U.S., chronic or intermittent AF, mean age 68, 75% male	1.5-2.7	~2.1	Ischemic stroke
EAFT (group I)	12 European countries and Israel, nonrheumatic AF and a recent (< 3 months) TIA or minor ischemic stroke, mean age ~71, ~56% male; (2.3 years mean)	2.5-4.0	~2.9	Composite: vascular death, nonfatal stroke, nonfatal myocardial infarction, systemic embolism
Blinded				
CAFA	Canada, chronic or paroxysmal AF, mean age 67, 75% male (~1.3 years/subject)	2.0-3.0	~2.4	Ischemic stroke, systemic embolism, intracranial or fatal hemorrhage
SPINAF	U.S., chronic AF, mean age 67, 100% male	1.4-2.8	~2.0	Ischemic stroke

[Sources: Aguilar et al. 2005; EAFT. 1993]

†ASA permitted in control group

These six trials were included in two published meta-analyses by Hart et al. which addressed the efficacy of anticoagulant therapy for the prevention of stroke (ischemic and hemorrhagic). The table below shows the number of strokes per patients/patient-years in the warfarin and control treatment arms as well as the relative and absolute risk reduction in stroke for subjects without a baseline history of stroke or transient ischemic attack. According to the 2007 meta-analysis of these studies, warfarin reduced the risk of stroke (ischemic and hemorrhagic) by 64% (95% CI, 49% to 74%) and the risk of ischemic stroke by 67% (95% CI, 54% to 77%).

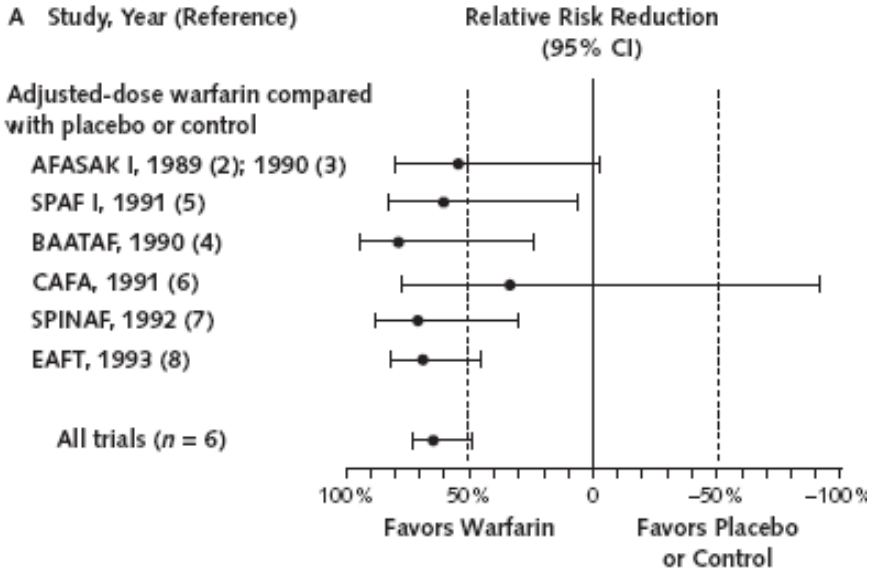
Table 2. **Adjusted-Dose Warfarin Compared with Placebo or No Treatment***

Study, Year (Reference)	Secondary Prevention, %†	Participants, *n*	Target INR	Strokes/Patients/Patient-Years; Warfarin vs. Placebo or Control, *n/n/n*	Relative Risk Reduction (95% CI), %‡	Absolute Risk Re %/y‡
AFASAK I, 1989 (2); 1990 (3)	6	671	2.8–4.2	9/335/413 vs. 19/336/398	54	2.6
SPAF I, 1991 (5)	8	421	2.0–4.5§	8/210/263 vs. 19/211/245	60‖	4.7
BAATAF, 1990 (4)¶	3	420	1.5–2.7§	3/212/487 vs. 13/208/435	78‖	2.4
CAFA, 1991 (6)	4	378	2.0–3.0	6/187/237 vs. 9/191/241	33	1.2
SPINAF, 1992 (7)	8	571	1.4–2.8§	7/281/489 vs. 23/290/483	70‖	3.3
EAFT, 1993 (8)**	100	439	2.5–4.0	20/225/507 vs. 50/214/405	68‖	8.4
6 trials††	20	2900	–	53/1450/2396 vs. 133/1450/2207	64 (49 to 74)	Primary preventic secondary prev

* Please see footnote in Table 1 for definitions of study acronyms. INR = international normalized ratio.
† Proportion of patients who had previous stroke or transient ischemic attack.
‡ Risk reduction for combined ischemic and hemorrhagic strokes by intention-to-treat analysis.
§ Prothrombin time ratios were used with INR equivalents estimated by the investigators.
¶ A total of 46% of exposure in the control group was during self-selected use of various dosages of aspirin.
‖ $P < 0.05$, 2-sided.
** Several oral vitamin K antagonists were used (warfarin was not exclusively used).
†† Meta-analysis estimates of relative risk reductions ($P > 0.2$ for homogeneity) and absolute risk reductions ($P > 0.2$ for homogeneity) for trials of primary preve with ≤20% of participants with previous stroke) vs. secondary prevention; see Methods.

[Source: Hart RG et al. 2007]

A forest plot of warfarin's effect on stroke (ischemic and hemorrhagic), taken from the 2007 meta-analysis, is shown below.



[Source: Hart RG et al. 2007]

A Cochrane review published in 2005 also addressed the efficacy of warfarin for the prevention of all-cause mortality and myocardial infarction using available data from the five primary prevention trials for subjects with no previous history of stroke or transient ischemic attack. The effect of warfarin on these outcomes, as reported in this review, is shown in the figures below. The meta-analysis suggests favorable effects on all-cause mortality in these historical trials. As noted in the Cochrane review, few MIs occurred in these trials, making it difficult to ascertain what, if any effect, warfarin therapy has on this outcome.

Analysis 1.10. Comparison 1 Anticoagulants versus control, Outcome 10 All cause mortality.

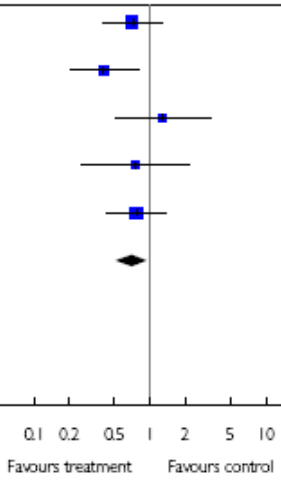
Review: Oral anticoagulants for preventing stroke in patients with non-valvular atrial fibrillation and no previous history of stroke or transient ischemic attacks

Comparison: 1 Anticoagulants versus control

Outcome: 10 All cause mortality

Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
AFASAK 1	20/335	28/336		28.7 %	0.70 [0.39, 1.26]
BAATAF	11/212	26/208		21.7 %	0.40 [0.21, 0.79]
CAFA	10/187	8/191		11.0 %	1.29 [0.50, 3.32]
SPAF 1	6/210	8/211		8.7 %	0.75 [0.26, 2.17]
SPINAF	22/281	29/290		29.9 %	0.77 [0.43, 1.36]
Total (95% CI)	**1225**	**1236**		**100.0 %**	**0.69 [0.50, 0.94]**

Total events: 69 (Treatment), 99 (Control)
Heterogeneity: $Chi^2 = 4.27$, df = 4 (P = 0.37); $I^2 = 6\%$
Test for overall effect: Z = 2.34 (P = 0.019)



Analysis 1.4. Comparison 1 Anticoagulants versus control, Outcome 4 Myocardial infarction.

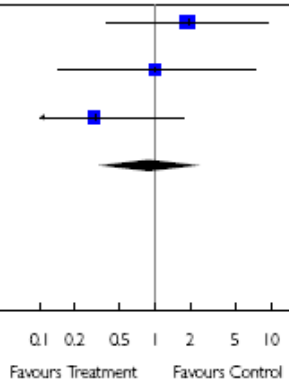
Review: Oral anticoagulants for preventing stroke in patients with non-valvular atrial fibrillation and no previous history of stroke or transient ischemic attacks

Comparison: 1 Anticoagulants versus control

Outcome: 4 Myocardial infarction

Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
BAATAF	4/205	2/201		39.9 %	1.93 [0.38, 9.64]
SPAF 1	2/193	2/194		26.7 %	1.01 [0.14, 7.19]
SPINAF	1/260	4/265		33.4 %	0.30 [0.05, 1.77]
Total (95% CI)	**658**	**660**		**100.0 %**	**0.87 [0.32, 2.42]**

Total events: 7 (Treatment), 8 (Control)
Heterogeneity: $Chi^2 = 2.33$, df = 2 (P = 0.31); $I^2 = 14\%$
Test for overall effect: Z = 0.26 (P = 0.80)



[Source for all figures: Aguilar et al. 2005.]

The quality of INR control: An INR range of 2-3 is thought to maximize protection against ischemic stroke in patients with atrial fibrillation without incurring a marked increase in the risk of intracranial bleeding. In observational studies, the percent of time spent out of this range by patients has been associated with the risk of death, ischemic stroke and other thromboembolic events (Jones et al. 2005). Among patients randomized to warfarin therapy in randomized-controlled trials, the risk of death, MI, major bleeding and stroke or SEE have also been shown to be related to INR control as assessed by the percentage of time in the therapeutic range (White et al. 2007).

It has also been shown that the time in therapeutic range measured at the center-level and country-level (determined by averaging the individual times in therapeutic range for all of the subjects randomized to oral anticoagulant therapy within a center or country to yield a value for that center or country), has an important impact on the treatment benefit of warfarin in intervention trials. The benefit of oral anticoagulants over antiplatelet agents has been shown to be dependent upon the quality of INR control achieved as measured by the time in therapeutic range at the center and country level. In ACTIVE W, for patients at centers below the median time in therapeutic range (65%), no treatment benefit was demonstrated as measured by the relative risk for vascular events of clopidogrel plus aspirin versus oral anticoagulation; however, for patients at centers with a time in therapeutic range above the study median, oral anticoagulation was associated with a statistically significant ~ 2-fold reduction in the relative risk of vascular events (Connolly et al. 2008).

Reviewer's comment: Though these studies all support the concept that a greater percentage of time in the therapeutic range is associated with a better outcome on warfarin, different approaches to censoring INR values from the calculation of a subject's time in therapeutic range have been used in studies, making it difficult to compare the quality of INR control across studies using the reported time in therapeutic range. Further, the reported time in therapeutic range reflects the percentage of measured and reported values falling within a given range; depending upon the adequacy of INR monitoring, it may or may not be indicative of the percentage of time trial participants were actually in the reported ranges. These factors limit the ability to use the time in therapeutic range as the sole metric for assessing the relative quality of INR control in RE-LY and emphasize the need for additional metrics to help ascertain the adequacy of anticoagulation in warfarin-treated subjects in clinical trials of new anticoagulants.

9.5 Rankin Scale

For the purposes of this review, the term "Rankin Scale" refers to the Modified Rankin Scale.

Table 80. Rankin Scale

Score	Symptoms	Description

0	No symptoms	
1	No significant disabling symptoms	No significant disability despite symptoms; able to carry out all usual duties and activities.
2	Slight disability	Unable to carry out all previous activities but able to look after their own affairs without assistance.
3	Moderate disability	Requiring some help but able to walk without assistance.
4	Moderate / Severe disability	Unable to walk without assistance and unable to attend to own bodily needs without assistance.
5	Severe disability	Bedridden, incontinent and requiring constant nursing care and attention.
6	Dead	

9.6 RE-LY protocol additional information

9.6.1. Full Inclusion/Exclusion Criteria

Inclusion criteria

1.) AF documented as follows (Amendment 1 changed this to 'documented by one of the'):
   a. There is ECG documented AF on the day of screening or randomization (Amendment 1 changed this to within 1 week of)
   b. The patient has had a symptomatic episode of paroxysmal or persistent AF documented by 12 lead ECG within six months prior to randomization
   c. There is documentation of symptomatic or asymptomatic paroxysmal or persistent AF on two separate occasions, at least one day apart, one of which is within six months prior to randomization. In this case, AF may be documented by 12 lead ECG, rhythm strip, pacemaker/ICD electrogram, or Holter ECG. The duration of AF should be at least 30 seconds. Electrograms (not marker channels or mode switch episodes) from pacemakers and defibrillators can be used to document only one episode of paroxysmal or persistent AF

2.) In addition to documented AF, patients must have one of the following additional risk factors for stroke:
   a. History of previous stroke, transient ischemic attack, or systemic embolism
   b. Left ventricular ejection fraction <40% documented by echocardiogram, radionuclide or contrast angiogram (Amendment 1 changed this to in the last 6 months)
   c. Symptomatic heart failure, documented to be NYHA Class 2 or greater (Amendment 1 changed this to in the last 6 months)
   d. Age ≥ 75 years
   e. Age ≥ 65 years and one of the following additional risk factors:
   i) diabetes mellitus on treatment (Amendment 1 specified treatment to include diet)

ii) documented coronary artery disease (any of: prior MI, positive stress exercise test, positive nuclear perfusion study, prior CABG surgery or PCI, angiogram showing ≥75% stenosis in a major coronary artery
iii) hypertension requiring medical treatment
3.) Age ≥18 years at entry
4.) Written, informed consent.

Exclusion criteria
• History of heart valve disorders (i.e., prosthetic valve or hemodynamically relevant valve disease) Amendment 1 specified
Patients with prosthetic heart valves requiring anticoagulation per se, or with haemodynamically relevant valve disease that is expected to require surgical intervention during the course of the study

• Severe, disabling stroke within the previous 6 months, or any stroke within the previous 14 days
• Conditions associated with an increased risk of bleeding:
a. Major surgery in the previous month
b. Planned surgery or intervention in the next 3 months
c. History of intracranial, intraocular, spinal, retroperitoneal or atraumatic intra-articular bleeding (Amendment 1 added, "unless the causative factor has been permanently eliminated or repaired (e.g. by surgery))
d. Gastrointestinal hemorrhage within the past year (Amendment 1 added, "unless the cause has been permanently eliminated (e.g. by surgery))
e. Symptomatic or endoscopically documented gastroduodenal ulcer disease in the previous 30 days
f. Hemorrhagic disorder or bleeding diathesis
g. Need for anticoagulant treatment for disorders other than atrial fibrillation
h. Fibrinolytic agents within 48 hours of study entry
i. Uncontrolled hypertension (SBP >180 mmHg and/or DBP >100 mmHg)
j. Recent malignancy or radiation therapy (=6 months) and not expected to survive 3 years
5.) Contraindication to warfarin treatment
6.) Reversible causes of atrial fibrillation (e.g., cardiac surgery, pulmonary embolism, untreated hyperthyroidism).
7.) Plan to perform a pulmonary vein ablation or surgery for cure of the AF
8.) Severe renal impairment (estimated creatinine clearance ≤30 mol/min)
9.) Active infective endocarditis
10.) Active liver disease, including but not limited to
a. Persistent ALT, AST, Alk. Phos. >2 x ULN
b. Known active hepatitis C* (as evidenced by positive HCV RNA by sensitive PCR-based assay, such as Roche Monitor or Bayer TMA assay)
c. Active hepatitis B* (HBs antigen +, anti HBc IgM+) (Amendment 1 clarified (HBs antigen +or anti HBc IgM+)
d. Active hepatitis A
11.) Women who are pregnant or of childbearing potential who refuse to use a medically acceptable form of contraception throughout the study (NOTE: A negative pregnancy test must be obtained for any woman of childbearing potential prior to entry into the study) (Amendment 2 added "lactating")

12.) Anemia (hemoglobin <10g/dL) or thrombocytopenia (platelet count <100 x 109/L)
13.) Patients who have developed transaminase elevations upon exposure to ximelagatran.
14.) Patients who have received an investigational drug in the past 30 days
15.) Patients considered unreliable by the Investigator concerning the requirements for follow-up during the study and/or compliance with study drug administration, has a life expectancy less than the expected duration of the trial due to concomitant disease, or has any condition which in the opinion of the Investigator, would not allow safe participation in the study (e.g., drug addiction, alcohol abuse).
*Patients with a known history of hepatitis B or C must undergo hepatitis serology for hepatitis B and C prior to inclusion in the study.

9.6.2. Liver abnormality follow-up

Alert Status 1: ALT or AST > 2x ULN and ≤ 3x ULN or Alk Phos > 2x ULN

- Weekly LFTs until ALT, AST and Alk Phos < 2x ULN

Alert Status 2: ALT or AST > 3x ULN and ≤ 5x ULN or Tbili > 2x ULN*

- Weekly LFTS until ALT, AST and Tbili < 2x ULN
- Evaluate for liver disease by reviewing alcohol intake, medications, concomitant disease, and further lab analyses. Additional evaluations including abdominal ultrasound with special attention to the liver, biliary tree, and pancreas should be considered.[3]

Note that a bulletin sent to investigators dated Oct 16, 2006 clarified that the "enhanced hepatic function kit"[1] be used for the first occurrence of an Alert 2. All subsequent LFT testing should be done using the LFT visit kit.[2] The abdominal ultrasound with special attention to liver, biliary tree and pancreas are clinically indicated and **must** be performed. Results of any tests or investigations must be sent to PHRI. (This bulletin note was also applicable for Alert Status 3).

Alert Status 3: ALT or AST > 5x ULN or ALT or AST > 3x ULN with a Tbili > 2x ULN*
Or development of hepatic disease related symptoms

- Discontinue medication. If first abnormal LFT, the test should be repeated for verification. Alert sponsor.
- Evaluate for liver disease (as specified for Alert Status 2)
- If jaundice or other symptoms (in the investigator's judgement) likely attributable to hepatic disease (e.g., fatigue, nausea, vomiting, loss of appetitie, new onset itching, upper abdominal pain, especially right upper quadrant abdominal pain), then withhold study medication and perform hepatic lab screening.

The sponsor and investigator had to agree that there was no evidence of liver disease to restart medication.

*If patient has Gilbert's Syndrome, the total bilirubin must be > 4 xULN to be classified as Alert Status 2/3.
1. Enhanced Hepatic Function Kit includes ALT, AST, AlkPhos, TBili, indirect bilirubin if TBili elevated, glucose, transferring saturation, amylase, lipase, cholesterol,

trigylcerides, TSH, Hepatitis B Surface Antigen (HBsAg) screen w/ confirmation, Hepatitis C Antibody (Anti-HCV), HBV PCR, HVC PCR, Anti-Liver-Kidney-Microsome (Anti-LKM-1), Anti-Mitochondrial Antibody (AMA), Anti-Nuclear Antibody (ANA), Anti-Smooth Muscle Antibody (ASMA), Ceruloplasmin, and alpha 1-anti-trypsin. Use instituted with Protocol Amendment 2 (dated May 24 2007).

The bulletin noted that if the LFTs normalize and then rise, then the enhanced hepatic function kit should be repeated because of the possibility of acute viral hepatitis.
2. Liver Function Test kit includes AST, ALT, AlkPhos and TBili (and indirect bilirubin if TBili elevated).

Subjects discontinuing medication should receive appropriate anticoagulation per the investigator.

For any subject being followed with weekly monitoring, if after 4 weeks of monitoring, these values are either stable or improving, but remain > 2 xULN, or if the cause of the LFT abnormality is deemed by the investigator and the sponsor not to be drug related, the monitoring may be decreased.

9.7 Additional information on FDA liver review

Drug induced liver injury is a diagnosis of exclusion; hence, to make a diagnosis, the results of tests excluding other etiologies of injury (pertinent positive as well as negative findings) are needed. The cases of interest reviewed by Drs. Senior and Seefe were scored for completeness of information (CMP) and informative use of the data (INF). These scores were based primarily on information provided to the Agency at the time of NDA filing, including brief sponsor narratives, case report forms and any available source documents. In some cases, additional information submitted in response to an Agency request was also considered.

The CMP score was based on the extent to which alternative causes for liver findings were investigated. The INF score was based on whether the information obtained from testing supported the likelihood decision. For example, whether or not the result of hepatitis A IgM testing was positive (and if so, just once or serially), when the test was done relative to the course of acute liver injury, and whether the result was confirmed by PCR and later, by the development of IgG.

The CMP and INF scores are shown below for the 55 liver cases reviewed. Very few cases had all key elements/enough for a definite conclusion of cause (CMP scale). Very few cases were scored as having a good basis for the causal decision/an incontrovertible causality assessment. This should be viewed as a limitation of the data.

Table 81. Completeness and Information scores for 55 liver cases

CMP	Definition	D110	D150	W
0	No information provided	0	2	0
1	A couple of items	4	1	5
2	Several items	6	6	11
3	Most of the key items	6	5	7
4	All key items	0	2	0
5	Enough for definite conclusion of cause	0	0	0

INF	Definition	D110	D150	W
0	Completely unsupported attribution	0	1	0
1	Very poor or weak attribution	4	1	3
2	Somewhat supported attribution	5	6	8
3	Very well supported conclusion	5	6	9
4	Very good basis for causal decision	2	2	3
5	Incontrovertible causality assessment	0	0	0

9.9 Timing of events following medication discontinuation

Table 82. Strokes or SEEs occurring off of therapy

	DE 110mg bid	DE 150mg bid	Warfarin N
After permanent stop of study medication	72	62	44
1<= and <2 days	6	2	0
2<= and <3 days	1	3	2
3<= and <4 days	2	0	0
4<= and <=6 days	5	3	2
6< and <=14 days	9	8	9
14< and <= 30 days	5	6	1
30< and <=60 days	7	8	2
60< and <=90 days	4	4	2
> 90 days	33	28	26
Randomized but not treated	0	0	0
After temporary stop of study medication	10	6	10
1<= and <2 days	0	2	2
2<= and <3 days	0	0	1
3<= and <4 days	0	0	0
4<= and <=6 days	1	1	1
6< and <=14 days	3	1	1
14< and <= 30 days	3	1	2
30< and <=60 days	2	0	0
60< and <=90 days	0	1	0
> 90 days	1	0	3
Before start of study medication	0	2	0

[Source: Sponsor, Table 15.3.5.4:1]

Table 83. Major bleeds occurring off of study medication

	DE 110mg bid	DE 150mg bid	Warfarin N
After permanent stop of study medication	102	107	84
1<= and <2 days	16	10	8
2<= and <3 days	5	6	5
3<= and <4 days	4	2	1
4<= and <=6 days	11	6	7
6< and <=14 days	9	5	15
14< and <= 30 days	8	6	9
30< and <=60 days	4	10	6
60< and <=90 days	6	5	4
> 90 days	39	57	29
Randomized but not treated	0	0	1
After temporary stop of study medication	50	53	66
1<= and <2 days	8	9	7
2<= and <3 days	8	5	5
3<= and <4 days	4	10	5
4<= and <=6 days	13	10	19
6< and <=14 days	9	10	19
14< and <= 30 days	3	3	3
30< and <=60 days	1	3	3
60< and <=90 days	2	1	0
> 90 days	2	2	5
Before start of study medication	0	2	0

[Source: sponsor, Table 15.3.5.4:2]

9.10 RE-LY Follow-up visit CRF

RE-LY 1 MONTH FOLLOW-UP VISIT FORM CRF 14

DataFax #177 Plate #014 Visit #004

PATIENT ID: Centre No. Patient No. PATIENT INITIALS: F M L

1. Date of Visit: year month day

2. Type of Visit
- ☐ Clinic Visit
- ☐ Home Visit
- ☐ Telephone Visit
- ☐ Other _____

PART A. STUDY OUTCOME EVENTS

Since the last follow-up visit, up to and including this visit, has the patient experienced any of the following study outcomes:

	No	Yes		Report Number(s) Submitted
1. Stroke	☐	☐	→ Stroke Report CRF 110	# ☐☐ TO ☐☐
2. Myocardial Infarction	☐	☐	→ MI Report CRF 114	# ☐☐ TO ☐☐
3. Non-CNS systemic embolism	☐	☐	→ Non-CNS Systemic Embolus Report CRF 116	# ☐☐ TO ☐☐
4. Transient ischemic attack	☐	☐	→ TIA Report CRF 118	# ☐☐ TO ☐☐
5. Major bleeding	☐	☐	→ Major Bleeding Report CRF 122	# ☐☐ TO ☐☐
6. Minor Bleeding	☐	☐	→ Minor Bleeding Report CRF 124	# ☐☐ TO ☐☐
7. Pulmonary Embolism	☐	☐	→ Pumonary Embolism Report CRF 128	# ☐☐ TO ☐☐
8. Death	☐	☐	→ Death Report CRF 126 and 127	

PART B. OTHER INFORMATION

Since the last follow-up visit, up to and including this visit, has any of the following occurred:

1. Cardioversion	☐	☐	→ Cardioversion Report CRF 132	# ☐☐ TO ☐☐
2. Emergency/Elective Surgery	☐	☐	→ Interruption of Anticoagulant Report CRF 140	# ☐☐ TO ☐☐
3. Admission to hospital	☐	☐	→ Hospitalization Report CRF 120	# ☐☐ TO ☐☐
4. Serious Adverse Event	☐	☐	→ Serious Adverse Event (SAE) Report, Page 1 and 3 (Page 2 is optional)	# ☐☐☐ TO ☐☐☐
5. Experienced any other untoward medical occurrence	☐	☐	→ Adverse Event CRF 155	# ☐☐☐ TO ☐☐☐
6. Change in concomitant medications	☐	☐	→ Concomitant Medications Report CRF 09	# ☐☐ TO ☐☐
7. INR Evaluations done	☐	☐	→ INR Log CRF 60	# ☐☐ TO ☐☐

Please fax this form to the PHRI Project Office within 48 hours of the patient follow-up visit

PART C. CLINICAL ASSESSMENT AT THIS VISIT:

1. Sitting Heart Rate: ☐☐☐ beats/min
(Patient sits for 3 min. before measuring)

2. Sitting Arm BP: ☐☐☐ / ☐☐☐ mmHg (Systolic / Diastolic)
(Patient sits for 3 min. before measuring)

PART D. STUDY MEDICATION

1. Was study medication discontinued (temporary or permanent) or re-started ☐ No ☐ Yes → Complete Study Medication Discontinuation/Restart CRF 151 # ☐☐ TO ☐☐

2. Was study medication dispensed since last visit? ☐ No ☐ Yes → Complete Study Medication Dispensation CRF 04 Report # ☐☐

3. Was study medication returned at this visit? ☐ ☐

4. Study medication compliance: (dabigatran patients only) ☐☐☐ %

PART E. LABORATORY EVALUATIONS

1. Was blood collected since the last follow-up visit, up to and including this visit?

☐ No → Explain: _____

☐ Yes → Specify where sample sent:

a. Central Lab: ☐ No ☐ Yes → Blood Collection and Shipment Report CRF 66 Report# ☐☐

→ PK/PD/aPTT Blood Collection and Shipment Report CRF 68 ☐☐ OR ☐ Indicate if Not Done

b. For Hepatic Function lab tests:
Complete the Hepatic Function Laboratory Report CRF 62 → Report # ☐☐

PA

1. Has the patient reported a stroke since the last visit: ☐ Yes → *Ensure you have completed CRF 110 and recorded the report # on CRF 14*

☐ No → *Complete questions below*

NOTE: Please ask these questions exactly as they are written and record patient's response.

a. Since the last visit, have you been told by a physician that you had a stroke?

☐ No ☐ Yes

b. Since the last visit, have you had a sudden numbness or painless weakness on one side of your body that lasted for more than one day?

☐ No ☐ Yes

c. Since the last visit, have you had a sudden painless loss of vision on one side or in one or both eyes that lasted for more than one day?

☐ No ☐ Yes

d. Since the last visit, have you suddenly lost the ability to understand what people are saying or lost the ability to express yourself verbally or in writing for more than one day?

☐ No ☐ Yes

PART G. BLEEDING EVALUATION

1. Has the patient reported a bleed since the last visit: ☐ Yes → *Ensure you have completed CRF 122 or CRF 124 and recorded the report # on CRF 14*

☐ No → *Complete questions below*

NOTE: Please ask these questions exactly as they are written and record patient's response.

a. Since the last visit, have you had any unusual bleeding?

☐ No ☐ Yes → Specify: _____

b. Since the last visit, have you had any unusual black tarry bowel movements?

☐ No ☐ Yes → Specify: _____

c. Since the last visit, have you been told about any reduced blood count/haemoglobin?

☐ No ☐ Yes → Specify: _____

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22512	ORIG-1	BOEHRINGER INGELHEIM PHARMACEUTICALS INC	PRADAXA (DABIGATRAN ETEXILATE MESYLATE)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

BACH N BEASLEY
08/25/2010

ALIZA M THOMPSON
08/25/2010

CLINICAL PHARMACOLOGY REVIEW

NDA:	**22-512 N000**
Submission Dates:	**12/15/2009, 4/19/2010**
Brand Name:	**Pradaxa**
Generic Name:	**Dabigatran etexilate mesylate**
Dosage Form & Strength:	Capsules 110 & 150 mg
Indication:	**1.** Prevention of stroke and systemic embolism in patients with atrial fibrillation **2.** The reduction of vascular mortality in patients with atrial fibrillation
Applicant:	Boehringer Ingelheim GmbH
Submission:	Original NDA
Divisions:	DPEI and Cardio-Renal Drug Products, HFD-110
Primary Reviewers:	Elena V. Mishina, Ph.D., Peter Hinderling, M.D., Sudharshan Hariharan, Ph.D.
Pharmacometrics Reviewer:	Kevin Krudys, Ph.D.
Pharmacometrics Team Leader:	Pravin Jadhav, Ph.D.
Genomics Reviewer:	Michael Pacanowski, Pharm D., M.P.H.
Genomics Team Leader:	Issam Zineh, Pharm D., M.P.H.
Team Leader:	Rajanikanth Madabushi, Ph.D.

TABLE OF CONTENTS

1 EXECUTIVE SUMMARY 5

1.1 RECOMMENDATIONS: 5
1.2 POST MARKETING REQUIREMENTS 6
1.3 PHASE IV COMMITMENTS: 6

2 SUMMARY OF OCPB FINDINGS 8

2.1.1 Background 8
2.1.2 Current Submission 8
2.1.3 Pharmacokinetics 8
2.1.4 Exposure-Response Relationships 9
2.1.5 Intrinsic Factors 9
2.1.6 Drug-drug interaction information 10
2.1.7 Biopharmaceutics 12

3 QUESTION BASED REVIEW 14

3.1 GENERAL ATTRIBUTES 14
3.1.1 History of Regulatory Development 14
3.1.2 Highlights of chemistry and physical-chemical properties of the drug substance and product 14
3.1.3 What are the proposed mechanisms of action and therapeutic indication? 15
3.1.4 What are the proposed dosages and route of administration? 16
3.2 GENERAL CLINICAL PHARMACOLOGY 16
3.2.1 What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims? 16
3.2.2 Were the correct moieties identified and properly measured to assess clinical pharmacology? 16
3.2.3 What are the characteristics of the exposure-response relationships for efficacy? 17
3.2.4 What are the characteristics of the exposure-response relationships for safety? 17
3.2.5 What is the impact of dabigatran and warfarin on liver function? 18
3.2.6 Does dabigatran prolong the QT or QTc interval? 19
3.2.7 What are the single dose and multiple dose PK parameters? 19
3.2.8 How does the PK of the drug and its major active metabolites in healthy volunteers compare to that in patients? 20
3.2.9 What are the characteristics of drug absorption (possible transporters and pH impact)? .. 20
3.2.10 What are the characteristics of drug distribution (including plasma protein binding?) . 21
3.2.11 Does the mass balance study suggest renal or hepatic as the major route of elimination? 21
3.2.12 What are the characteristics of drug metabolism? 21
3.2.13 Based on PK parameters, what is the degree of linearity or nonlinearity in the dose-concentration relationship? 22
3.2.14 What is the inter- and intra-subject variability of the PK parameters, and what are the major causes of variability? 23
3.3 INTRINSIC FACTORS 23
3.3.1 What intrinsic factors (age, gender, race, weight, height, disease, genetic polymorphism, pregnancy, and organ dysfunction) influence exposure (PK usually) and/or response, and what is the impact of any differences in exposure on efficacy or safety responses? 23
3.3.2 Based on what is known about exposure-response relationships, what dosage regimen adjustment, if any, are recommended based upon exposure-response relationship? 30
3.4 EXTRINSIC FACTORS 30
3.4.1 What is the impact of skipping the dose(s) of dabigatran? 30
3.4.2 What is the Interaction Liability of Dabigatran? 31
3.4.3 Is there an in vitro basis to suspect in vivo drug-drug interactions? 31

3.4.4 Is the drug a substrate of CYP enzymes? ... *31*
3.4.5 Is the drug an inhibitor and/or an inducer of enzymes? ... *31*
3.4.6 Is the drug a substrate, an inhibitor and/or an inducer of transporters? ... *31*
3.4.7 Are there other metabolic/transporter pathways that may be important? ... *32*
3.4.8 What extrinsic factors influence exposure and/or response, and what is the impact of any differences in exposure on effectiveness or safety responses? ... *32*
3.4.9 What are the drug-drug interactions? ... *32*
3.5 GENERAL BIOPHARMACEUTICS ... 37
3.5.1 What is the quantitative and qualitative composition of formulation? ... *37*
3.5.2 What is the effect of food on the bioavailability (BA) of the drug from the dosage form? What dosing recommendation should be made, if any, regarding administration of the product in relation to meals or meal types? ... *39*
3.5.3 Can capsule shell be opened and pellets ingested as such? ... *39*
3.5.4 How the elevated gastric pH affect the dabigatran bioavailability ... *40*
3.6 ANALYTICAL SECTION ... 40
3.6.1 How the active moieties are identified and measured in the plasma in the clinical pharmacology and biopharmaceutics studies? ... *40*
3.6.2 What is the range of the standard curve? How does it relate to the requirements for clinical studies? What curve fitting techniques are used? ... *40*
3.6.3 What analytical methodologies were used to assess pharmacodynamic action? ... *40*
3.6.4 Were the validation characteristics of the assays acceptable? ... *41*
3.7 WHAT IS THE OVERALL CONCLUSION REGARDING NDA 22-512? ... 41

4 LABELING RECOMMENDATIONS *(DRAFT)* ... **42**

LIST OF FIGURES

Figure 1. X-ray crystal structure of BIBR953 in complex with thrombin in a surface representation. The lipophilic potential is mapped on the protein surface. ... 15
Figure 2. Probability of ischemic stroke within 1 year vs. dabigatran pre-dose concentration. The blue shaded region represents the standard error. The bars on the bottom on the plot region represent the 10th to 90th percentiles of observed dabigatran pre-dose concentrations in the RE-LY trial. ... 17
Figure 3. Probability of a major bleed within 1 year vs. dabigatran pre-dose concentration.The blue shaded region represents the standard error. The bars on the bottom on the plot region represent the 10th to 90th percentiles of observed dabigatran pre-dose concentrations in the RE-LY trial. ... 18
Figure 4. Time course of ALT > 3x ULN for warfarin, ximelagtran and dabigatran in the Sportif and RELY trials. ... 19
Figure. 5. Geometric mean total dabigatran plasma concentration vs. time (hrs) ... 20
Figure 6. Dose proportionality of total dabigatran Cmax and AUCinf after the single doses of BIBR1048MS ... 22
Figure 7. Comparison of the geometric mean ratios for AUC and Cmax (mean and 90%CI) in subjects with renal impairment vs. healthy subjects ... 24
Figure 8. Correlation between individual values of total dabigatran renal clearance (0-24) and creatinine clearance ... 25
Figure 9. Dose-normalized pre-dose dabigatran concentration vs. creatinine clearance in RE-LY ... 25

Figure 10. Baseline corrected mean maximum prolongation of blood coagulation parameters (aPTT, ECT, INR, and TT) 26
Figure 11: Probability of ischemic stroke with 1 year vs. dabigatran pre-dose concentration in a patient with no history of stroke/TIA by creatinine clearance category. 26
Figure 12: Simulated mean steady state total dabigatran plasma concentration for subjects with normal renal function and moderate renal impaired administered 150 mg BID and severe renal impaired patients administered 75 mg QD and 75 mg every other day. 28
Figure 13. Total dabigatran exposure by *ABCB1* 3435C>T genotype in healthy subject drug interaction studies (monotherapy phases) AUC0-∞ is presented for single dose studies (1160.74, 1160.82, 1160.100); AUC0-τ and Cmax,ss are presented for multiple dose studies (1160.75, 1160.90). Horizontal blue lines reflect study mean. 29
Figure 14: Simulated mean steady state total dabigatran plasma concentration following last dose for subjects with normal renal function and moderate renal impaired administered 150 mg BID and severe renal impaired patients administered 75 mg QD. 30
Figure 15: X-axis represents the geometric mean ratios. The fine and bold broken vertical lines represent the unscaled and scaled average bioequivalence limits. Data is represented as geometric mean ratio of the PK metrics (C_{max}, $AUC_{0-\infty}$) with 90% CI around the point estimate. 38
Figure 16 : Effect of a high fat meal on total dabigatran exposure. X-axis represents the geometric mean ratios. The fine broken vertical lines represent 80-125% limits. Data is represented as geometric mean ratio of the PK metrics (C_{max}, $AUC_{0-\infty}$) with 90% CI around the point estimate. 39
Figure 17: Relative bioavailability of total dabigatran when administered as pellets when compared to pellets in capsules. X-axis represents the geometric mean ratios. The fine broken vertical lines represent 80-125% limits. Data is represented as geometric mean ratio of the PK metrics (C_{max}, $AUC_{0-\infty}$) with 90% CI around the point estimate. 39

LIST OF TABLES

Table 1 Frequency and yearly event rate of stroke/SEE by renal function. *Source: Table 11.4.1.4.1: 1 of sponsor report 1160-0026—01-15—study-report-body.pdf*..... 27
Table 2 Frequency and yearly event rate of major bleeds by renal function (randomized set). *Source: Table 12.2.2.5: 1 of sponsor report 1160-0026—01-15—study-report-body.pdf*..... 27
Table 3 Impact of Other Drugs on Exposure to Dabigatran 33
Table 4. Impact of Dabigatran on Exposure to Other Drugs 35
Table 5 Composition of final marketing image of dabigatran etexilate capsules. *Note*: 75 mg dose is not filed for approval. 37

1 EXECUTIVE SUMMARY

Boehringer Ingelheim GmbH. submitted NDA 22-512 for dabigatran etexilate capsules for the prevention of stroke and systemic embolism in patients with atrial fibrillation (SPAF). Dabigatran is a synthetic, non-peptide, competitive, oral direct thrombin inhibitor (oral DTI), that specifically and reversibly inhibits thrombin, the final enzyme in the coagulation cascade. Dabigatran etexilate is the oral pro-drug of the active moiety dabigatran and does not possess any anticoagulant activity. The pro-drug dabigatran etexilate is used in its salt form dabigatran etexilate mesylate.
A single pivotal efficacy and safety trial (RE-LY) is the basis for seeking the approval. RE-LY was a randomized, open-label trial of stroke prevention in subjects with nonvalvular atrial fibrillation and at least one risk factor for stroke. A total of 18,113 subjects were randomized to one of the two blinded doses of dabigatran (110 mg or 150 mg twice daily) or to adjusted warfarin dose titrated to a target INR of 2 to 3. The population included balanced proportions of Vitamin K antagonist (VKA) naïve and VKA-experienced subjects. The primary objective was to demonstrate that the efficacy and safety dabigatran etexilate was non-inferior to adjusted dose warfarin in the studied population. A non-inferiority margin of 1.46 for hazard ratio was used to design the study.
The following dosage strengths are proposed for commercial distribution: 110 mg and 150 mg. The clinical pharmacology study program of dabigatran etexilate (BIBR 1048) comprised 41 Phase I studies, 6 Phase II, and a Phase III study where the population data analyses were performed.

1.1 RECOMMENDATIONS:

The Office of Clinical Pharmacology has reviewed the clinical pharmacology and biopharmaceutics (CPB) information submitted to NDA 22-512. The CPB information provided in NDA 22-512 is acceptable following agreement with sponsor regarding specific labeling language and post-marketing requirements. The Office has the following specific recommendations:

- Dabigatran 150 mg BID shows favorable risk-benefit profile and should be approved.
- Patients with severe renal impairment should receive 75 mg QD.
- The 110 mg dose can be given to mitigate the risk of bleeding in patients at high risk of bleeding, specifically patients older than 75 years of age with concomitant aspirin use or patients who are unable to tolerate 150 mg dabigatran.
- The RE-LY trial provides evidence to believe that dabigatran dose higher than 150 mg twice daily may provide more benefit in terms of reduction of stroke with acceptable increase in bleeding risk. There was a significant dose-dependent decrease in occurrence of ischemic stroke from the 110 mg to the 150 mg dose (1.3%/year to 0.9%). The exposure-ischemic stroke relationship indicates potential for further improvement in efficacy. Higher doses will also result in increased risk for major and life-threatening bleeding as evident from the exposure-response (bleeding)

relationship. On that end, a 2 fold increase in dabigatran exposures in moderate renal impaired patients (compared to patients with normal renal function) did not result in higher bleeding rate but an increase in stroke reduction compared to warfarin, indicating that higher doses might have a favorable benefit/risk ratio. It is possible that this finding is specific to the moderate renal impairment population. However, there is no clear reason to believe moderate renal impaired patients represent a different population apart from a natural extension of being at higher risk for stroke and bleeding compared to patients with normal and mild-impaired renal function. Hence post-approval, there is a value for evaluating the risk/benefit of a dose higher than 150 mg (for example, 300 mg BID) for prevention of stroke in patients with non-valvular atrial fibrillation.

1.2 POST MARKETING REQUIREMENTS

The sponsor should manufacture a lower strength of 75 mg and demonstrate bioequivalence following the administration of 2x75 mg versus 150 mg for BIBR 1048 MS. This strength will allow for the dose adjustment in severe renal impaired patients.

1.3 PHASE IV COMMITMENTS:

Since amiodarone and dronederone will be among the most commonly used anti-arrhythmic drugs, in *vitro* studies should be conducted to identify the mechanism responsible for the augmentation of the renal clearance of dabigatran in the presence of these drugs.

_____ Date_____
Elena Mishina, Ph. D.
Clinical Pharmacology Reviewer

_____ Date_____
Peter Hinderling, MD
Clinical Pharmacology Reviewer

_____ Date_____
Sudarshan Hariharan, Ph. D.
Clinical Pharmacology Reviewer

_____ Date_____
Mike Pacanowski, Pharm.D., M.P.H.
Genomics Reviewer

_____ Date_____
Kevin Krudys, Ph. D.
Pharmacometric Reviewer

_____ Date_____
Issam Zineh, Pharm.D., M.P.H.
Genomics Team Leader

_____ Date_____
Jadhav Pravin, Ph. D.
Pharmacometric Team Leader

_____
Raj Madabushi, Ph. D.
Cardio-Renal Team Leader

CP Briefing was held on August 4, 2010.
Attendees: Drs.Lesko, Lawrence J; Huang, Shiew Mei; Zineh, Issam; Lazor, John A; Zhao, Ping; Zhang, Lei K; Karkowsky, Abraham M; Beasley, Bach Nhi t; Blaus, Alison; Childers, Alexis; Liu, Jiang; Dimova, Hristina; Zhou, Lin; Shukla, Chinmay; Tompkins, Leslie *; Zheng, Hui; Choi, Young M; Yu, Bei; Booth, Brian P; Vaidyanathan, Jayabharathi; Habtemariam, Bahru; Reynolds, Kellie S; Hejazi, Nadia *; Mulugeta, Yeruk; Li, Zhihong; Brar, Satjit S.; Florian, Jeffry; Menon-Andersen, Divya; Fang, Lanyan (Lucy); Zhang, Hua Lillian; Zhao, Liang; Gobburu, Jogarao V; Green, Dionna; Sahajwalla, Chandrahas G; Grillo, Joseph; Schrieber, Sarah J; Wu, Ta-Chen; Mummaneni, Padmaja; Zdrojewski, Immo; Dunnmon, Preston; Song, Pengfei; Agarwal, Sheetal; Grant, Stephen; Stockbridge, Norman L; Rose, Martin; Uppoor, Ramana S; Thompson, Aliza; Rahman, Nam Atiqur; Abernethy, Darrell; Bai, Jane; Hinderling, Peter; Hariharan, Sudharshan; Krudys, Kevin; Pacanowski, Michael A; Jadhav, Pravin; Mishina, Elena V; Madabushi, Rajnikanth.

cc list: NDA 22-034, MehulM, UppoorR, MishinaE, MadabushiR, HinderlingP; HariharanS; KrudysK; PacanowskiM; JadhavP; HFD 110 BIOPHARM

2 Summary of OCPB Findings

2.1.1 Background

Boehringer Ingelheim Pharmaceuticals, Inc. is seeking the approval of dabigatran for the prevention of stroke and systemic embolism in patients with atrial fibrillation.

2.1.2 Current Submission

The investigation of dabigatran was performed under IND 65813. The clinical pharmacology program for NDA 22-512 includes 48 clinical studies.
An assessment of dabigatran PK and PD in healthy subjects: a single and a multiple dose PK, a dose ascending, a mass-balance and a food-effect, and 14 drug-drug interaction PK and PD studies were also performed. The influence of Asian/Japanese race, age, hepatic and renal impairment on dabigatran PK and PD were evaluated. The PK and PD in subjects with atherosclerotic vascular disease were evaluated in 4 studies. The efficacy of dabigatran as an anti-thrombotic therapy in the treatment of patients with atrial fibrillation was evaluated in the Phase III study RE-LY.
A population PK/PD data analysis and a thorough QT study were also performed.
In total, 38 studies submitted under the NDA 22-512 were reviewed.

2.1.3 Pharmacokinetics

- Dabigatran etexilate mesylate (BIBR1048MS) is a double pro-drug with low solubility at pH ≥ 3. Dabigatran etexilate base is quickly absorbed (t_{max} 1 hour in fasted state) and converted by esterase-catalyzed hydrolysis to the active moiety dabigatran (BIBR953ZW)
- Dabigatran's pharmacokinetics is dose proportional after single oral doses from 10 to 400 mg
- Dabigatran's absolute BA is 3-7%
- Dabigatran's half life is 12-17 hours. Stopping the treatment in a subject with normal renal function receiving 150 m BID at steady-state will result in mean exposures lower than the average trough concentrations associated with 110 mg BID dose by 15 hrs post-dose and complete washout by ~48 hrs
- Dabigatran is 35% bound to plasma proteins
- Dabigatran's accumulation is 1.6-2.3 both for AUC and Cmax
- Dabigatran is not a substrate, inhibitor or inducer of CYP450 enzymes
- Dabigatran etexilate is a substrate of the efflux transporter P-gp
- Dabigatran's volume of distribution is 50-70L
- Renal clearance of dabigatran is 80% of total clearance after intravenous admnistration, recovery of radioactivity in urine and feces after oral administration is 7% and 86%, respectively
- The red blood cell to plasma partitioning of dabigatran is less than 0.3.

2.1.4 Exposure-Response Relationships

Effectiveness

- There is a significant relationship between dabigatran exposures and reduction of ischemic stroke. The probability of an ischemic stroke decreases with increasing dabigatran concentration. Going from the 10th to 90th percentile of observed pre-dose dabigatran concentrations (22.9 ng/mL to 238.3 ng/mL) in RE-LY, the probability of an ischemic stroke within one year in a typical patient is predicted to decrease from 1.05% to 0.52%.

Safety

- There is a significant relationship between dabigatran exposures and incidence of bleeding events (major bleeding or life-threatening bleeding). The probability of a life-threatening bleed, defined as fatal bleeding, symptomatic intracranial bleeding, bleeding associated with a reduction in hemoglobin levels of at least 50 g/L or leading to a transfusion of at least 4 units of blood or packed cells or bleeding necessitating surgical intervention, increases with increasing dabigatran concentration. Going from the 10th to 90th percentile of observed pre-dose dabigatran concentrations (22.9 ng/mL to 238.3 ng/mL) in RE-LY, the probability of a life-threatening bleed within 1 year in a typical patient is predicted to increase from 0.27% to 1.82%.
- No dose-dependent increase in AST, ALT or bilirubin was observed.
- Dabigatran does not prolong the QT interval.

2.1.5 Intrinsic Factors

Body Weight

- In the population pharmacokinetic analysis, an increase of 1 kg above the median weight of 80 kg increases the volume of distribution by 1.1%. In the RE-LY trial, patients weighing < 50 kg and 50 to < 100 kg had 1.5-fold and 1.3-fold higher dabigatran pre-dose concentrations, respectively, compared to patients weighing ≥ 100 kg. No dose adjustment is required based on body weight.

Gender

- In the population pharmacokinetic analysis, females had a 14% higher steady state exposure ($AUC_{tau,ss}$) than males. No dose adjustment is required based on the gender.

Age

- In the population pharmacokinetic analysis, an increase in 1 year above the median age of 68 years decreases clearance by 0.66%.
- In the RE-LY trial, pre-dose dabigatran concentrations were 1.3-fold and 1.7-fold higher in patients aged 65 to 75 years and ≥ 75 years of age, respectively, compared to patients < 65 years of age.

Renal Impairment

- Exposure to dabigatran increases with the severity of renal function impairment as demonstrated in the dedicated renal impairment study. In subjects with mild,

moderate and severe impairment AUC of total dabigatran increased 1.5, 3.2, and 6.3-fold compared to subjects with normal renal function. A similar finding was observed in the phase III trial where patients with mild, moderate and severe renal impairment had 1.5-fold (N = 3745), 2.3-fold (N = 1443) and 3.3-fold (N = 19) higher pre-dose dabigatran concentration compared to patients with normal creatinine clearance (< 80 mL/min; N = 2573). The probability of ischemic stroke decreased with the increase in exposures across all the renal function groups. Further, in the moderate renal impaired group, the bleeding risk is not different when both dabigatran dose arms are compared to warfarin. Hence, no dose adjustment is needed in patients with moderate renal impairment.

- At mid-cycle meeting, the review team expressed the need to propose a dosing regimen in severe renal impaired subjects for the current indicated population. Based on the simulation of the pharmacokinetics in severe renal impaired subjects, a dose of 75 mg dabigatran QD will provide exposures reasonably similar to patients with mild renal impaired function. With this dosing regimen a 75% increased Cmax and AUC can be expected compared to patients with normal renal function. This increase in exposures is lower than the experience with moderate renal impaired subjects in the phase III trial. It should be noted that there is no efficacy or safety information available at the proposed dosing regimen of 75 mg dabigatran QD in severe renal impairment.
- Hemodialysis effectively removes dabigatran from blood. Based on the differences between the inlet and outlet concentrations ~60% of the drug was removed.

Hepatic Impairment

- In patients with moderate hepatic impairment, a ~30% decrease in Cmax and no change in AUC was noted. Hence, no dose adjustment is needed in patients with moderate hepatic impairment.

Pediatrics

- The pharmacokinetics of dabigatran in children has not been studied in this NDA. The sponsor has requested a full waiver which is reasonable for this indication. The PeRC meeting is scheduled for September 1st 2010.

2.1.6 Drug-drug interaction information

DDI information was obtained in dedicated studies in healthy volunteers as well as in the phase III trial. The sponsor ensured co-administration of the drugs on the PK sample collection days in the phase III trial. This enabled the joint assessment of the dedicated studies and the results of the phase III along with exposure-response relationship to assess labeling implications.

Further, as described above, patients with moderate renal impairment in the phase III trial had a 2.3 fold increase in exposure compared to patients with normal renal function without excessive bleeding risk compared to warfarin. Hence, for the current submission, any interaction that will result in an increase in the exposure to dabigatran greater than 2.5 fold (or greater than 150%) will require a dose/regimen adjustment.

Impact of Other Drugs on Dabigatran

Gastric pH Raising Drugs

- The exposure to dabigatran in the presence of pantoprazole in healthy subjects is significantly reduced (AUC to 71%, Cmax to 60%). In the phase III study, dabigatran exposure was reduced to 85% in patients on proton-pump inhibitors including pantoprazole. Administration of ranitidine 2 hrs post-dabigatran does not impact the bioavailability of dabigatran. Hence, no dose adjustment is required for dabigatran when gastric pH raising drugs are co-administered.

P-gp Inhibitors

- Under similar conditions in healthy volunteers, largest increase in exposure to dabigatran is observed when dabigatran is co-administered with verapamil and ketoconazole, followed by quinidine and amiodarone. The regression parameters of the dabigatran concentration-effect relationship in the presence and absence of the co-administered drugs are similar indicating absence of pharmacodynamic interaction.

- The greatest increase in exposure to dabigatran (AUC increase to 243%) is observed when a single dose of verapamil as IR tablet is given 1 h prior to BIBR 1048 MS. The increase in exposure to dabigatran is smaller after concomitant administration of a single dose of a 240 mg ER tablet of verapamil and BIBR 1048 MS (AUC increases to 171%).

- The impact of verapamil (IR tablet 120 mg bid) administered 1h before BIBR 1048 MS is smaller than that after a single dose given 1 h prior to BIBR 1048 MS (AUC of dabigatran increases to 154%). This is due to the known weakening of the P-gp inhibition associated with repeat administration of verapamil. This is consistent with the findings of the phase III trial where the mean exposure increase of dabigatran is to 123%.

- Importantly, reversing the order of dosing, i.e. administering BIBR 1048 MS 2 h prior to verapamil (IR tablet, bid regimen), does not increase the exposure to dabigatran significantly (AUC increases to 118%), indicating that the impact of verapamil is restricted to the inhibition of intestinal P-gp and the extrusion of BIBR 1048.

- A 2.4 and 2.5 fold increase in exposure of dabigatran is observed following concomitant administration of ketoconazole 400 mg single dose and 400 mg QD for 8 days, respectively. The ketoconazole data show no mitigation of the P-gp effect on repeat administration.

- Amiodarone not only inhibits the extrusion of BIBR 1048, but also increases the renal clearance of dabigatran to 169%. The increase in exposure to dabigatran (AUC increases to 158%) suggests that the inhibition of the intestinal extrusion of

BIBR 1048 must be substantial to more than compensate for the increase in renal clearance. The exposure of dabigatran increases to 112% in patients on amiodarone in the phase III trial.

- No dose adjustment is required when the P-gp-inhibitors verapamil, ketoconazole, quinidine or amiodarone are co-administered with dabigatran in the target population.

- Atorvastatin and clarithromycin do not impact the exposure to dabigatran indicating that not all P-gp inhibitors interfere with the extrusion. The absence of a change in clotting time of dabigatran in the presence of atorvastatin confirms the PK findings.

P-gp Inducer

- After a 6.5 day pretreatment with the P-gp inducer rifampin the relative exposure to dabigatran is clinically significantly decreased (AUC and Cmax decreased to 33% and 35%, respectively. A 3-fold increase in dose of dabigatran will mitigate the reduced exposure in the presence of rifampin.

Other Drugs

- A marginal increase in exposure to dabigatran is seen when loading doses of 300 or 600 mg clopidogrel are co-administered. The maintenance dose of 75 mg clopidogrel QD has no impact on the exposure to dabigatran. No pharmacodynamic interaction is noted.

- Diclofenac and digoxin do not impact the exposure to dabigatran nor do they affect the clotting time of dabigatran. The exposure to dabigatran is unchanged after a 3 day pretreatment with enoxaparin.

Impact of Dabigatran on Other Drugs

- Dabigatran does not impact the exposure of co-administered verapamil, amiodarone, quinidine, ketoconazole, clarithromycin and digoxin.

2.1.7 Biopharmaceutics

- Bioequivalence was established between the 1st generation product used in the RE-LY trial and the 2nd generation product which is the final market image (FMI) formulation.
- Bioequivalence was also established between polymorphs I and II. Therefore, the composition of these polymorphs in the final marketing image formulation will not have an impact on safety and efficacy.

- A 40% increase in dabigatran exposures occurs if pellets are removed from the capsule and ingested alone (with a teaspoon of baby cereal). Therefore, the capsule in general should not be opened and pellets administered as such.
- A high fat meal does not have a clinically significant effect on the exposure of total and free dabigatran (no change in C_{max}, 18% increase in $AUC_{0-\infty}$). However, the time to peak to maximum concentration (T_{max}) is delayed by 2 h in the fed state.

3 QUESTION BASED REVIEW

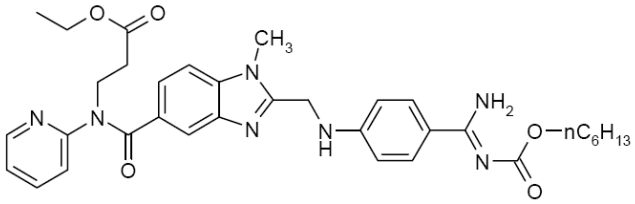
3.1 General Attributes

3.1.1 History of Regulatory Development

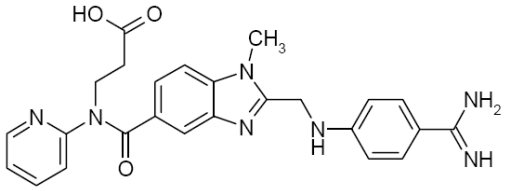
Dabigatran is a synthetic, non-peptide, competitive, oral direct thrombin inhibitor (oral DTI), that specifically and reversibly inhibits thrombin, the final enzyme in the coagulation cascade. Dabigatran etexilate is the oral pro-drug of the active moiety dabigatran and does not possess any anticoagulant activity. The pro-drug dabigatran etexilate is used in its salt form dabigatran etexilate mesylate. Dabigatran etexilate (75 mg QD) has been already approved in Europe and several other countries for the primary prevention of venous thromboembolism (VTE) post total elective knee or hip replacement surgery.
In the present submission, the sponsor is seeking the approval of PRADAXA (dabigatran etexilate mesylate) for the prevention of stroke and systemic embolism in patients with atrial fibrillation.

3.1.2 Highlights of chemistry and physical-chemical properties of the drug substance and product

The chemical name (IUPAC) of dabigatran etexilate mesylate is ethyl N-{[2-({[4-((E)-amino {[(hexyloxy) carbonyl] imino} methyl) phenyl] amino} methyl)-1-methyl-1H-benzimidazol- 5-yl] carbonyl}-N-pyridin-2-yl-ß-alaninate methanesulfonate corresponding to the molecular formula C35H45N7O8S. The CAS number of dabigatran etexilate mesylate is 593282-20-3.
The molecular mass is 723.86 for the salt and 627.75 for the free base.
The chemical structure of the free base form of dabigatran etexilate is shown below



Dabigatran etexilate is the pro-drug of the active substance, dabigatran, which corresponds to the molecular formula C25H25N7O3 and molecular mass 471.5. The CAS numbers of dabigatran etexilate and dabigatran are 211915-06-9 and 211914-51-1, respectively.
The chemical structure of dabigatran is shown below:



Dabigatran etexilate mesylate is a yellow-white or yellow non-hygroscopic crystalline powder. The apparent partition coefficient of the neutral form (free base) is log P = 3.8, and the dissociation constants are $pKa_1 = 4.0 \pm 0.1$ (benzimidazol moiety) $pKa_2 = 6.7 \pm 0.1$ (carbamaic acid hexyl ester moiety). Solubility is strongly pH dependent with increased solubility at acidic pH. A saturated solution of the drug substance in pure water was found to have a solubility of 1.8 mg/ml. Because of the low solubility of dabigatran etexilate mesylate in water (pH 3 to pH 7.5) and the high intrinsic passive permeability, dabigatran etexilate mesylate is considered to be a Class II drug substance according to the Biopharmaceutical Classification System.
Dabigatran has no chiral centers. Geometric isomers (tautomers) are possible. Dabigatran etexilate mesylate exhibits polymorphism. Two anhydrous forms, modification I and II are known. Dabigatran etexilate mesylate is stable in the solid state when protected from moisture. In solution, sensitivity to oxidation and sensitivity to hydrolysis is observed, especially in acidic and basic aqueous media. The compound is not sensitive to photolysis.

3.1.3 What are the proposed mechanisms of action and therapeutic indication?

Dabigatran etexilate is a pro-drug of dabigatran, a representative of a new therapeutic class of direct thrombin inhibitors. Thrombin is a serine protease produced by the proteolitic cleavage of prothrombin. It is a final mediator in the formation of fibrin in the coagulation cascade and a potential platelet activator. As a specific and reversible inhibitor of thrombin, dabigatran has a potential to improve the management of thromboembolic disorders. The structure of dabigatran molecule was designed to improve the in vivo potency of binding with thrombin. The figure below shows the X-ray structure of dabigatran (BIBR953 ZW) in a complex with thrombin.

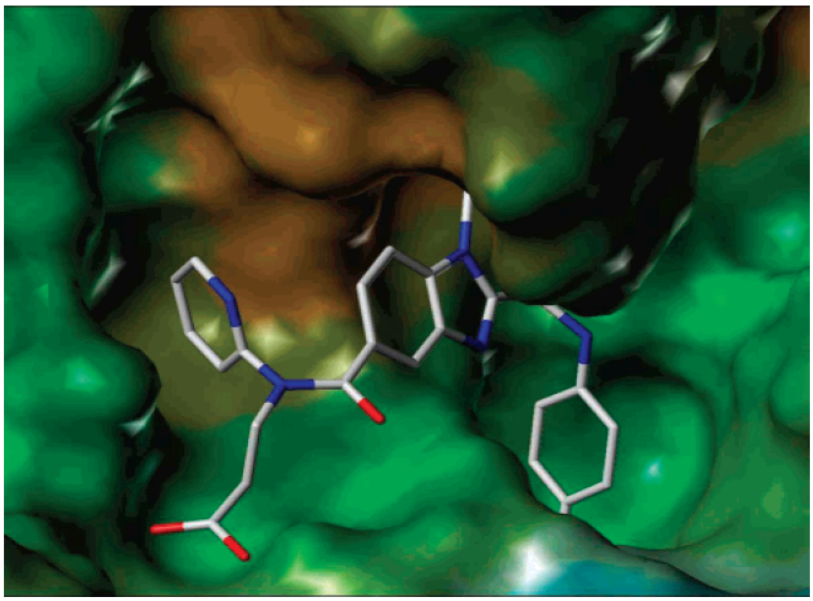


Figure 1. X-ray crystal structure of BIBR953 in complex with thrombin in a surface representation. The lipophilic potential is mapped on the protein surface.

The ligand interacts with thrombin residues of the specificity pocket and the P-pocket. The D-pocket is occupied by the pyridine ring, while the propionic acid substituent on the amide nitrogen projects into bulk solvent without forming further interactions with the protein (J Med Chem, 2002, Vol. 45, 1757-66).

3.1.4 What are the proposed dosages and route of administration?

The sponsor recommends that Pradaxa capsules 110 mg and 150 mg will be administered orally BID with or without food for both indications. The capsules should not be opened to swallow the pellets inside.

3.2 General Clinical Pharmacology

3.2.1 What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

The investigation of dabigatran was performed under IND 65813. The clinical pharmacology program for NDA 22-512 includes 48 studies.
An assessment of dabigatran PK and PD in healthy subjects was performed in 41 Phase I studies, 6 Phase II studies and one pivotal Phase III study RELY.
A single and a multiple dose PK, a dose ascending, a mass-balance, absolute BA, and a food-effect study were performed. The influence of race, age, hepatic and renal impairment on dabigatran PK and PD were evaluated.
Drug-drug PK and PD interaction studies of dabigatran and diclofenac, pantoprazole, ranitidine, ketoconazole, rifampicin, amiodarone, atorvastatin, digoxin, verapamil, quinidine, clarithromycin, enoxaparin, and clopidogrel were performed. The bioequivalence studies linked the to-be-marketed HPMS hard capsule formulation with the early investigational formulations of dabigatran.
Also, protein binding, the interaction with CYP450 enzymes, P-gp transport (both induction and inhibition potential) of dabigatran were studied in 7 in vitro studies.
In total, 38 studies submitted under the NDA 22-512 were reviewed.

3.2.2 Were the correct moieties identified and properly measured to assess clinical pharmacology?

Yes. The sponsor measured the concentrations of active moieties: dabigatran (BIBR953ZW), its glucuronides, and total dabigatran (sum of the active moieties). In the studies which used the high doses of dabigatran etexilate, the inactive parent drug (BIBR1048 MS) and 2 inactive intermediate compounds (BIBR 1087 and BIBR 951) were measured in plasma. In the pivotal clinical study, BIBR 953 was measured at through and peak plasma concentrations, population PK model was developed based on the previous information from Phase I-II studies where plasma sampling was more frequent.
For the assessment of pharmacodynamics, the array of the coagulation parameters (aPTT, INR, ECT, and TT) was measured.

3.2.3 What are the characteristics of the exposure-response relationships for efficacy?

The probability of an ischemic stroke decreases with increasing dabigatran concentration (Figure below). Going from the 10th to 90th percentile of observed pre-dose dabigatran concentrations (22.9 ng/mL to 238.3 ng/mL) in RE-LY, the probability of an ischemic stroke within one year in a typical patient is predicted to decrease from 1.05% to 0.52%.

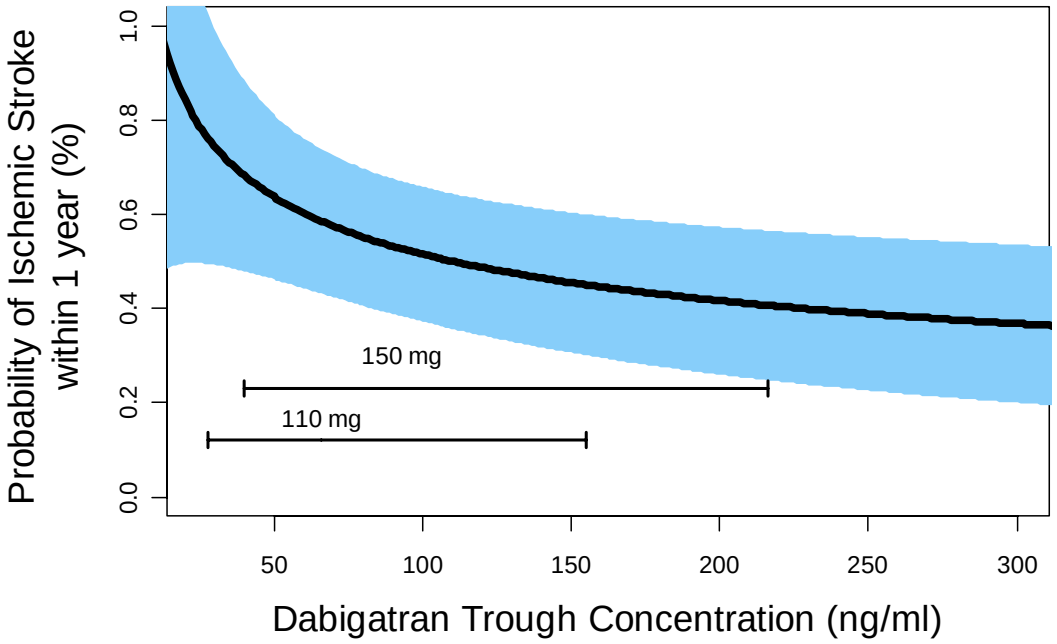


Figure 2. Probability of ischemic stroke within 1 year vs. dabigatran pre-dose concentration. The blue shaded region represents the standard error. The bars on the bottom on the plot region represent the 10th to 90th percentiles of observed dabigatran pre-dose concentrations in the RE-LY trial.

3.2.4 What are the characteristics of the exposure-response relationships for safety?

The probability of a life-threatening bleed, defined as fatal bleeding, symptomatic intracranial bleeding, bleeding associated with a reduction in hemoglobin levels of at least 50 g/L or leading to a transfusion of at least 4 units of blood or packed cells or bleeding necessitating surgical intervention, increases with increasing dabigatran concentration. Going from the 10th to 90th percentile of observed pre-dose dabigatran concentrations (22.9 ng/mL to 238.3 ng/mL) in RE-LY, the probability of a major bleed within 1 year in a typical patient is predicted to increase from 0.27% to 1.82%.

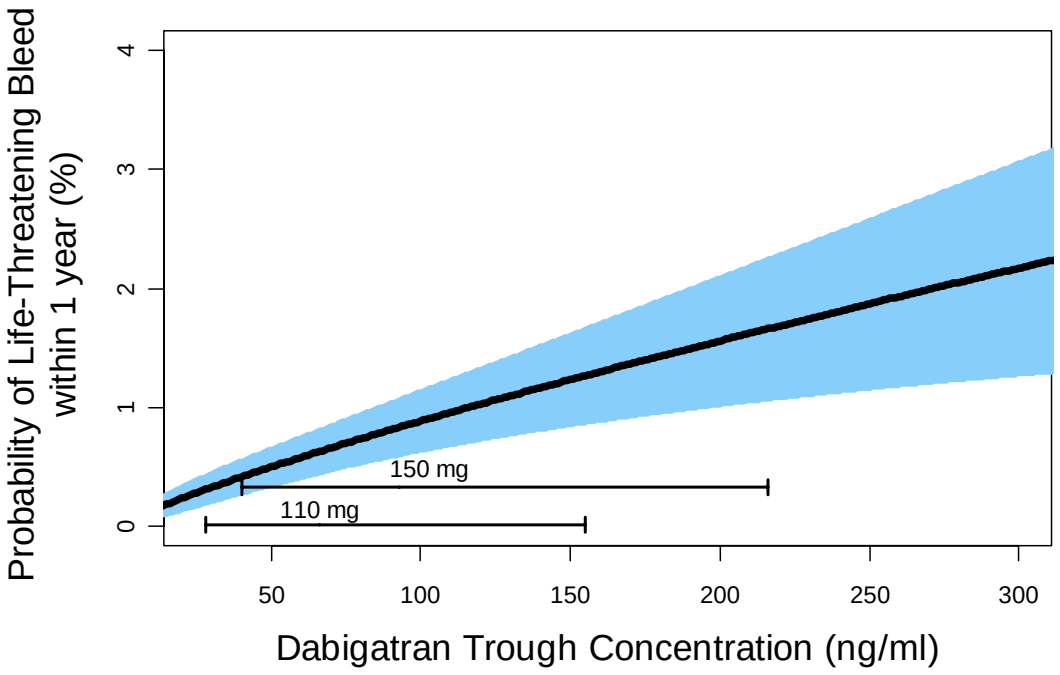


Figure 3. Probability of a major bleed within 1 year vs. dabigatran pre-dose concentration. The blue shaded region represents the standard error. The bars on the bottom on the plot region represent the 10th to 90th percentiles of observed dabigatran pre-dose concentrations in the RE-LY trial.

3.2.5 What is the impact of dabigatran and warfarin on liver function?

The impact of dabigatran and warfarin on liver function was assessed PM review (Appendix).

Dabigatran and warfarin were found to have a similar impact on liver function as measured by the proportion of subjects with AST or ALT > 3x ULN or bilirubin > 2xULN. The incidence of these events was less than 1% in the 110 mg dabigatran, 150 mg dabigatran and warfarin treatment arms in RE-LY. Historical data from the Sportif 3 and Sportif 5 trials with ximelagatran were also examined as a positive control because ximelagatran is known to have adverse effects on liver function. The percentage of subjects receiving ximelagatran in these trials and having ALT and AST > 3x ULN was much higher, 3-7% (Figure 4) and 1-3%, respectively. The warfarin treatment arms in the Sportif 3 and Sportif 5 trials were quantitatively similar to the warfarin treatment arm in RE-LY.

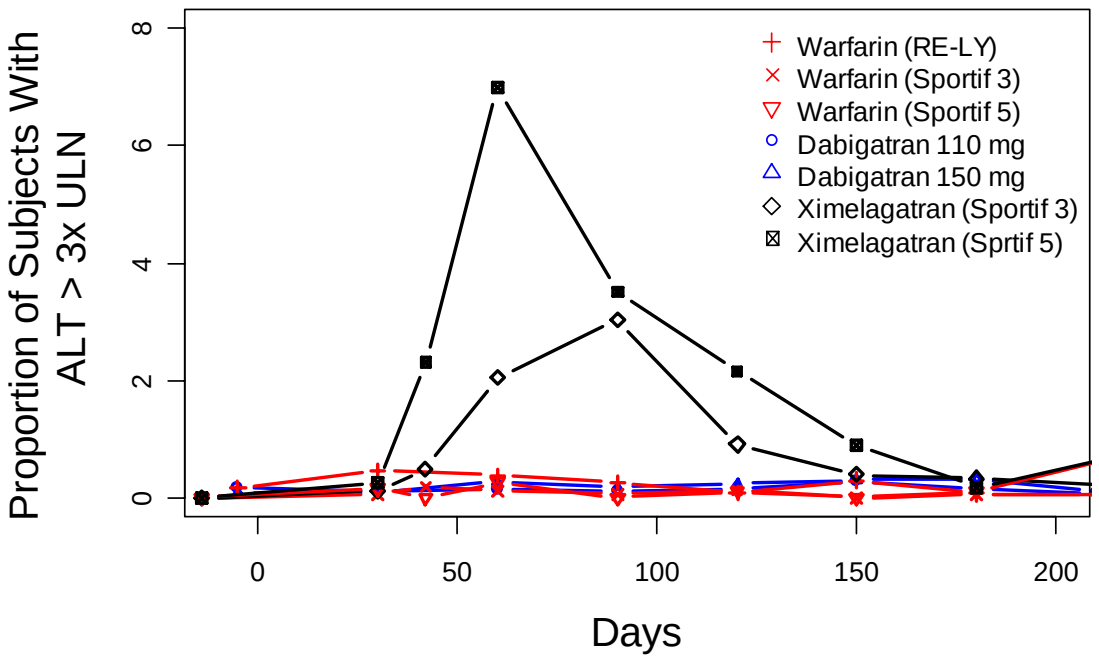


Figure 4. Time course of ALT > 3x ULN for warfarin, ximelagtran and dabigatran in the Sportif and RELY trials.

3.2.6 Does dabigatran prolong the QT or QTc interval?

No. The sponsor performed a thorough QT study (1160.54) to assess the electrophysiological effects of dabigatran as single 150 and 600 mg doses on QT interval prolongation. The QT Consult is performed by the Interdisciplinary Review Team for QT Studies Consultation.
Link to review: \\Cdsnas\transfer\OCP\DCP1_CR\NewFolder\NDA\22512_dabigatran

PK CHARACTERISTICS OF THE DRUG AND ITS MAJOR METABOLITE(S)

3.2.7 What are the single dose and multiple dose PK parameters?

The sponsor conducted the first single ascending and multiple dose studies with the early formulations. Since these formulations were linked with the to-be-marketed HPMC capsule, the results obtained in these early studies are valid. The majority of clinical pharmacology studies reported the pharmacokinetic profiles and parameters for the active moiety, dabigatran, as well as the total dabigatran. The latter values were obtained after the hydrolysis of dabigatran glucuronides and represent a sum of active moieties. In this review, we consider the total dabigatran concentrations to be the most relevant moiety to describe the dabigatran pharmacokinetics and pharmacodynamics. The mean plasma concentration vs. time profiles of total dabigatran after the single and multiple doses of BIBR1048MS are shown below.

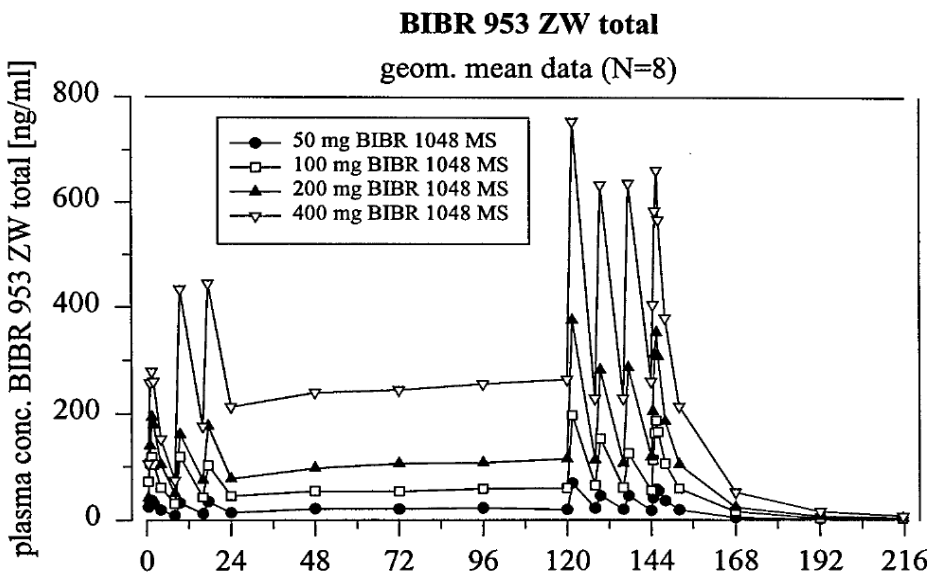


Figure. 5. Geometric mean total dabigatran plasma concentration vs. time (hrs)

With chronic BID dosing, dabigatran accumulates in plasma: the ratios of accumulation (Cmax,ss/Cmax,dayl) were in the range of 1.6 to 2.3 for the doses from 50 to 400 mg.

3.2.8 How does the PK of the drug and its major active metabolites in healthy volunteers compare to that in patients?

The results of the population pharmacokinetic analysis indicated that the pharmacokinetics of dabigatran was similar between healthy volunteers and patients.

3.2.9 What are the characteristics of drug absorption (possible transporters and pH impact)?

Following oral administration to healthy subjects, dabigatran etexilate is rapidly absorbed and converted by esterase-catalyzed hydrolysis to dabigatran. Peak plasma concentrations of dabigatran occur 1-2 hours after drug administration. During the conversion of the pro-drug dabigatran etexilate two intermediates, BIBR 951 (an active thrombin inhibitor) and BIBR 1087 (a pharmacologically inactive intermediate) were measured in plasma. After the oral doses of 150 mg, the concentrations of the intermediates were close to the detection limits; they were measured up to 2 hours post single 600 mg dose, and in patients with hepatic impairment up to 2 (BIBR 1087) and 8 (BIBR 951) hours post 150 mg dose. The involvement of microsomal carboxylesterases in the hydrolysis of dabigatran etexilate and BIBR 1087 SE was confirmed in the in vitro experiments.
The pro-drug's conversion does not depend on cytochrome P450 isoenzymes; however, the pro-drug, dabigatran etexilate, but not dabigatran, is a substrate of the efflux transporter P-glycoprotein (P-gp).
Absorption of dabigatran etexilate is incomplete; the absolute bioavailability of dabigatran after oral administration of dabigatran etexilate is approximately 3-7%. The

low bioavailability is most likely caused by the narrow range of suitable pH for sufficient dissolution of mesylate salt of dabigatran etexilate (drug substance) in addition to being a P-gp substrate. Absorption is most likely one of the major factors influencing the inter– and intra-subject variability in bioavailability of dabigatran.

3.2.10 What are the characteristics of drug distribution (including plasma protein binding?)

Dabigatran is extensively distributed into the tissues. Its estimates of apparent volume of distribution ranged from 50-70 L in healthy subjects and in patients.
The dabigatran binding to plasma proteins was not determined in vivo, and in vitro, it was about 35%. Protein binding was independent of the dabigatran concentrations (50-500 ng/ml). This range covers the possible therapeutic dabigatran plasma concentrations; therefore, the interaction potential of dabigatran with other drugs on the basis of protein binding is low.
The whole-blood-to-plasma ratio measured by total radioactivity after the IV dose of dabigatran was generally less than 0.3, which indicates on low penetration dabigatran into red blood cells.

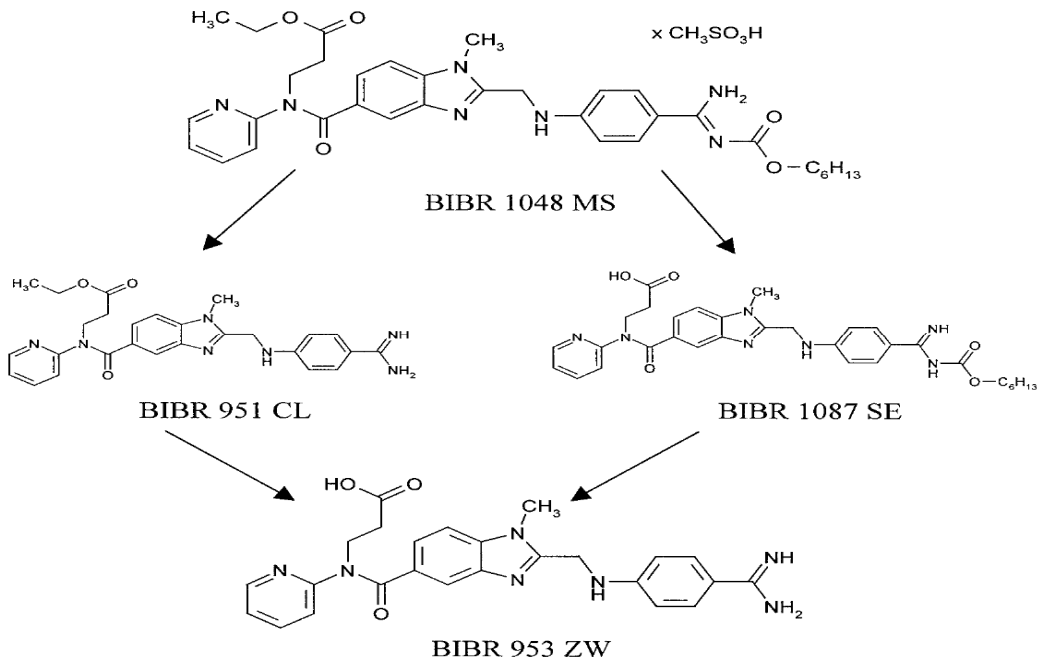
3.2.11 Does the mass balance study suggest renal or hepatic as the major route of elimination?

The major route of dabigatran elimination is via kidneys. Following intravenous administration of [^{14}C]-labeled dabigatran to healthy male volunteers, a mean of 85% of the administered dose was recovered in urine and 6% in feces over 168 h post-dose (measurement of total radioactivity). Following oral administration of [^{14}C]-labeled dabigatran etexilate, a mean of 7% of the administered dose was recovered in urine and 86% in feces over 168 h post-dose (total radioactivity), most likely due to unabsorbed dabigatran etexilate. Renal clearance represented 80% of total dabigatran clearance.
Dabigatran conjugates with glucuronic acid, and its 1-O-acyl glucuronide is pharmacologically active. Due to its isomerisation, several positional dabigatran glucuronides isomers occur in plasma. The dabigatran glucuronide isomers represent about 20% of the total dabigatran after oral dosing (comparison of the AUC values). After IV administration, the glucuronides accounted for about 10% of total dabigatran in plasma. The glucuronidation rate was independent of dose and intrinsic (gender, age, race, renal- or hepatic impairment) or extrinsic factors.

3.2.12 What are the characteristics of drug metabolism?

After oral administration, pro-drug dabigatran etexilate was not detected in urine, and the major excreted in urine moiety was dabigatran. The predominant metabolic reaction is the cleavage of the pro-drug by esterase catalyzed hydrolysis of the ethyl ester and the hexyloxycarbonyl moiety via the intermediates BIBR 1087 and BIBR 951 to the active dabigatran (BIBR 953). Dabigatran is not a substrate or inhibitor of cytochrome P450 enzymes, and they do not catalyze metabolism of dabigatran.

The sponsor properly characterized all metabolites and intermediates in the mass-balance study 1160.06. The simplified metabolic pathway is shown below.



Dabigatran conjugates with activated glucuronic acid to form a pharmacologically active 1-O- acyl glucuronide which further is subject to non-enzymatic isomerization and hydrolytic cleavage.

3.2.13 Based on PK parameters, what is the degree of linearity or nonlinearity in the dose-concentration relationship?

Dabigatran dose-proportionality was assessed in the studies 1160.1, 1160.02, 1160.05, and during the population PK data analyses. The pharmacokinetics of dabigatran were dose proportional over the range of oral doses from 10 to 400 mg.
The figure below shows the power function fitting to the PK parameters vs. dose data.

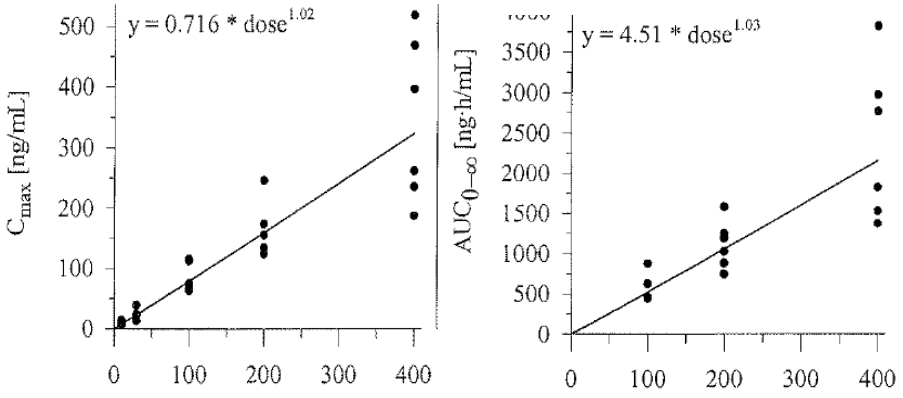


Figure 6. Dose proportionality of total dabigatran Cmax and AUCinf after the single doses of BIBR1048MS

3.2.14 What is the inter- and intra-subject variability of the PK parameters, and what are the major causes of variability?

Dabigatran is a moderately variable dug. The estimates of between-patient variability in apparent clearance in these studies have been moderate, ranging from 40% to 60%. Between-patient variability in apparent volume of distribution (Vd/F) was moderate at 26% and was explained by body weight.

3.3 Intrinsic Factors

3.3.1 What intrinsic factors (age, gender, race, weight, height, disease, genetic polymorphism, pregnancy, and organ dysfunction) influence exposure (PK usually) and/or response, and what is the impact of any differences in exposure on efficacy or safety responses?

Body Weight
In the population pharmacokinetic analysis, an increase of 1 kg above the median weight of 80 kg increased the volume of distribution by 1.1%. A male patient weighing 103 kg is expected to have an 8.3% increase in pre-dose concentration and a decrease in post-dose concentration by 5.5% compared to an 80 kg male. A male patient weighing 61 kg is expected to have an 8.6% reduction in pre-dose concentration and a 4.4% increase in post-dose concentration relative to an 80 kg male.
In the RE-LY trial, patients weighing < 50 kg and 50 to < 100 kg had 1.5-fold and 1.3-fold higher dabigatran pre-dose concentrations, respectively, relative to patients weighing ≥ 100 kg. No dose adjustment is required based on body weight.
Gender
In the population pharmacokinetic analysis, females had a 14% higher steady state exposure ($AUC_{tau,ss}$) than males.
In the RE-LY trial, pre-dose and post-dose dabigatran concentrations were approximately 30% higher in female patients relative to male patients. No dose adjustment is required based on the gender.
Age
In the population pharmacokinetic analysis, an increase in 1 year above the median age of 68 years decreased clearance by 0.66%. A 93 year old patient is expected to have a 20% increase in steady-state exposure ($AUC_{tau,ss}$) relative to a 68 year old patient.
In the RE-LY trial, pre-dose dabigatran concentrations were 1.3-fold and 1.7-fold higher in patients aged 65 to 75 years and ≥ 75 years of age, respectively, compared to patients < 65 years of age.

Race, in particular differences in exposure and/or response in Caucasians, African Americans, and/or Asians

In the pivotal study RE-LY, majority of subjects were Caucasians. There were no obvious differences in hazard ratios for stroke/SEE observed across different ethnic groups, except that for black subjects both dabigatran groups had relatively low hazard ratios compared to warfarin. It should be noted that there were less than 100 black subjects in each group.

The study 1160.61, which used dabigatran 110 mg and 150 mg bid dose regimen, allowed the direct comparison of dabigatran PK in Caucasian and Asian/Japanese according to the proposed in NDA 22-512 claim. The exposure to dabigatran in Japanese subjects was about 30% higher than in Caucasian subjects who received 110 mg BID dose of dabigatran. The differences were less pronounced in the 150 mg BID dose. Similar differences were demonstrated between the coagulation parameters.
The ethnic difference in PK and PK/PD between Caucasian and Asian/Japanese subjects described in study 1160.61 were also supported by data from RELY and the combined PopPK analysis.
The PK/PD relationship of dabigatran in African-Americans has not been evaluated by the sponsor in the current submission.
In the labeling recommendations it should be stated, that the differences between Caucasians and Japanese subjects are not clinically significant, and that the effect of any other ethnic groups on dabigatran PK and PD has not been evaluated.

Renal Impairment

Dabigatran PK and PD after the single 150 mg dose were compared in subjects healthy and subjects with mild, moderate, severe renal impairment, and patients on dialysis (dabigatran dose of 50 mg) to the same in healthy subjects.
While in healthy subjects dabigatran terminal half-life was estimated as 13 hours, it increased with the decrease of renal function and was estimated as 15 hours, 18 hours, and 27 hours in mild (MI), moderate (MOI) and severe-renal impaired (SI) subjects respectively. The geometric mean ratios (folds) and 90% CI of the comparisons of the exposure parameters (AUC and Cmax) between subjects with mild, moderate, and severe renal impairment are shown in the figure below.

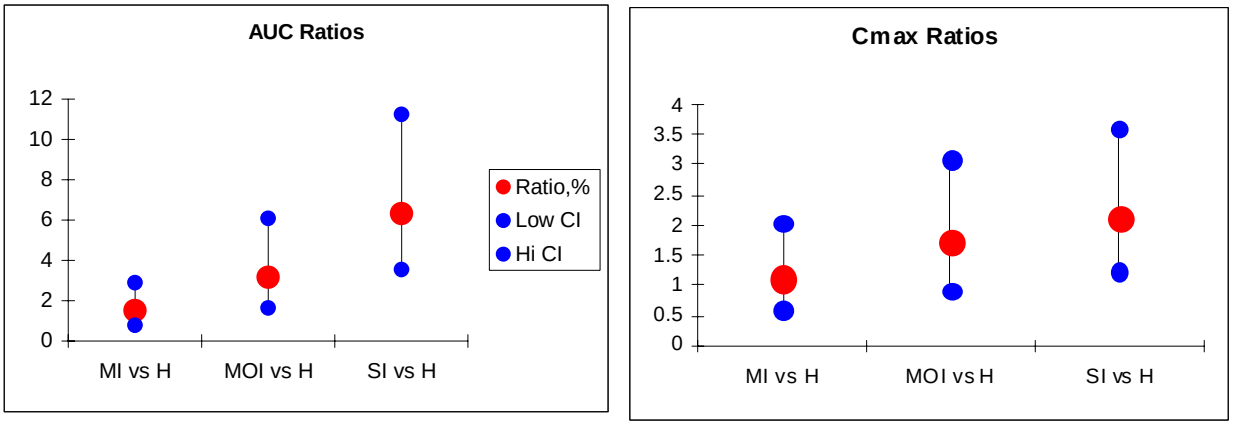


Figure 7. Comparison of the geometric mean ratios for AUC and Cmax (mean and 90%CI) in subjects with renal impairment vs. healthy subjects

Although excretion was not completed for SI subjects (over 24 hours), the data for HC, MI & MOI groups demonstrate that the relationship is linear.

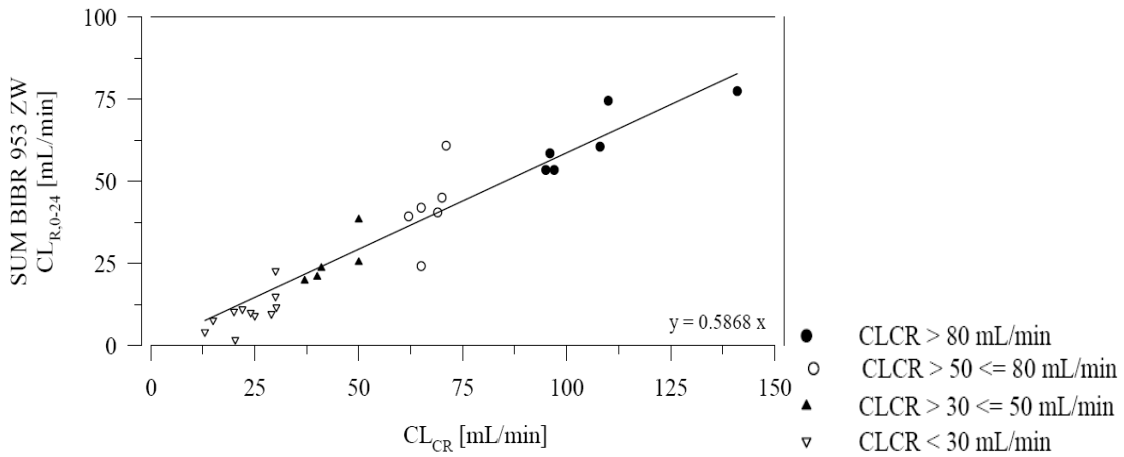


Figure 8. Correlation between individual values of total dabigatran renal clearance (0-24) and creatinine clearance

A similar continuous relationship was observed based on the data from the RE-LY trial Patients with mild, moderate and severe renal impairment had 1.5-fold, 2.3-fold and3.3-fold higher pre-dose dabigatran concentration compared to patients with normal creatinine clearance (< 80 mL/min).

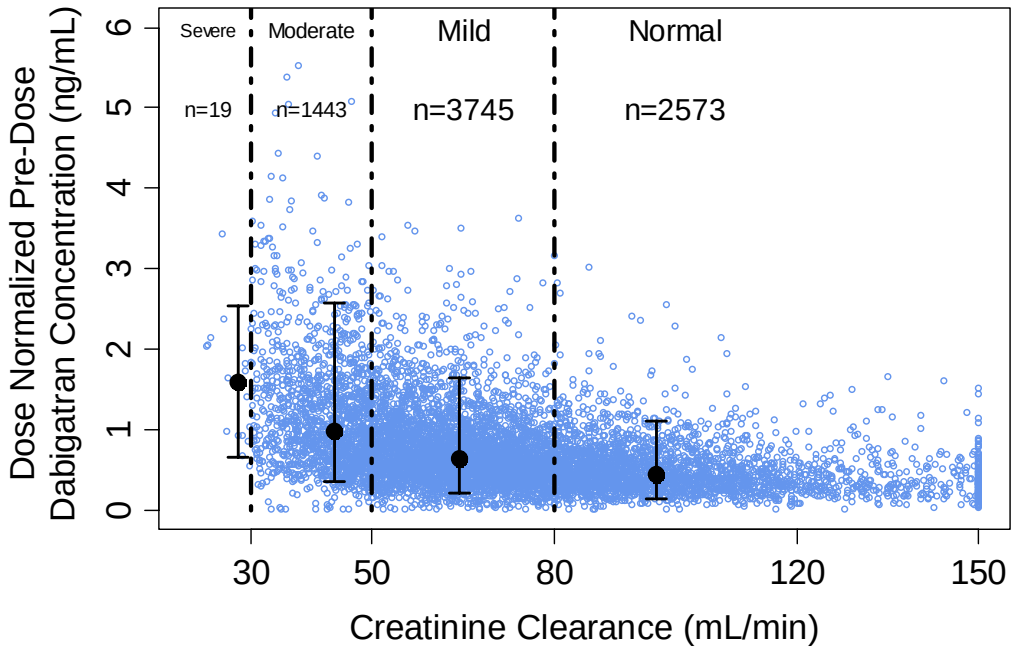


Figure 9. Dose-normalized pre-dose dabigatran concentration vs. creatinine clearance in RE-LY.

Despite of the differences in pharmacokinetics, the effect of dabigatran on prolongation of coagulation parameters was not so dramatic. Mean maximum prolongation (fold-change) of blood coagulation times determined for baseline corrected parameters is compared in the figure below.

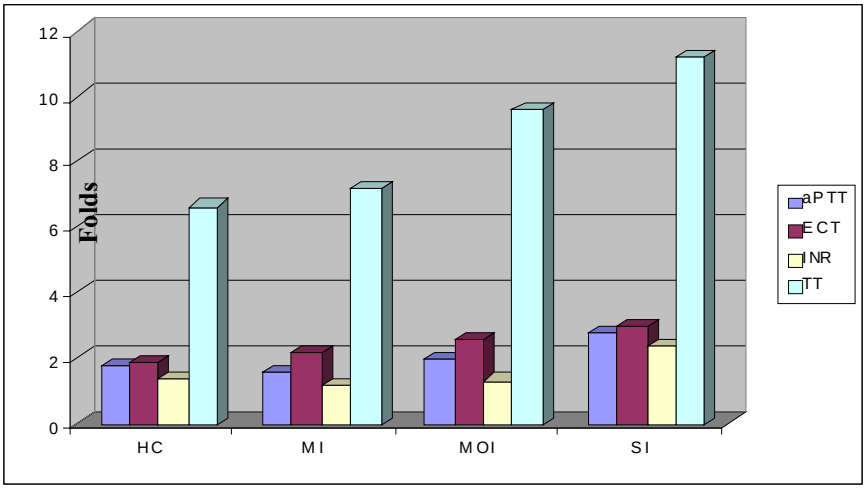


Figure 10. Baseline corrected mean maximum prolongation of blood coagulation parameters (aPTT, ECT, INR, and TT)

The most sensitive parameter was thrombin time (TT). TT was similar in mildly renally impaired and healthy subjects; however, in moderately and severely impaired subjects TT increased 1.5 and 2 folds relatively to the healthy subjects.

In the RE-LY study, the median CrCl for all subjects was 68.6 mL/min. Overall 31.6% of subjects had a CrCl >80 ml/min, 45.8% of the subjects had a CrCl from 50 to 80 ml/min, 18.2% of the subjects had a CrCl from 30 to 50 mL/min (4.0% baseline value missing).

The probability of ischemic stroke decreased with the increase in exposures across all the renal function groups as shown in the figure and table below.

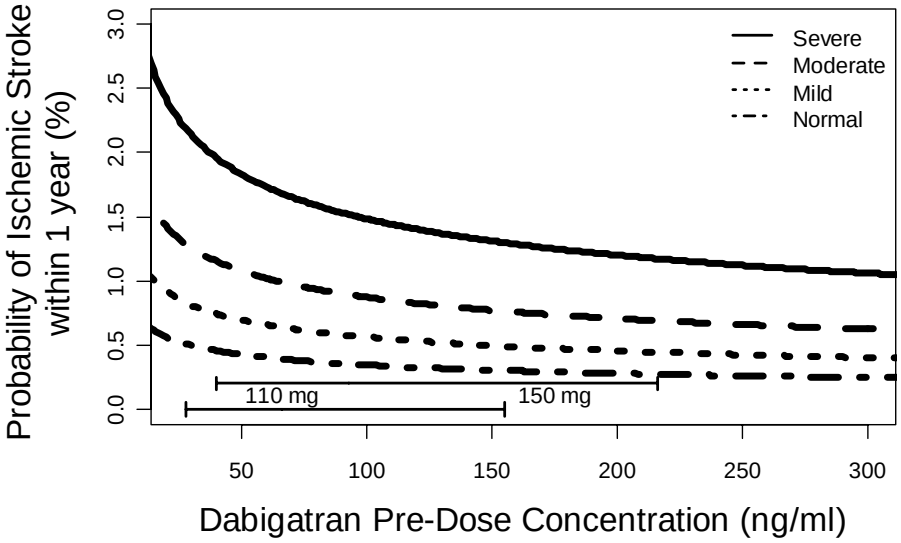


Figure 11: Probability of ischemic stroke with 1 year vs. dabigatran pre-dose concentration in a patient with no history of stroke/TIA by creatinine clearance category.

Table 1 Frequency and yearly event rate of stroke/SEE by renal function. *Source: Table 11.4.1.4.1: 1 of sponsor report 1160-0026—01-15—study-report-body.pdf*

	DE 110		DE 150		Warfarin	
	# of subject	Event rate	# of subject	Event rate	# of subject	Event rate
CrCL (ml/Min)						
30<= and <50	1136	2.36	1157	1.23	1050	2.64
50<= and <80	2714	1.69	2777	1.21	2807	1.82
>=80	1899	0.86	1882	0.73	1877	1.03

Further, in the moderate renal impaired group, the bleeding risk is not different when both dabigatran dose arms compared to warfarin arm as shown in table below.

Table 2 Frequency and yearly event rate of major bleeds by renal function (randomized set). *Source: Table 12.2.2.5: 1 of sponsor report 1160-0026—01-15—study-report-body.pdf*

	DE 110		DE 150		Warfarin	
	#of subjects	Yearly event rate (%)	# of subjects	Yearly event rate (%)	# of subjects	Yearly event rate (%)
CrCL (ml/min)						
<30	15	0.00	32	13.31	30	0.00
30<= and <50	1136	5.42	1157	5.08	1050	5.28
50<= and <80	2714	2.59	2777	3.17	2807	3.63
>=80	1899	1.40	1882	1.86	1877	2.27

Therefore, no dose adjustment is needed in patients with moderate renal impairment.

Severe renal impaired patients were excluded from the pivotal RELY study. However, at mid-cycle meeting, the review team expressed the need to propose a dosing regimen in severe renal impaired subjects for the current indicated population. Based on the simulations of the mean time-course of plasma dabigatran concentrations in severe renal impaired subjects, a dose of 75 mg QD and 75 mg QOD will provide exposures reasonably comparable to patients with normal function as shown in figure below.

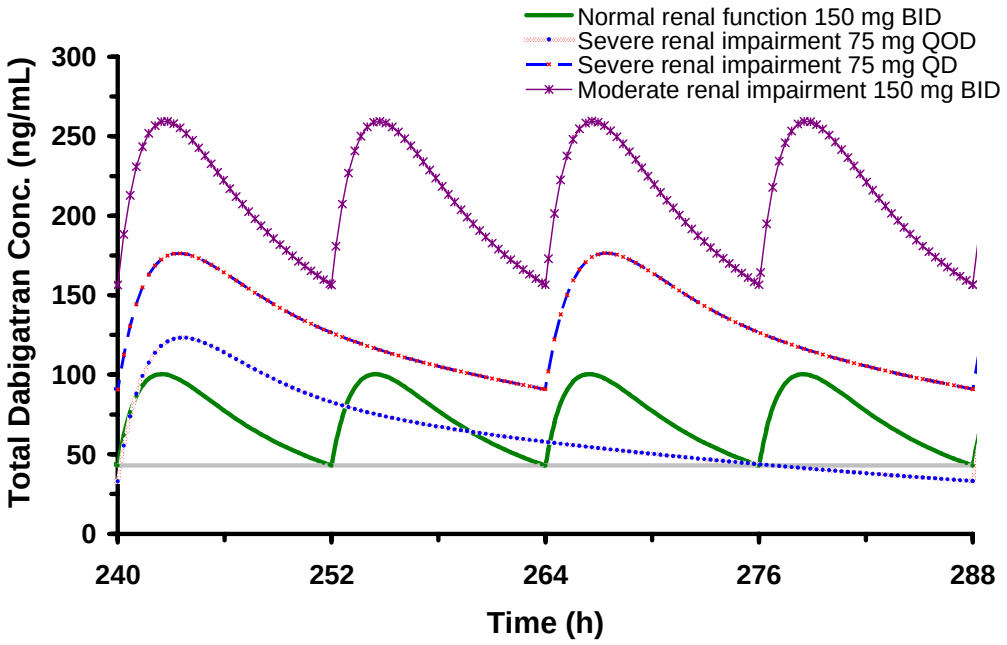


Figure 12: Simulated mean steady state total dabigatran plasma concentration for subjects with normal renal function and moderate renal impaired administered 150 mg BID and severe renal impaired patients administered 75 mg QD and 75 mg every other day.

It can be clearly seen with the 75 mg dose administered every other day, the total dabigatran plasma concentrations fall below the exposures seen in subjects with normal renal function for a 12 h period before getting their next dose. Since, we do not understand the relationship between drop in exposures and efficacy; the best option would be to recommend 75 mg dabigatran QD as the dosing regimen. With this regimen, the 75% increase of Cmax and AUC can be expected compared to patients with normal renal function. This increase in exposures is lower than the experience with moderate renal impaired subjects in the phase III trial. Therefore, we recommend a dose of 75 mg dabigatran QD in severe renal impaired subjects.

The geometric mean (dose normalized) AUC0-∞ in subjects on hemodialysis was 2 fold higher than in the healthy control group (14.1 versus 7.0 ng·h/mL/mg). However, the geometric mean C_{max} (dose-normalized) was 67% lower than in the healthy controls, indicating that a considerable fraction of dabigatran from plasma was removed by hemodialysis. This was confirmed by comparison of the concentrations in inlet and outlet dialysis lines over the collection intervals, accounting for 61% of dabigatran removed by dialysis. Hence, hemodialysis should be considered to address accidental overdosing or in situations that require urgent surgical intervention.

Hepatic Impairment

Subjects with moderate hepatic impairment (Child-Pugh B) were compared to the healthy subjects (study 1160-51). Approximately 30% lower Cmax 5% lower AUC was observed. The pro-drug and its intermediates were present at higher concentrations

compared to healthy subjects. The relative exposures to these products were low, not exceeding 2% of total exposure, therefore, not affecting the exposure to the active component. The degree of dabigatran glucuronidation and protein binding were not affected by hepatic impairment. Subjects with severe hepatic impairment were excluded from the RE-LY study.
A dose adjustment for the hepatically impaired subjects is not required. Dabigatran should be contraindicated in subjects with severe hepatic impairment since there is no information on PK and/or PD in this patient population.

Genetics

ABCB1 genotype does not appear to be a major determinant of dabigatran exposure. *ABCB1* polymorphisms (2677 G>T/A [substrate specific transport function] and 3435 C>T [low expression]), were genotyped in five of the Phase 1 drug interaction studies (1160.74, 1160.75, 1160.82, 1160.90, and 1160.100; total N = 114) and a small subset of subjects in RE-LY (N = 2966). Dabigatran exposures were variable and no consistent pharmacogenetic effects were observed across the studies, as shown in the figure below. In RE-LY, small but nominally significant increases in median dose-normalized C_{2hr} were observed in *ABCB1* 3435 T allele carriers (C/T 8% higher, T/T 15% higher). In the RE-LY genomics sub study, the primary efficacy and safety endpoint event rates were low, precluding meaningful analysis of pharmacogenetic effects on outcomes. Published literature suggests that *ABCB1* polymorphisms do not consistently alter transporter expression or function, or P-gp substrate exposure or response.

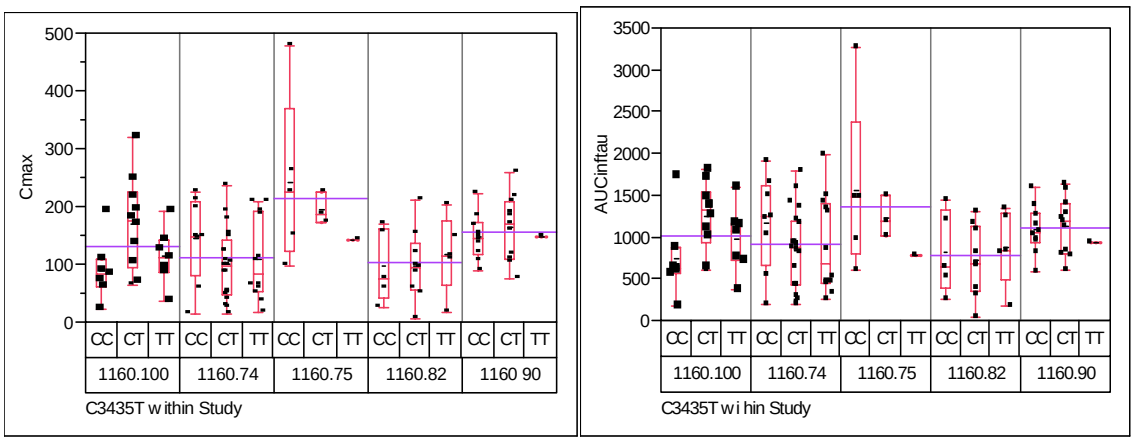


Figure 13. Total dabigatran exposure by *ABCB1* 3435C>T genotype in healthy subject drug interaction studies (monotherapy phases) AUC0-∞ is presented for single dose studies (1160.74, 1160.82, 1160.100); AUC0-τ and Cmax,ss are presented for multiple dose studies (1160.75, 1160.90). Horizontal blue lines reflect study mean.

In RE-LY study, warfarin time in treatment range (TTR) differed in subjects with variant *VKORC1* (3673 G>A) and *CYP2C9* (*2, *3) alleles as expected. Again, the small sample size of the RE-LY genomics sub-study precluded meaningful analysis of clinical outcomes according to *VKORC1* and *CYP2C9* genotype.

3.3.2 Based on what is known about exposure-response relationships, what dosage regimen adjustment, if any, are recommended based upon exposure-response relationship?

Based on the known exposure-response relationship, patients with severe renal impairment should receive 75 mg of dabigatran QD. This will result in dabigatran exposures within the current studied experience.

3.4 Extrinsic Factors

3.4.1 What is the impact of skipping the dose(s) of dabigatran?

The simulation of the mean steady-state total dabigatran plasma time course in subjects with normal renal function receiving 150 mg BID, indicates that dabigatran plasma concentrations fall below the average trough concentrations corresponding to 100 mg BID (~ 32 ng/mL) by 15 hrs post last dose (Figure 14 below). Hence, non-compliance to dabigatran treatment will put the patients at risk for inadequate anticoagulation.
However, in subjects with moderate renal impairment receiving dabigatran 150 mg BID or severe renal impairment receiving dabigatran 75 mg QD, it takes ~65 hrs for the mean total dabigatran plasma concentrations to fall below the threshold of 35 ng/mL i.e., trough dabigatran exposures associated with 110 mg BID.

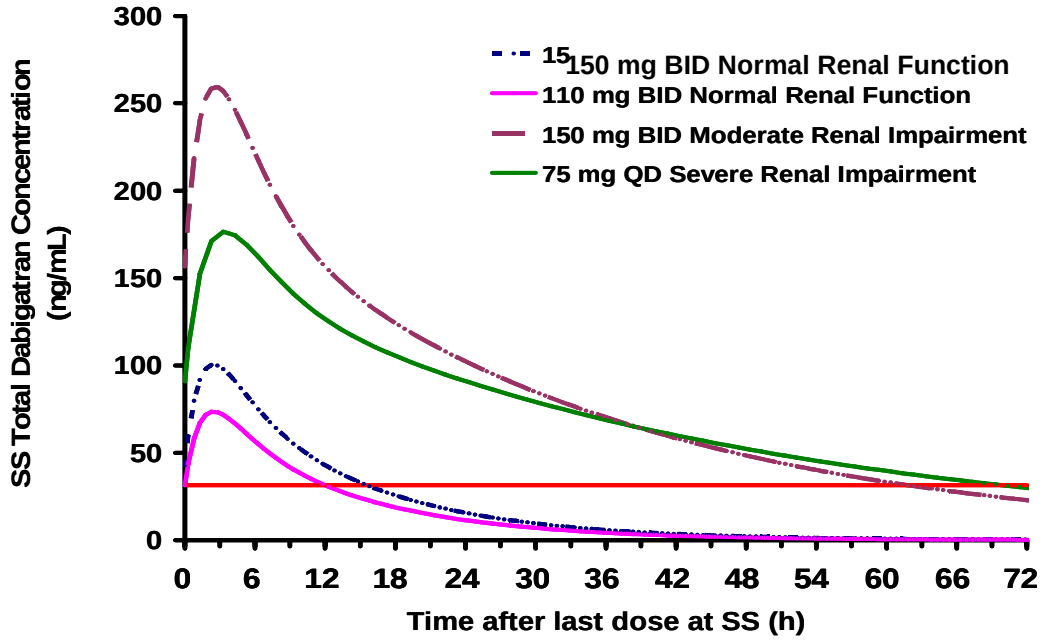


Figure 14: Simulated mean steady state total dabigatran plasma concentration following last dose for subjects with normal renal function and moderate renal impaired administered 150 mg BID and severe renal impaired patients administered 75 mg QD.

3.4.2 What is the Interaction Liability of Dabigatran?

The interaction liability of a drug depends on its biopharmaceutic, pharmacokinetic and pharmacodynamic characteristics. Because the drug substance administered, BIBR 1048 MS, is a pro-drug that must be metabolized first to the main active moiety, dabigatran, the interaction liability assessment should not only consider dabigatran, but also the precursors, i.e. BIBR 1048, BIBR 1087 SE and BIBR 951 TS. The biopharmaceutical and kinetic characteristics of dabigatran and its precursors and metabolite that are potentially responsible for the vulnerability of dabigatran towards co-administered drugs are summarized below:

- BIBR 1048 SE: solubility ≥ pH 3.0
  substrate of P-gp
- Precursors: substrates of carboxylesterases
- Dabigatran: substrate of tissue uptake transporter(s)
- Dabigatran: susceptible to additive effects by co-administered anticoagulants and platelet aggregation inhibitors

The likelihood of dabigatran and precursors to affect the exposure to other drugs is considered small.

3.4.3 Is there an in vitro basis to suspect in vivo drug-drug interactions?

Yes. As described in 2.4..1 (above) in vitro studies indicate an interaction liability of dabigatran and precursors to be impacted by gastric pH raising drugs, P-gp-inhibitors and inducers, carboxylesterase inhibitors and inducers, other anticoagulants and platelet aggregation inhibitors.

3.4.4 Is the drug a substrate of CYP enzymes?

No. In vitro experiments using human liver microsomes and human expressed CYPs show that neither dabigatran nor its precursors are metabolized by CYPs.

3.4.5 Is the drug an inhibitor and/or an inducer of enzymes?

At therapeutic concentrations dabigatran and its precursors are neither inhibitors nor inducers of CYPs. The inhibition and induction potential of dabigatran and precursors towards Phase II enzymes is not known.

3.4.6 Is the drug a substrate, an inhibitor and/or an inducer of transporters?

BIBR 1048 MS is a substrate of P-gp, but not of MRP2. Dabigatran and BIBR 951 TS are neither substrates nor inhibitors of P-gp. The intermediate BIBR 1087 SE is not an inhibitor of P-gp. The status of BIBR 1087 SE as a possible P-gp substrate is undetermined. Also the possible involvement of dabigatran and its precursor with other transporters is not known. The induction of transporters by dabigatran and precursors is undetermined as well.

3.4.7 Are there other metabolic/transporter pathways that may be important?

An *in vivo* interaction study with amiodarone shows an increase in renal clearance and volume of distribution in the presence of amiodarone suggesting dabigatran may be a substrate of tissue uptake transporters such as OATP, OCT or OAT.

3.4.8 What extrinsic factors influence exposure and/or response, and what is the impact of any differences in exposure on effectiveness or safety responses?

Co-administered drugs are the major extrinsic factor that could affect the dose/exposure-response of dabigatran. The target population is expected to be on several drugs simultaneously. Dabigatran seems to exhibit a steep dose-response relationship over the range of 110 and 150 mg bid. The pivotal study shows that benefit (prevention of stroke) varies between the two dose levels even though they differ by 36% only. Therefore, a relative small decrease in exposure and/or response to dabigatran by interfering, co-administered drugs may result in loss of effectiveness of dabigatran.
The exposure-response relationship shows a clear increase in efficacy with an increase in bleeding risk. However, the exposure of dabigatran resulting in unacceptable major bleeding outweighing the benefit of debilitating stroke prevention is not clearly understood. It should be noted that major bleeding according to the current definition is manageable risk. Further, moderate renal impaired patients in the phase III trial had 2.3 folds increase in exposure compared to patients with normal renal function without excessive bleeding risk compared to warfarin. Hence for the current submission, any interaction that will result in an increase greater than 2.5 fold (or an increase greater than 150%) requires a dose/regimen adjustment.

3.4.9 What are the drug-drug interactions?

Dedicated Studies
The drug-drug interaction studies were performed in healthy young to middle age subjects of both sexes. To be marketed formulation of BIBR 1048 MS was administered in all but the clopidogrel interaction study. In the ketoconazole-, the second quinidine- and the pantoprazole study drug administration was in the fed state. In all other studies the drugs were administered in the fasted state. The doses of the co-administered drugs used were usually the highest recommended in the label. The quinidine interaction study was repeated because the initial study was terminated prematurely due to intolerance of the acutely administered dose of 600 mg quinidine sulfate. In the large majority of the trials the anticoagulant effect of dabigatran was measured using the activated partial thromboplastin time (aPTT), and the Ecarin coagulation time (ECT). In the studies with clopidogrel the impact of dabigatran on capillary bleeding time and anti-platelet aggregation was determined. The key findings are presented in the table below:

Table 3 Impact of Other Drugs on Exposure to Dabigatran

Other Drugs		BIBR 1048 MS	ΔTime[a]	Rel. Exposure to Dabigatran in Presence of Other Drug	
	Dose, mg	Dose, mg	h	AUC[b] %	Cmax[b] %
R/S Verapamil	120 IR bid	150	-1	154 (119-199)	163 (122-217)
	120 IR bid	150	+2	118 (91-152)	112 (84-149)
	120 IR qid	150	-1	139 (107-181)	134 (100-184)
	120 IR	150	-1	243 (191-308)	279 (215-362)
	120 IR	150	0	208 (164-264)	229 (176-297)
	240 ER	150	0	171 (134-217)	191 (147-248)
Ketoconazole	400	150	0	238 (217-261)	235 (205-270)
	400 qd	150	0	253 (233-275)	249 (223-279)
Quinidine 1[c]	600	150 bid	-1	186[d]	ND
Quinidine 2	1000[e]	150 bid	0	153 (144-162)	156 (149-167)
Amiodarone	600	150 bid	0	158 (128-195)	150 (117-190)
Clopidogrel	300	75 bid[f]	0	74	72
	300	150 bid	0	136	168
	600	150 bid	0	132 (112-156)	143 (120-170)
	75 qd[g]	150 bid	0	92 (79-107)	95 (79-114)
Rifampicin	600 qd	150	-0.5[h]	33 (27-41)	35 (27-44)
		150	-7.5[h]	82 (65-104)	81 (65-102)
		150	-14.5[h]	86 (68-109)	82 (63-106)
Clarithromycin	500	150	-1	91 (62-132)	87 (58-131)
	500 bid	150	-1	119 (90-158)	115 (84-157)
Atorvastatin	80 qd	150 bid	0	82 (73-93)	80 (70-91)
Diclofenac	50	150 bid	0	101 (79-126)	98 (75-129)
Digoxin	0.25 qd[i]	150 bid	0	103 (86-122)	107 (87-130)
Enoxaparin	40 qd[k]	220	-24	84 (67-105)	86 (67-110)
Ranitidine	150 qd[l]	200	-10	102	100
Pantoprazole	40 mg bid[m]	150	-1	72 (57-90)	60 (46-79)

[a] Difference between time of administration of perpetrator and victim [b] point estimates based on geometric mean ratios and 90% CI [c] study prematurely terminated because of intolerance of quinidine sulfate [d] trough concentrations, [e] 200 mg q2h [f] film coated tablet [g] loading dose =300 mg [h] days [i] after a loading dose of 0.5 mg [k] after sc administration [l] 2 day pre-treatment [m] 2 day pretreatment fasted or fed ND=not determined

The verapamil study identified the typical co-factors important for drug interaction studies such as the time interval between administration of perpetrator and victim, dose, formulation (IR vs. ER) and the impact of acute vs. multiple dose co-administration of the perpetrator. The greatest increase in exposure to dabigatran is observed when a single dose of verapamil as IR tablet is given 1 h prior to BIBR 1048 MS. The increase in exposure to dabigatran is smaller after concomitant administration of a single dose of a 240 mg ER tablet of verapamil and BIBR 1048 MS. The impact of verapamil (IR tablet 120 mg bid) administered 1 hour before BIBR 1048 MS is smaller than that after a single dose given 1 hour prior to BIBR 1048 MS. This is due to the known weakening of the P-gp inhibition by repeat administration of verapamil. Importantly, reversing the order of dosing, i.e. BIBR 1048 MS is given 2 h prior to verapamil (IR tablet, bid regimen), does not increase the exposure to dabigatran significantly. This finding indicates that impact of verapamil is restricted to inhibition of the intestinal P-gp and extrusion of BIBR 1048.

Thus, an interaction can be avoided entirely if BIBR 1048 MS is administered in the fasted state 2 hours prior to verapamil as food delays the absorption of BIBR 1048 MS.

Although not demonstrated experimentally it is likely that the effect of the P-gp inhibitors ketoconazole, quinidine and amiodarone is restricted as with verapamil to an inhibition of the intestinal extrusion of BIBR 1048. A 2.4 and 2.5 fold increase in exposure of dabigatran was observed following concomitant administration with ketoconazole 400 mg single dose and 400 mg QD for 8 days, respectively. The ketoconazole data show no mitigation of the P-gp effect on repeat administration.

Amiodarone not only inhibits the extrusion of BIBR 1048 as shown by the increased net exposure, but also increases the renal clearance of dabigatran to 165%. The increase in exposure to dabigatran despite the increased renal clearance suggests that the true inhibition of the intestinal extrusion of BIBR 1048 by amiodarone must be similar to that of ketoconazole.

The observed increase in the clotting times with verapamil, quinidine, and amiodarone are consequential to the increase in exposure to dabigatran. The regression parameters of the effect-concentration relationship of BIBR 953 ZW in presence and absence of the co-administered drugs are comparable indicating absence of a pharmacodynamic interaction.

Not all tested P-gp inhibitors inhibit extrusion of the P-gp substrate BIBR 1048 *in vivo*. Atorvastatin and clarithromycin have no impact on the exposure to dabigatran indicating that the selection of P-gp inhibitors to be studied *in vivo* cannot be based on *in vitro* data.

The P-gp inducer rifampicin decreases AUC and Cmax of dabigatran clinically significantly and the dose of BIBR 1048 MS should be increased accordingly. Residual induction of P-gp by rifampin is measurable after a washout of up to 14 days.

Loading doses of 300 or 600 mg clopidogrel increase the exposure to dabigatran marginally. An increase in Tmax of BIBR 953 ZW or a smaller Cmax is not observed casting doubt on the relevance of the *in vitro* found inhibition of carboxylesterases for the *in vivo* situation. No interaction is seen with the clopidogrel maintenance dose of 75 mg QD. No dose adjustment of BIBR 1048 MS is required. The mechanism responsible for the increased exposure to dabigatran in the presence of clopidogrel administered in loading doses of 300 mg or 600 mg is unclear. *In vitro* clopidogrel inhibits the hydrolysis of the precursors of dabigatran so that in vivo a delayed and mitigated peak exposure to dabigatran is expected. However, in the presence of clopidogrel neither a lower peak concentration nor an increase in Tmax of dabigatran is observed *in vivo* suggesting that a mechanism other than inhibition of the hydrolysis of the precursors of dabigatran is responsible for the observed interaction *in vivo.*

A 3 day pretreatment with enoxaparin has no impact on the exposure to dabigatran. The anti-FIIa/anti-FXa activity of dabigatran 24 h after the last dose of enoxaparin is increased, but this may be due to residual activity of enoxaparin. The anti-FIIa/anti-FXa activity after enoxaparin alone was not assessed.

Impact of Dabigatran on Exposure to Co-Administered Drugs

The impact of dabigatran on the exposure to the tested co-administered drugs is summarized in the below table:

Table 4. Impact of Dabigatran on Exposure to Other Drugs

Other Drugs		**Dabigatran Etexilate**	**ΔTime[a]**	**Rel. Exposure to Other Drug in Presence of Dabigatran**	
	Oral Dose mg	**Oral Dose mg**	**h**	**AUC[b] %**	**Cmax[b] %**
Amiodarone	600	150 bid	0	110 (84-145)	112 (82 -153)
Desethylamiodarone				93 (71-120)	90 (70-117)
Atorvastatin	80 qd	150	0	117 (105-132)	106 (90-125)
2-OHAtorvatatin				98 (86-111)	84 (69-103)
4-OHAtorvastatin				115 (102-131)	107 (90-127)
Clarithromycin	500 bid	150	-1	102 (85-109)	107 (98-118)
Clopidogrel	75 qd	150 bid	0	115 (104-127)	108 (87-134)
	600[c]	150 bid	0	103 (80-131)	100 (67-148)
Enoxaparin	40 qd[d]	220	-24	ND	ND
Diclofenac	50	150 bid	0	89 (79-100)	85 (66-110)
4'-OHDiclofenac				88 (83-93)	83 (72-96)
Digoxin	0.25 qd[e]	150 bid	0	101 (97-104)	114 (105-123)
Ketoconazole	400	150	0	ND	ND
	400 qd	150	0	ND	ND
Quinidine 1	600	150 bid	-1	ND	ND
Quinidine 2	1000[f]	150	-1	111 (104-118)	99 (93-106)
3-Hydroxyquinidine				103	ND
Rifampin	600 qd	150	-12	ND	ND
R/S Verapamil	120 IR bid	150	-1	106	106
R/S Norverapamil	120 IR bid	150		106	106
R/S Verapamil	120 IR bid	150	+2	98	94
R/S Norverapamil	120 IR bid	150		102	99
R/S Verapamil	120 IR	150	-1	112 (102-124)	115 (97-137)
R/S Norverapamil				107 (102-112)	108 (96-121)
R/S Verapamil	120 IR	150	0	105	102
R/S Norverapamil				101	101

[a] difference between time of administration of perpetrator and time of administration of dabigatran etexilate [b] point estimates based on geometric mean ratios and 90% CI [c] loading dose of 300 mg [d] after sc administration [e] after a loading dose of 0.50 mg [f] 200 mg q2 h ND=not determined

Platelet aggregation inhibition and increased bleeding time by clopidogrel are not impacted by the presence of dabigatran.

RE-LY Study

The major findings are:

- The mean exposure to dabigatran increases to 123% in patients on verapamil.
- The mean exposure to dabigatran increases to 112% in patients on amiodarone.
- The mean exposure to dabigatran decreases to 15% in patients on PPI including pantoprazole

Comparison between Findings of Dedicated Drug Interaction Studies- and RE-LY Trial

In the RE-LY study the exposure to dabigatran increases to 123% in patients on verapamil 1, 2,3 6 an 12 months after initiation of the dabigatran treatment. .In the dedicated study dabigatran was co-administered after a 2 day pre-treatment with verapamil. The discrepancy between the values obtained in the two studies is caused by the longer duration of the verapamil treatment in the RE-LY study resulting in a more pronounced mitigation of the P-gp inhibitory effect on BIBR 1048 BS. The cause for the similarly smaller impact of amiodarone on the exposure to dabigatran in the RE-LY is not known. It may be speculated that amiodarone, similar to verapamil, exhibits a time dependent mitigated inhibitory effect on P-gp after long term exposure. Alternatively, an extended co-administration of amiodarone could augment the renal clearance of dabigatran more than a single dose.

Dose Adjustments

P-gp inhibitors

Based on the cut-off set, i.e. a > 2.5 fold or a >150% increase in exposure to dabigatran, no dose adjustment of dabigatran is necessary when verapamil ketoconazole, quinidine or amiodarone is co-administered.

P-gp inducer

The dose of dabigatran needs to be increased 3 fold in patients on rifampicin. In patients on dabigatran the dose of dabigatran should be increased 6 days after initiation of a treatment with rifampicin.

Avoidance of Co-administration

Co-administration of untested P-gp inhibitors and -inducers and dabigatran should be avoided.

Deficiencies

- Amiodarone increases the renal clearance of dabigatran significantly. Whereas the inhibition of P-gp is responsible for the increased bioavailability of BIBR 1048 BS, the mechanism responsible for the increased renal clearance of dabigatran by amiodarone is not known. Because amiodarone is one of the most prescribed antiarrhythmics, the mechanism responsible for the increased renal clearance of dabigatran in the presence of amiodarone should be identified. The structurally related dronedarone should be included in the *in vitro* studies.
- In vitro studies show an inhibition of carboxylesterase mediated hydrolysis of the precursors of dabigatran by clopidogrel. However, an increase in tmax of BIBR 953 ZW or a smaller Cmax is not observed *in vivo* casting doubt on the relevance of the *in vitro* found inhibition of carboxylesterases for the *in vivo* situation. The mechanism responsible for the increase in exposure of dabigatran observed in the presence of loading doses of clopidogrel remains to be demonstrated.

3.5 General Biopharmaceutics

3.5.1 What is the quantitative and qualitative composition of formulation?

The final marketing image will be a HPMC capsule shell (b) (4)

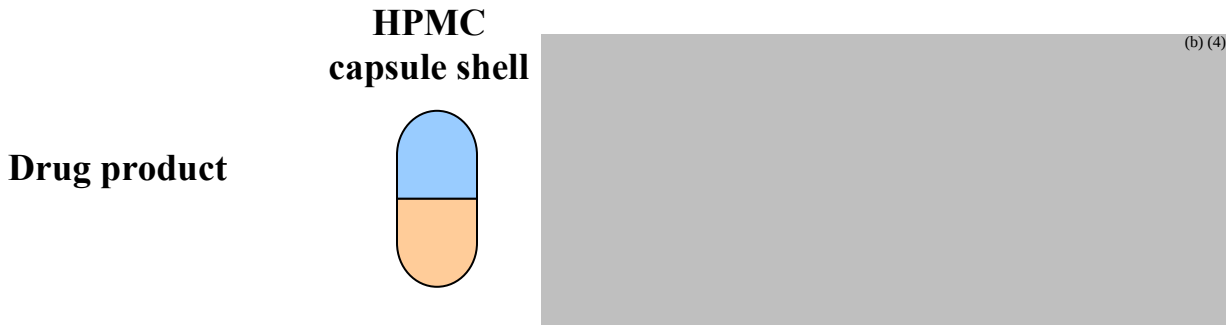


Figure 9: Final marketing image of dabigatran etexilate capsules

The composition of dabigatran etexilate capsules are shown in the table below:

Table 5 Composition of final marketing image of dabigatran etexilate capsules. *Note*: 75 mg dose is not filed for approval.

Ingredient	Amount [mg] per 75 mg capsule	Amount [mg] per 110 mg capsule	Amount [mg] per 150 mg capsule
Dabigatran etexilate mesilate	86.48 (1)	(b) (4)	172.95 (3)
(b) (4)			
Acacia			(b) (4)
Tartaric acid, (b) (4)			
(b) (4)			
Hypromellose			
Dimeticone			
Talc			
(b) (4)			
Hydroxypropylcellulose			
HPMC capsule (8) (imprinted with Black ink (b) (4)			
Total Weight	**276.2**	(b) (4)	**522.4**

(1) Equivalent to 75 mg free base.
(b) (4)
(3) Equivalent to 150 mg free base.
(b) (4)
(8) Carrageenan, potassium chloride, titanium dioxide, FD&C Blue 2 (b) (4), FD&C Yellow 6 (b) (4) (b) (4) hypromellose, (b) (4)
(b) (4)

What is the relative bioavailability of the proposed to-be-marketed formulation to the pivotal clinical trial?

The sponsor carried out two pivotal bioequivalence studies to compare the RE-LY trial formulation with the final marketing image formulation. The first study compared 1st and 2nd generation drug products and the second study compared 100% of polymorph I and II manufactured as a 2nd generation drug product. The results of both studies are shown in Figure 15 below.

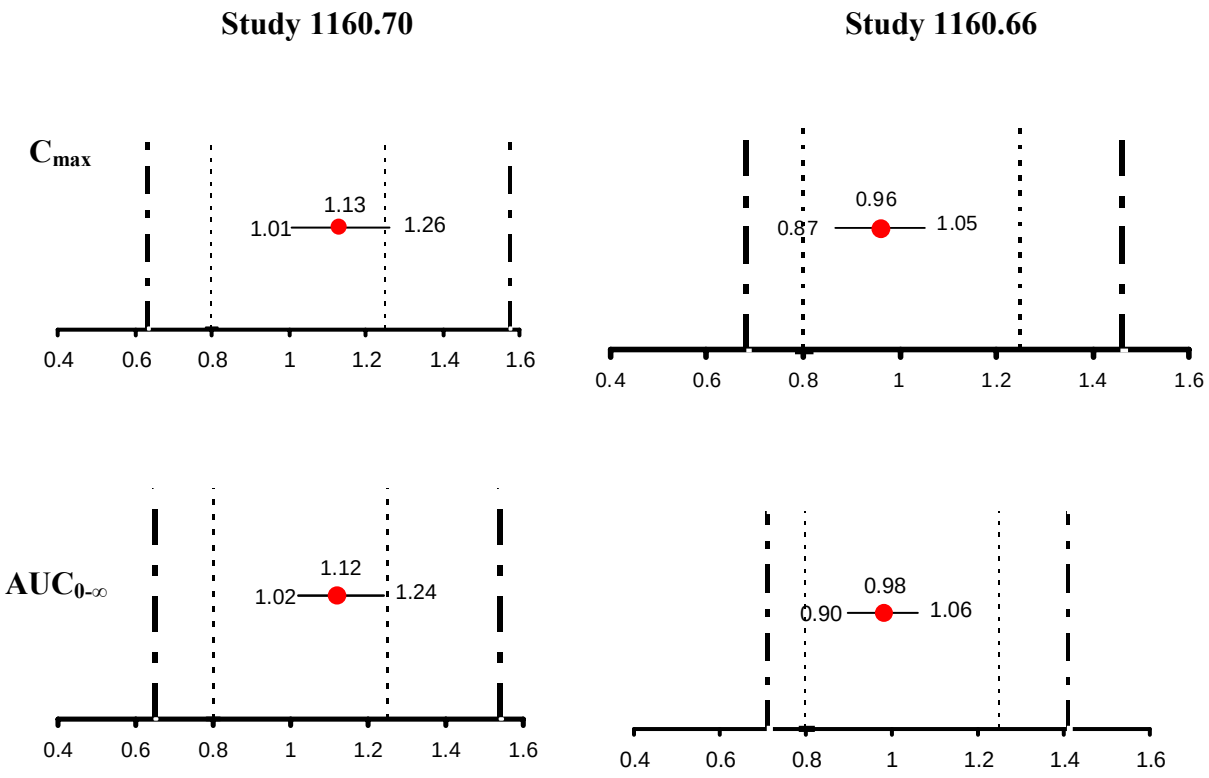


Figure 15: X-axis represents the geometric mean ratios. The fine and bold broken vertical lines represent the unscaled and scaled average bioequivalence limits. Data is represented as geometric mean ratio of the PK metrics (C_{max}, $AUC_{0-\infty}$) with 90% CI around the point estimate.

For Study 1160.70, the upper 90% confidence interval for C_{max} just exceeded the upper bioequivalence limit of 1.25. It should be noted that the sponsor has used a scaled average bioequivalence approach as the primary analysis and prospectively powered. The power to reject null hypothesis using an unscaled bioequivalence approach is less than 75%. Given the high within subject variability of dabigatran (40-50%) and the nature of the study design, it can be concluded that the 1st and 2nd generation drug products are bioequivalent. Bioequivalence was also established between polymorphs I and II (Study 1160.66); hence, the composition of these polymorphs in the final marketing image formulation is not a concern.

3.5.2 What is the effect of food on the bioavailability (BA) of the drug from the dosage form? What dosing recommendation should be made, if any, regarding administration of the product in relation to meals or meal types?

When dabigatran was coadministered with high-fat meal, there was no change in C_{max} and 18% increase in $AUC_{0-\infty}$ of total dabigatran (Figure below). The time to reach peak concentration (T_{max}) was delayed from 2 h to 4 h because of a high fat meal. This slight increase in $AUC_{0-\infty}$ is not of clinical relevance. In addition, another food effect study which used gelatine capsule shell of dabigatran etexilate as the formulation showed no change in either C_{max} or $AUC_{0-\infty}$ of dabigatran. Therefore, dabigatran etexilate capsules can be administered without regard to food. (*Note*: Exposures of HPMC and gelatine capsule shell of dabigatran etexilate are similar).

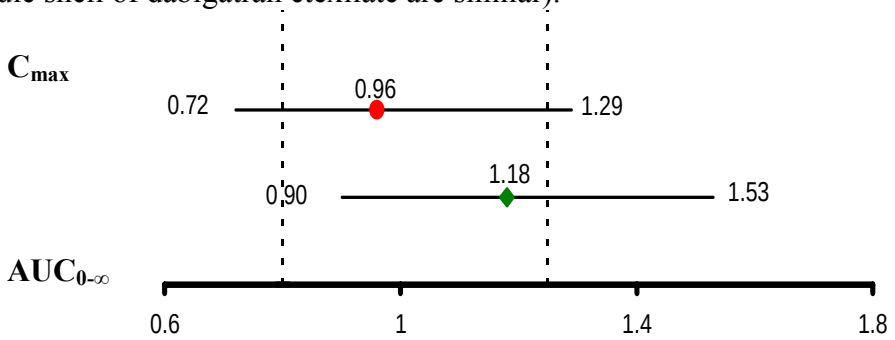


Figure 16 : Effect of a high fat meal on total dabigatran exposure. X-axis represents the geometric mean ratios. The fine broken vertical lines represent 80-125% limits. Data is represented as geometric mean ratio of the PK metrics (C_{max}, $AUC_{0-\infty}$) with 90% CI around the point estimate.

3.5.3 Can capsule shell be opened and pellets ingested as such?

Relative bioavailability of total dabigatran increased by 40% when HPMC capsule shell formulation was opened and pellets ingested as such (Figure below). Therefore, the capsules should not be opened and pellets ingested as such. (*Note*: Though the pellet formulation was provided with food, the increase in exposure is unlikely due to the food effect since it was just administered with one teaspoon of baby cereal).

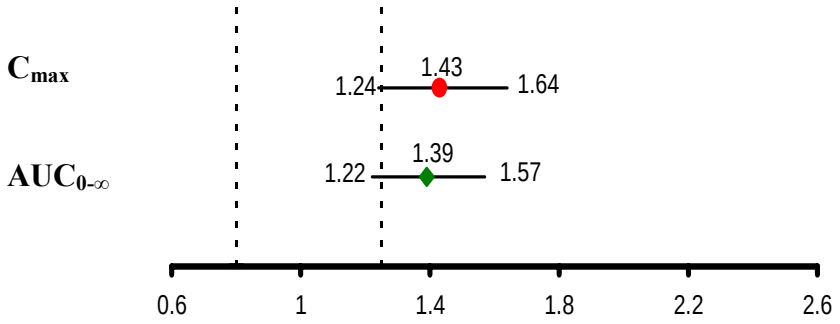


Figure 17: Relative bioavailability of total dabigatran when administered as pellets when compared to pellets in capsules. X-axis represents the geometric mean ratios. The fine broken vertical lines represent 80-125% limits. Data is represented as

geometric mean ratio of the PK metrics (C_{max}, $AUC_{0-\infty}$) with 90% CI around the point estimate.

3.5.4 How the elevated gastric pH affect the dabigatran bioavailability

The effect of PPIs and ranitidine are discussed in detail in Section 2.1.4

3.6 Analytical section

3.6.1 How the active moieties are identified and measured in the plasma in the clinical pharmacology and biopharmaceutics studies?

A validated the HPLC coupled with tandem mass spectrometry methods were used for the quantitation of free dabigatran (BIBR953ZW) and total dabigatran after alkaline cleavage of conjugates (SUM BIBR953ZW, sum of free, non-conjugated drug plus glucuronic acid conjugated dabigatran) in human plasma and urine. Since the dabigatran glucuronides have similar pharmacodynamic activity as dabigatran itself, total dabigatran was considered the primary measurement for the assessment of dabigatran pharmacokinetics, and it is presented in the majority of the individual study reviews.

3.6.2 What is the range of the standard curve? How does it relate to the requirements for clinical studies? What curve fitting techniques are used?

The assay methods were repeatedly cross validated for different laboratories (Boehringer Ingelheim Germany (BI), at AAI Pharma, Germany (AAI) and at Nippon Boehringer Ingelheim, Japan (NBI))
In BI and AAI methods, samples were extracted by on-line solid phase extraction and assayed on an analytical reversed phase column in gradient mode. Concentration ranges for the calibration curves were from 1.00 – 400 ng/mL for both plasma and urine and from 0.100 - 40.0 ng/mL for dialysate. The NBI methods used a solid phase extraction procedure on Oasis HLB material followed by chromatography on a reversed phase analytical column in isocratic mode. Concentration ranges for the calibration curves were from 1.00 – 400 ng/mL and 2.00 - 2000 ng/mL for plasma and urine, respectively.
These standard curves covered all possible dabigatran concentrations measured in clinical studies.

3.6.3 What analytical methodologies were used to assess pharmacodynamic action?

Pharmacodynamic measurements of coagulation parameters (aPTT, ECT, INR, and TT) were performed in majority of clinical pharmacology studies.

Activated Partial Thromboplastin Clotting Time (aPTT)

A mixture of cephalin and microcrystalline kieselguhr was added to plasma sample and incubated at 37°C. Then 0.025M $CaCl_2$ solution was added. The time lag between the addition of $CaCl_2$ and the clot formation was detected in seconds as aPTT.

Ecarin Clotting Time (ECT)

By adding Echis carinatus venom (Ecarin, 6 IU/mL) to human plasma, Prothrombin (F II) is activated into Thrombin (F IIa) when incubated at 37°C. The time lag between the addition of Ecarin and the clot formation was detected as ECT.

3.6.4 Were the validation characteristics of the assays acceptable?

Yes. In all studies the bioanalytical assays for the quantitation of free dabigatran (BIBR 953 ZW) and total dabigatran after alkaline cleavage of conjugates (SUM BIBR 953 ZW, sum of free, non-conjugated drug plus glucuronic acid conjugated dabigatran) in human plasma and urine have their validation reports, they are acceptable.

3.7 What is the overall conclusion regarding NDA 22-512?

Overall the Clinical Pharmacology and Biopharmaceutics section is acceptable provided the agreement with sponsor regarding specific labeling language and post-marketing requirements (see Section 1.1).

4 LABELING RECOMMENDATIONS *(Draft)*

- Severe renal impaired: Dabigatran 75 mg QD
- DDIs
  - Rifampin + Dabigatran: 3 capsules of Dabigatran 150 mg (450 mg)
- Patients older than 75 years of age with concomitant aspirin: Dabigatran 110 mg
- Co-administration of untested P-gp inhibitors and inducers and dabigatran should be avoided.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22512	ORIG-1	BOEHRINGER INGELHEIM PHARMACEUTICALS INC	PRADAXA (DABIGATRAN ETEXILATE MESYLATE)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ELENA V MISHINA
08/16/2010

PETER H HINDERLING
08/17/2010

SUDHARSHAN HARIHARAN
08/17/2010

MICHAEL A PACANOWSKI
08/17/2010

KEVIN M KRUDYS
08/17/2010

ISSAM ZINEH
08/17/2010

PRAVIN R JADHAV
08/17/2010

RAJANIKANTH MADABUSHI
08/17/2010
Concur.
Note: On page 30 Section 3.4.1 line 3, the sentence should read "...corresponding to 110 mg BID..."

OFFICE OF CLINICAL PHARMACOLOGY: PHARMACOMETRIC REVIEW

1 SUMMARY OF FINDINGS

1.1 Key Review Questions

The purpose of this review is to address the following key questions.

1.1.1 Is the 150 mg twice daily dose appropriate?

Dabigatran 150 mg BID is safe and effective for prevention of stroke in subjects with non-valvular atrial fibrillation. There is evidence that a dose higher than 150 mg twice daily may provide a more optimal risk/benefit profile for treatment of subjects with non-valvular atrial fibrillation. This conclusion is based on the following:

- The RE-LY trial has not established the 150 mg twice daily dose as achieving the maximum benefit in terms of reduction of stroke. There was a significant dose-dependent decrease in occurrence of ischemic stroke from the 110 mg to the 150 mg dose (1.3%/year to 0.9%) even though there was a two-thirds overlap in observed dabigatran concentration in the two doses. Therefore, these results are suggestive of the possibility of more reduction in stroke at higher dabigatran doses.
- A relationship between dabigatran trough concentration and probability of ischemic stroke has been established. Simulations predict additional reduction in occurrence of ischemic stroke at higher doses (Table 1).
- A relationship between dabigatran trough concentration and probability of life-threatening bleeding has also been established. Simulations predict an increase in major bleeding events at higher doses (Table 1). At a dose of 300 mg, the predicted rate of life-threatening bleeds approximates the rate calculated for the warfarin arm in RE-LY.
- Major bleeding events may not represent an appropriate marker of risk in this patient population. Life-threatening bleeds represent a more severe condition than major bleeding events and are possibly more relevant to dose exploration. The major bleeding events were primarily gastrointestinal and the life threatening bleeding events were lower on dabigatran as compared to warfarin. Hemorrhagic stroke occurred in 14 subjects on 110 mg (0.12%/year), 12 subjects on 150 mg (0.10%/year) and 45 subjects on warfarin (0.38%/year). Fatal bleeding events also occurred more frequently on warfarin (8.6% of major bleeds) than on dabigatran (6.6% for 110 mg BID and 6.1% for 150 mg BID).
- A favorable benefit-risk assumes that the prevention of an ischemic stroke is more important than a life-threatening bleeding event.

Table 1. Predicted probability of ischemic stroke and life-threatening bleed within 1 year in a typical patient

Dose	Probability of Ischemic Stroke within 1 year (%) [90% CI]	Probability of Life-Threatening Bleed within 1 year (%) [90% CI]
110 mg	0.79% [0.61% – 0.96%]	0.63% [0.46% – 0.80%]
150 mg	0.72% [0.56% - 0.89%]	0.83% [0.63% – 1.03%]
220 mg	0.66% [0.48% - 0.84%]	1.13% [0.85% – 1.41%]
260 mg	0.63% [0.44% - 0.82%]	1.30% [0.96% – 1.64%]
300 mg	0.61% [0.41% - 0.81%]	1.46% [1.06% – 1.87%]
Warfarin	0.96%	1.41%

1.1.2 Do the exposure-response relationships suggest dose adjustments in special population?

A dose reduction from 150 mg to 110 mg twice daily in patients at high risk, specifically patients older than 75 years of age is expected to decrease the risk of major bleeding (Table 2). The absolute risk of major bleeding, however, will still be elevated relative to a typical patient.

Table 2. Predicted probability of major bleed by age in for patients receiving 110 mg and 150 mg dabigatran

Age (years)	Probability of Life-Threatening Bleed within 1 year (%)	
	110 mg	150 mg
75	0.76%	1.00%
80	1.03%	1.36%
85	1.40%	1.86%
90	1.91%	2.52%

1.1.3 What is the impact of dabigatran and warfarin on liver function?

Dabigatran and warfarin were found to have a similar impact on liver function as measured by the proportion of subjects with AST or ALT > 3x ULN or bilirubin > 2xULN. The incidence of these events was less than 1% at any given visit in the 110 mg dabigatran, 150 mg dabigatran and warfarin treatment arms in RE-LY. Historical data from the Sportif 3 and Sportif 5 trials with ximelagatran were also examined as a positive control because ximelagatran is known to have adverse effects on liver function. The percentage of subjects receiving ximelagatran in these trials and having ALT and AST > 3x ULN at any given time was much higher, 3-7% and 1-3%, respectively. The warfarin

treatment arms in the Sportif 3 and Sportif 5 trials were quantitatively similar to the warfarin treatment arm in RE-LY.

1.2 Recommendations

- Dabigatran 150 mg BID is safe and effective for prevention of stroke in subjects with non-valvular atrial fibrillation and should be approved.
- The 110 mg dose can be given to mitigate the risk of bleeding in patients at high risk of bleeding, specifically patients older than 75 years of age.
- The RE-LY trial provides evidence to believe that dabigatran dose higher than 150 mg twice daily may provide more benefit in terms of reduction of stroke with bleeding risk approximately similar to the risk on warfarin treatment.

2 PERTINENT REGULATORY BACKGROUND

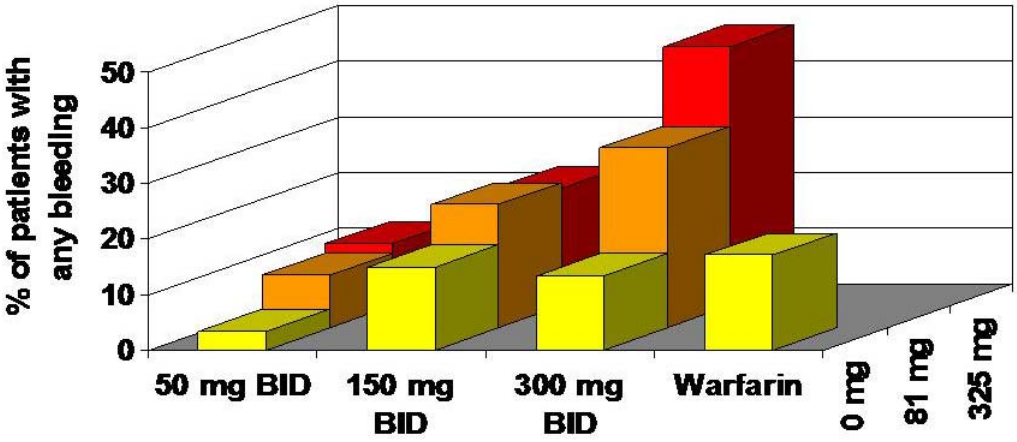
Dabigatran etexilate is a prodrug of dabigatran, a competitive, reversible direct thrombin inhibitor being developed for the prevention of stroke, non-CNS systemic embolism and reduction of vascular mortality in subjects with non-valvular atrial fibrillation. The proposed dose is 150 mg twice daily. The current submission includes the results of a single pivotal efficacy and safety trial (RE-LY) comparing dabigatran (110 and 150 mg twice daily) to warfarin titrated to a target INR of 2 to 3.

3 RESULTS OF SPONSOR'S ANALYSIS

3.1.1 Dose Selection

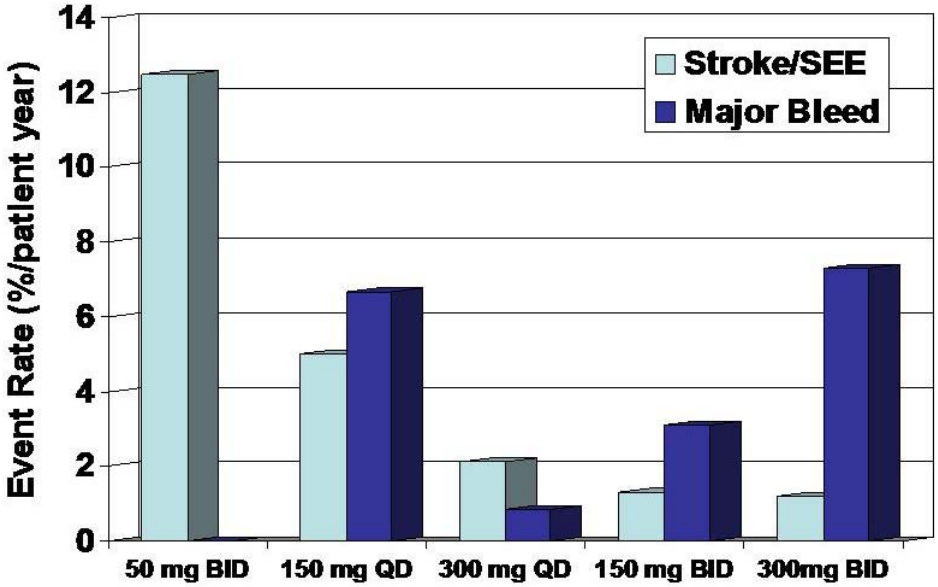
The dose ranging PETRO study randomized 502 subjects with chronic atrial fibrillation to 12 weeks treatment of 50, 150 or 300 mg dabigatran twice daily combined with 0, 81 or 325 mg aspirin in a factorial design with an additional arm of subjects treated with warfarin adjusted to INR 2 to 3. In the absence of aspirin, bleeding rates with the 150 mg dose were similar to those for the 300 mg dose and for warfarin. An increase in concomitant dose of aspirin increased the bleeding rate in all dabigatran treatment arms (Figure 1). Bleeding rates in the 300 mg dose arm with 81 or 325 mg aspirin were deemed unacceptably high.

Figure 1: Percentage of patients with any bleeding events in PETRO



The PETRO Extension (PETRO-Ex) trial was an open label, up to 5 year follow up to the PETRO study including 50 mg, 150 mg and 300 mg twice daily and 150 mg and 300 mg once daily doses with additional aspirin at the discretion of the investigator. The incidences of stroke/SEE and major bleeds are displayed in Figure 2.

Figure 2: Event Rate for Stroke/SEE and Major Bleeds in PETRO Ex



The stroke/SEE event rate was deemed unacceptably high in the 50 mg and 150 mg twice daily arms. The sample size in this study is too small to detect differences between the event rates in the other dose arms. Likewise, major bleeds were deemed high on the 300 mg twice daily arm. The 150 twice daily dose was therefore judged to provide an acceptable risk/benefit profile and chosen for further study. A 110 mg dose would be expected to provide fewer bleeds compared to the 150 mg dose and was therefore also chosen for the Phase 3 RE-LY study.

3.2 Phase 3 Study

RE-LY (Study 1160.26) Exposure-Response Data

RE-LY was a randomized, open-label trial of stroke prevention in subjects with nonvalvular atrial fibrillation and at least one risk factor for stroke. A total of 18,113 subjects were randomized to one of two blinded doses of dabigatran (110 mg or 150 mg twice daily) or to warfarin titrated to a target INR of 2 to 3. The population included balanced proportions of Vitamin K antagonist (VKA) naïve and VKA-experienced subjects. The primary endpoint was stroke (including hemorrhagic) and non-CNS systemic embolism (SEE). The results are presented in Table 3. A secondary endpoint was a composite of stroke, SEE and all cause death. Safety endpoints included bleeding and liver function abnormalities. Major bleeding was defined as bleeding associated with a reduction in hemoglobin levels of at least 20 g/L or leading to a transfusion of at least 2 units of blood or packed cells or symptomatic bleeding in a critical area or organ.

Table 3. Components of Efficacy Endpoint in RE-LY

	Dabigatran 110 N (%)	Dabigatran 150 N (%)	Warfarin N (%)
Subject years of follow up	11521	11658	11348
Subjects with stroke/SSE	183 (1.6)	134 (1.1)	202 (1.8)
Subjects with stroke	171 (1.5)	122 (1.0)	186 (1.6)
Ischemic	152 (1.3)	103 (0.9)	134 (1.2)
Hemorrhagic	14 (0.1)	12 (0.1)	45 (0.4)
SSE	15 (0.1)	13 (0.1)	21 (0.2)

The protocol allowed for collection of pre-dose and post-dose (2 hours after dose) samples for pharmacokinetic and pharmacodynamic evaluation at visit 4 after one month of treatment with 110 mg or 150 mg of dabigatran. Additional samples were obtained at 3, 6 and 1 months from subjects (N=2,143) who participated in a PK sub-study. Approximately 12% of observations were excluded from analysis due to questionable blood sampling or administrative date/time. Pre-dose samples were included in the analyses if they were collected within 10 to 16 hours after the previous dabigatran dose and post-dose samples were included if they were collected 1 to 3 hours after the dabigatran dose. The final dataset included pre-dose concentrations in 4223 subjects and post-dose concentrations in 4579 subjects receiving either 110 mg or 150 mg dabigatran.

3.3 Exposure-Response Analysis

To investigate potential relationships between dabigatran exposure and outcome events in RE-LY, descriptive statistics of concentrations in subjects with and without outcome events were summarized (Table 4). There was no trend between geometric mean plasma

concentration and the occurrence of the primary efficacy endpoint. For the two specified secondary efficacy endpoints, subjects who had an event had 18% higher pre-dose and 8% higher post-dose concentrations than subjects who did not have an event. Concentrations were higher in subjects with hemorrhagic stroke than subjects without (136 ng/mL vs. 76.5 ng/mL in pre-dose and 202 ng/mL vs. 148 ng/mL in post-dose concentrations). Pre-dose and post-dose concentrations were 57% and 37% higher, respectively, in subjects with a major bleed event than in subjects without any bleeding event. Logistic regression analysis was also explored as a tool to identify relationships between dabigatran concentration and efficacy or safety events.

Table 4: Trough plasma concentration of total dabigatran grouped by event occurrence

	Trough plasma concentration ($C_{pre,ss}$) of total dabigatran [ng/mL]								
	Major bleed	Any bleed	No bleed	Prim. (+)	Prim. (-)	Sec.1 (+)	Sec.1 (-)	Sec.2 (+)	Sec.2 (-)
N	297	2305	5901	128	8244	385	7784	388	7861
gMean	114	86.8	72.8	77.3	76.4	89.0	75.3	88.1	75.5
gCV [%]	79.8	81.4	84.0	82.4	83.9	83.9	83.3	89.2	83.1
Mean	142	111	92.4	98.2	97.5	115	95.7	116	95.9
CV [%]	69.4	75.0	73.5	70.9	74.9	77.6	74.1	82.5	73.6
SD	98.7	82.9	67.9	69.6	73.1	88.9	71.0	95.7	70.6
Min	5.22	3.22	1.04	9.80	1.04	9.80	1.04	5.34	1.04
10th percentile	46.7	35.6	30.7	28.2	32.1	33.7	31.8	31.2	32.0
1st quartile	74.6	54.9	48.1	50.3	49.9	55.7	49.4	54.5	49.6
Median	117	88.0	75.3	81.0	78.3	91.4	77.6	91.2	77.6
3rd quartile	184	143	115	128	122	146	119	151	119
90th percentile	270	211	175	185	186	226	181	231	181
Max	757	757	809	421	809	809	761	809	761

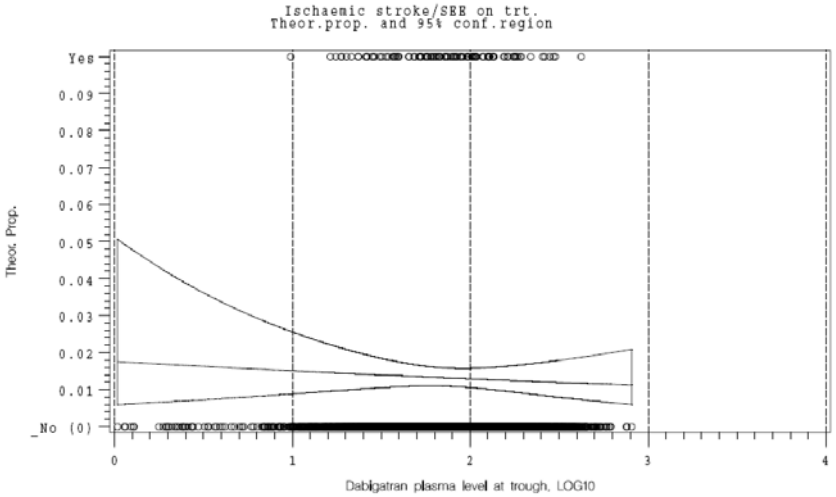
Source data: Table 15.6.3: 1
Prim.: primary endpoint (stroke, systemic embolism)
Sec.1: secondary endpoint 1 (stroke, systemic embolism, all death)
Sec.2: secondary endpoint 2 (stroke, systemic embolism, pulmonary embolism, myocardial infarction, vascular deaths)
(+): with event on treatment, (-): without event

Source: Clinical Study Report, P-167, Table 11.5.2.3:1.

Efficacy

The logistic regression analysis did not reveal a trend between plasma concentrations and the occurrence of ischemic stroke and SEE (Figure 3). The sponsor concluded that dose is a better predictor with respect to efficacy than concentration.

Figure 3: Probability of ischemic stroke and SEE vs. log trough plasma concentration of dabigatran in RE-LY

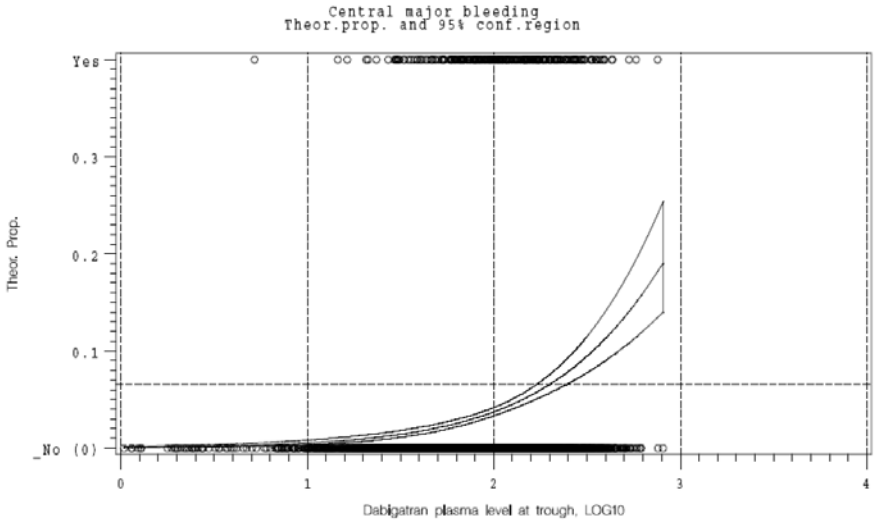


Source: Clinical Overview P-33, Figure 2.5.3.4.5: 3

Safety

The logistic regression analysis revealed a significant relationship between dabigatran concentrations and the occurrence of a major bleeding event (Figure 4). Sex, aspirin use and age were also identified as significant covariates, with females having a lower risk of and elderly (>75 years) and those with concomitant aspirin use having a higher risk of major bleed. An increase in dabigatran plasma concentration by a factor of 10 in subjects without concomitant aspirin use had an odds ratio for a major bleeding event of 5.92 (95% CI: 3.80 – 9.21).

Figure 4: Probability of major bleeds vs. log trough plasma concentration of dabigatran in RE-LY



Source: Re-LY Clinical Study Report P-169 Figure 11.5.2.3:3

Reviewer's Comments: The lack of a relationship between dabigatran concentration and ischemic stroke is surprising in light of the significant dose relationship. Possible explanations for this finding are the relatively small number of overall events and the limited range of doses studied in RE-LY. Also, dabigatran concentration is also positively correlated with factors which may increase the risk of ischemic stroke, such as age and creatinine clearance. A limitation of the logistic regression analysis performed by the sponsor is that it does not take into account the time to event. Subjects in RE-LY were not on study medication for the same amount of time, so treating the outcome as binary may result in the loss of important information.

4 REVIEWER'S ANALYSIS

4.1 Introduction

An independent analysis was conducted to explore potential relationships between dabigatran exposure and efficacy and safety events in RE-LY using a time to event analysis. As part of the safety analysis, the impact of dabigatran and warfarin on liver function tests was explored because dabigatran is chemically similar to ximelagtran, a compound known to have deleterious effects on the liver.

4.2 Objectives

Analysis objectives are:

1. Establish a relationship between dabigatran concentration and the probability of ischemic stroke
2. Establish a relationship between dabigatran concentration and the probability of a life-threatening bleed
3. Use exposure-response relationships to explore the impact of different doses on efficacy and safety events
4. Explore the time-courses of liver function tests in dabigatran and warfarin treated subjects in RE-LY in comparison to ximelagtran and warfarin in the Sportif trials.

4.3 Exposure-Efficacy Analysis

Time to first ischemic stroke was chosen as the efficacy endpoint because ischemic stroke dictated the majority of efficacy outcomes and showed a dose-response relationship. An initial plot of the time to ischemic stroke stratified by trough dabigatran quartile, however, did not suggest a relationship between dabigatran concentration and time to an ischemic stroke. A univariate time to event analysis also did not identify dabigatran concentration as a significant risk-factor. This could be expected because dabigatran concentrations are strongly correlated with other risk factors, such as age and creatinine clearance. For example, as age increases, the risk of stroke is expected to increase, even though dabigatran concentrations increase. To dissect the influence of these confounded factors, warfarin-treated subjects in RE-LY were simultaneously included in the exposure-efficacy analysis. These subjects are titrated to INR of 2 to 3, which allows for the evaluation of other risk factors like age and weight on ischemic stroke independent of warfarin exposure. These other risk factors are assumed to influence the risk of ischemic stroke in warfarin- and dabigatran-treated patients equally.

4.3.1 Data

The dataset used for the exposure-efficacy analysis comprised all warfarin patients and all dabigatran-treated patients for whom there were trough dabigatran measurements and complete covariate and ischemic stroke information. A total of 13,884 subjects were included in the final dataset. To approximate an on-treatment analysis, the time from first dose of study medication to last dose of study medication + 5 days was considered. If an outcome event did not occur during that timeframe, the time was censored at the last dose of study medication. Only time to first event was considered. For the exposure-efficacy analysis, the following risk factors were explored: treatment (warfarin or dabigatran), trough dabigatran concentration, age, sex, weight, history of stroke/TIA, diabetes mellitus and age ≥ 65 years, coronary artery disease and age ≥ 65 years, hypertension and age ≥ 65 years, and aspirin use. Aspirin use was defined as > 90% aspirin use during treatment with dabigatran. The logarithm of trough dabigatran concentration was also considered. Concentrations in warfarin-treated subjects were set to zero (or a very small number, i.e., 0.001 when log-transformation was used).

4.3.2 Methods

Time to first occurrence of ischemic stroke was modeled with a Cox proportional hazards model: $\lambda(t|X) = \lambda(t)\exp(X\beta)$ where β is the coefficient describing risk factor X. After a univariate search, significant risk factors ($p<0.05$) were studied further in a forward inclusion step ($p<0.05$). A backwards deletion step was undertaken where risk factors were retained in the model at the significance level of $p<0.05$. A treatment by trough concentration interaction was included in the model. Estimation was conducted in SAS using the phreg function. Data manipulation and plotting were performed in R version 2.10.0.

4.3.3 Results

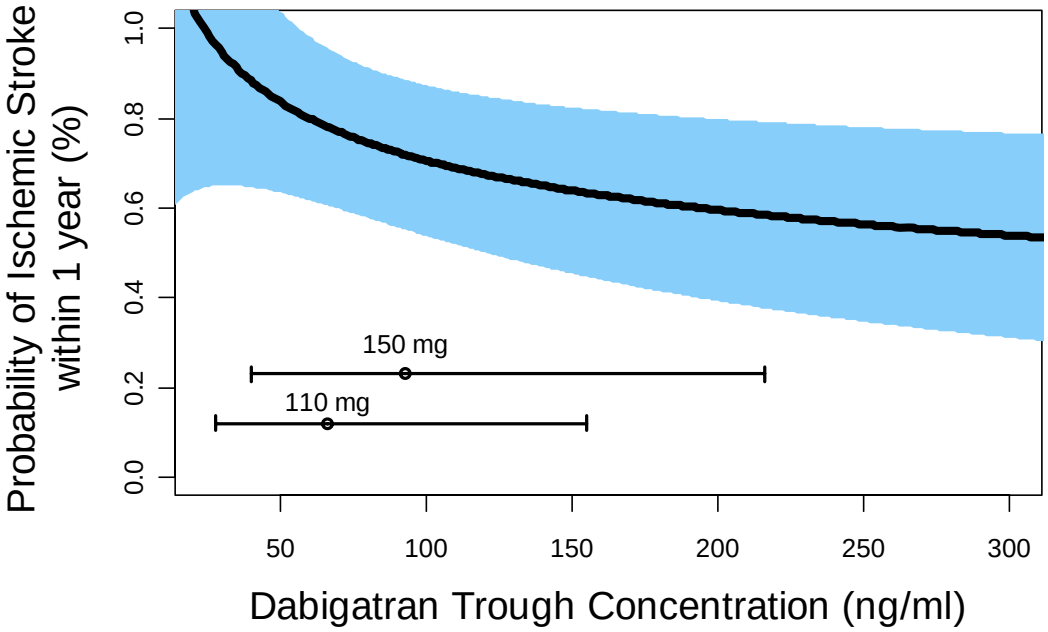
The exposure-efficacy analysis identified age, weight, history of stroke/TIA, diabetes mellitus and age ≥ 65 years and trough dabigatran concentration as significant risk factors. The parameter describing the relationship between dabigatran concentration and ischemic stroke was of marginal significance ($p=0.056$) but was included in the final model. Parameter estimates are presented in Table 5.

Table 5. Parameter estimates of the final ischemic stroke exposure-response model

Parameter	Estimate	Standard Error	p-value
Treatment	0.83	0.57	0.15
Weight	-0.014	0.0041	0.00053
Age	0.022	0.0090	0.015
History of Stoke/TIA	0.52	0.15	0.00038
Diabetes and Age ≥ 65 years	0.41	0.16	0.010
Treatment*log(trough concentration)	-0.25	0.13	0.056

The mean predicted probability of an ischemic stroke within one year was calculated. The results are illustrated in Figure 5. For 110 mg, 150 mg and 300 mg doses, the predicted probability of stroke in one year was 0.79%, 0.72% and 0.61%, respectively.

Figure 5. Probability of ischemic stroke within 1 year vs. dabigatran trough concentration. The blue shaded region represents the 95% confidence interval. The bars on the bottom on the plot region represent the 10th to 90th percentiles of observed dabigatran pre-dose concentrations in the RE-LY trial.



4.4 Exposure-Safety Analysis

Time to life-threatening bleed was chosen as the safety endpoint because it is expected to be related to dabigatran concentration and provided a more clinically serious endpoint than major bleed, although a similar relationship was found for major bleeding event. Warfarin data were found to be unnecessary for this analysis possibly because older age and poorer renal function are expected to increase dabigatran concentration *and* the risk of life-threatening bleed. When warfarin data were included in the analysis, the parameter estimates of the model did not change. Thus, for simplicity, only dabigatran data were included in the exposure-safety analysis.

4.4.1 Data

The dataset used for the exposure-safety analysis comprised all dabigatran-treated patients for whom there were trough dabigatran measurements and complete covariate and life-threatening bleed information. A total of 8432 dabigatran-treated subjects were included in the final dataset. To approximate an on-treatment analysis, the time from first dose of study medication to last dose of study medication + 5 days was considered. If an outcome event did not occur during that timeframe, the time was censored at the last dose

of study medication. Only time to first event was considered. For the exposure-safety analysis, the following risk factors were explored: trough dabigatran concentration, age, sex, weight, creatinine clearance, history of stroke/TIA, diabetes mellitus and age ≥ 65 years, coronary artery disease and age ≥ 65 years, hypertension and age ≥ 65 years, and aspirin use. Aspirin use was defined as > 90% aspirin use during treatment with dabigatran. The logarithm of trough dabigatran concentration was also considered.

4.4.2 Methods

Time to first occurrence of life-threatening was modeled with a Cox proportional hazards model: $\lambda(t|X) = \lambda(t)\exp(X\beta)$ where β is the coefficient describing risk factor X. After a univariate search, significant risk factors ($p<0.05$) were studied further in a forward inclusion step ($p<0.05$). A backwards deletion step was undertaken where risk factors were retained in the model at the significance level of $p<0.05$. Estimation was conducted in SAS using the phreg function. Data manipulation and plotting were performed in R version 2.10.0.

4.4.3 Results

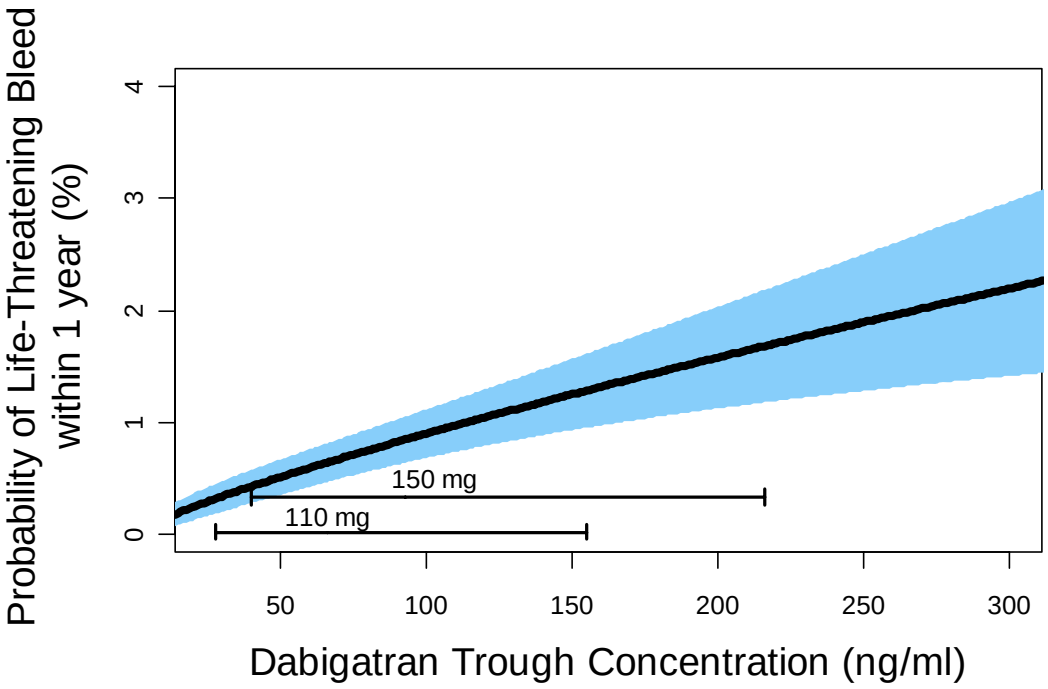
The exposure-efficacy analysis identified age, sex, trough dabigatran concentration, history of stroke/TIA and coronary artery disease and age ≥ 65 years as significant risk factors. These results are similar to the analysis conducted by the sponsor. Aspirin use was not identified as a significant covariate due to the strict definition (>90% use). If aspirin use was defined as (>50% use), the relationship became significant. It is possible that coronary artery disease was identified as a significant risk factor in part because these patients were more likely to be receiving concomitant aspirin. Parameter estimates of the final model are presented in Table 6.

Table 6. Parameter estimates of the final life-threatening bleed exposure-response model

Parameter	Estimate	Standard Error	p-value
Age	0.0623	0.0116	8.6e-8
Sex	-0.546	0.182	0.0026
History of Stoke/TIA	0.454	0.170	0.0076
Coronary Artery Disease and Age ≥ 65 years	0.334	0.167	0.045
Log(trough concentration)	0.821	0.132	4.3e-10

The predicted probability of a life-threatening bleed within one year was calculated. The results are illustrated in Figure 6. For 110 mg, 150 mg and 300 mg doses, the predicted probability of a life-threatening bleed in one year was 0.62%, 0.83% and 1.46%, respectively.

Figure 6. Probability of life-threatening bleed within 1 year vs. dabigatran trough concentration. The blue shaded region represents the 95% confidence interval. The bars on the bottom on the plot region represent the 10th to 90th percentiles of observed dabigatran pre-dose concentrations in the RE-LY trial.



Predictions

Efficacy and safety outcomes were predicted at higher doses and in special subgroups. To investigate the impact of higher doses, the probability of ischemic stroke and life-threatening bleeding events were predicted in a "typical" patient. The results are presented in Table 1. As expected, the results indicate a decreasing probability of ischemic stroke and increasing probability of major bleeding with increasing doses. Going from 150 mg to 300 mg, the probability of an ischemic stroke is predicted to decrease approximately 15% whereas the probability of a life-threatening bleed is predicted to increase by 76%.

Predictions were also used to explore the impact of dose adjustment on the risk of major bleeding in patients at highest risk, specifically older patients. The results are displayed in Table 2 and suggest that reducing the dose from 150 mg to 110 mg is predicted to decrease the risk of a major bleed to a minor extent, especially in patients older than 75 years of age. The absolute risk of life-threatening bleeding is still elevated compared to a typical patient (Table 1).

During the course of the review it was noted that dabigatran patients with moderate renal impairment had a much lower stroke event rate (1.23%/year) in the 150 mg arm compared to the 110 mg arm (2.36%/year). The model was therefore probed to determine if it reflected this degree of dose-response. The results indicate that the dose-response relationship was shallower for the subset of patients who had PK data (Table 7). For the 110 mg and 150 mg doses, the model predicts event rates of 0.93%/year and 0.59%/year, respectively.

Table 7. Ischemic Stroke Event Rate (%/year). Observed refers to the calculated event rate using the censoring rules described in 4.3.1. Model predicted is the predicted value based on the final model. RE-LY refers to the event rate observed in the intent-to-treat population in the RE-LY trial.

	Observed (PK population, as-treated)		**Model Predicted**		**RE-LY (ITT population)**	
Renal Function	**110 mg**	**150 mg**	**110 mg**	**150 mg**	**110 mg**	**150 mg**
Normal	0.31	0.55	0.58	0.44	0.86	0.73
Mild	1.11	0.59	0.79	0.55	1.69	1.21
Moderate	1.12	0.95	0.93	0.59	2.36	1.23

4.4.4 Liver Function

The time courses of ALT >3x ULN, AST >3x ULN and bilirubin > 2x ULN are presented in Figure 7, Figure 8 and Figure 9, respectively. For ALT and AST, the two key findings are:

- Dabigatran does not induce changes to AST and ALT similar to those observed with ximelagtran. In fact, the changes in AST and ALT in the dabigatran treated subjects are similar to those in warfarin-treated subjects.
- The time course of ALT and AST >3x ULN in warfarin treated subjects in the RE-LY trial is similar to the time course in warfarin treated subjects in the Sportif trials.

These results indicate that dabigatran does not induce elevations in AST and ALT. The time course of bilirubin > 2x ULN were similar across warfarin, dabigatran and ximelagatran treated subjects. The proportion of subjects experiencing this event at any given visit, however, was low (< 1%).

Figure 7: Time course of ALT > 3x ULN for warfarin, ximelagatran and dabigatran in the Sportif and RE-LY trials

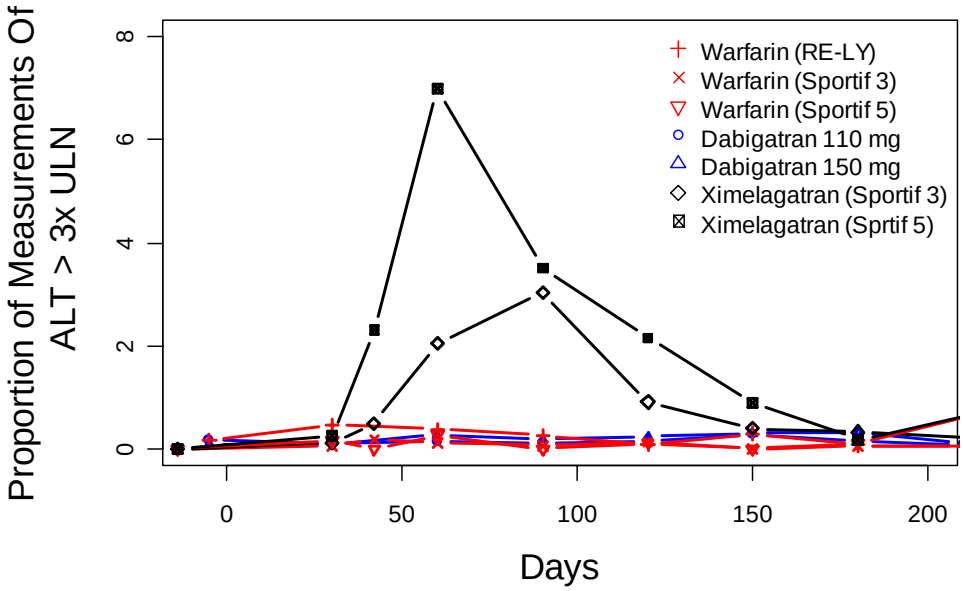


Figure 8: Time course of AST > 3x ULN for warfarin, ximelagatran and dabigatran in the Sportif and RE-LY trials

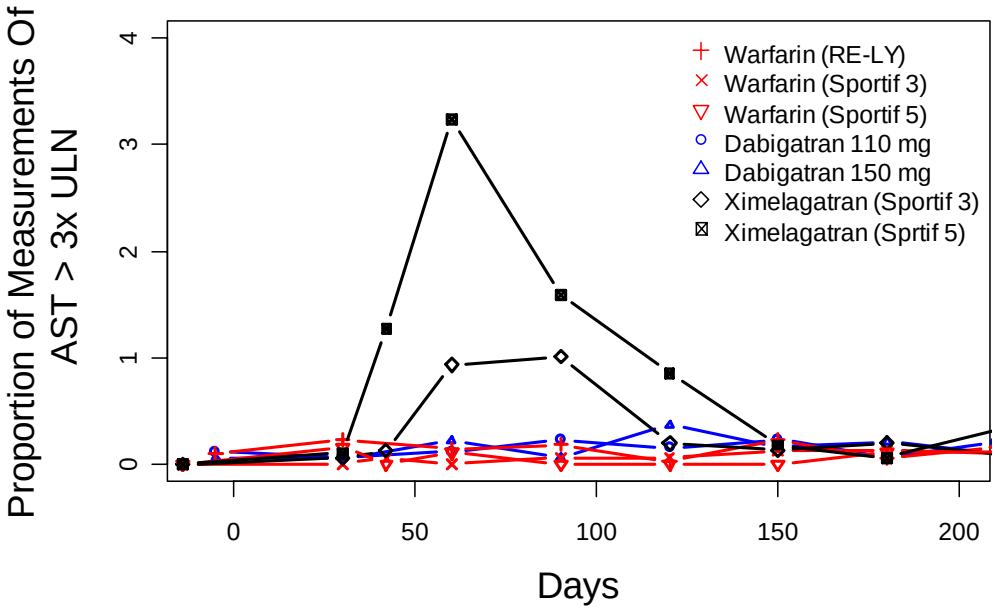
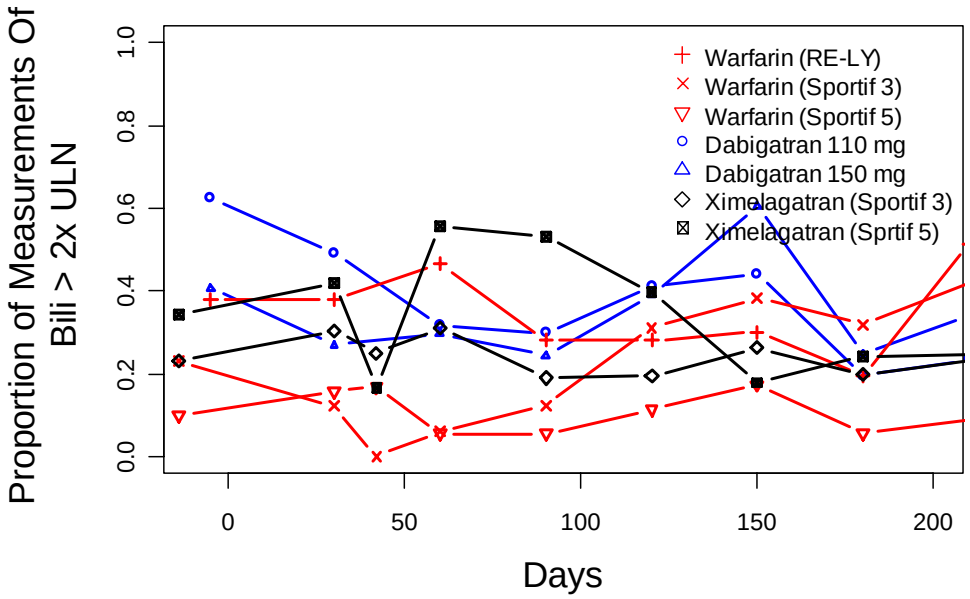


Figure 9: Time course of Bilirubin > 2x ULN for warfarin, ximelagatran and dabigatran in the Sportif and RE-LY trials



5 LISTING OF ANALYSES CODES AND OUTPUT FILES

File Name	Description	Location in \\cdsnas\pharmacometrics\
make.lifebleedcminCOX.R	Exposure-Response Analysis for Major Bleeding	Reviews\Ongoing PM Reviews\Dabigatran_NDA22512_KMK\ER Analyses\Bleeds
make.istrokesurvivalCminCOXAGE.R	Exposure-Response Analysis for Ischemic Stroke	Reviews\Ongoing PM Reviews\Dabigatran_NDA22512_KMK\ER Analyses\Efficacy
make.xliversportif5ALT.R	Liver Analysis (ALT)	Reviews\Ongoing PM Reviews\Dabigatran_NDA22512_KMK\ER Analyses\Hepatic
make.xliversportif5AST.R	Liver Analysis (AST)	Reviews\Ongoing PM Reviews\Dabigatran_NDA22512_KMK\ER Analyses\Hepatic
make.xliversportif5bili.R	Liver Analysis (bilirubin)	Reviews\Ongoing PM Reviews\Dabigatran_NDA22512_KMK\ER Analyses\Hepatic

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22512	ORIG-1	BOEHRINGER INGELHEIM PHARMACEUTICALS INC	PRADAXA (DABIGATRAN ETEXILATE MESYLATE)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

KEVIN M KRUDYS
08/24/2010

PRAVIN R JADHAV
08/24/2010

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA #/Serial #:	22-512
DRUG NAME:	Dabigatran Etexilate Mesylate
INDICATION:	Stroke Prevention in Atrial Fibrillation
APPLICANT:	Boehringer Ingelheim Pharmaceuticals Inc.
DATE OF RECEIPT:	12/15/2009
REVIEW PRIORITY:	Standard
BIOMETRICS DIVISION:	Division of Biometrics I
STATISTICAL REVIEWER:	Steve Bai, Ph.D.
CONCURRENT REVIEWER:	James Hung, Ph.D. Director DBI
MEDICAL DIVISION:	Division of Cardiovascular and Renal Products
CLINICAL TEAM:	Aliza Thompson, MD
	Bach Nhi Beasley, MD
PROJECT MANAGER:	Alison Blaus

Table of Contents

LIST OF TABLES **3**

LIST OF FIGURES **3**

1 EXECUTIVE SUMMARY **4**

1.1 CONCLUSIONS AND RECOMMENDATIONS 4
1.2 BRIEF OVERVIEW OF CLINICAL STUDY 4
1.3 STATISTICAL ISSUES AND FINDINGS 4

2 INTRODUCTION **5**

2.1 OVERVIEW 5
2.2 DATA SOURCES 6

3 STATISTICAL EVALUATION **6**

3.1 EVALUATION OF EFFICACY 6
3.1.1 Re-LY Study *6*
3.1.1.1 Patient Disposition, Demographic and Baseline Characteristics 9
3.1.1.2 Primary Efficacy Results 10
3.1.1.3 Sensitivity analyses for stroke/SEE 12
3.1.1.4 Secondary Efficacy Analysis 14
3.1.1.5 Reviewer's Results 15
3.2 EVALUATION OF SAFETY 18

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS **18**

4.1 GENDER, AGE AND RACE GROUP 18
4.1.1 Gender *18*
4.1.2 Age *19*
4.1.3 Race *19*
4.2 OTHER SUBGROUP POPULATIONS 20
4.2.1 Prior VKA use *20*
4.2.2 History of Stroke/SEE/TIA *21*
4.2.3 Subgroup analysis for baseline Medication use *21*

5 SUMMARY AND CONCLUSIONS **22**

5.1 STATISTICAL ISSUES AND COLLECTIVE EVIDENCE 22
5.2 CONCLUSIONS AND RECOMMENDATIONS 24

List of Tables

Table 1 Baseline Demographic Information 10
Table 2 Frequency for stroke/SEE in randomized set 11
Table 3 Hazard ratios and CIs for stroke/SEE, randomized set. 12
Table 4 Hazard ratios and CIs for stroke/SEE randomized set, data cutoff at the event onset date of the 450th adjudicated event 12
Table 5 Hazard ratios and 95% CI for stroke/SEE by INR control for warfarin 13
Table 6 Hazard ratios and CIs for stroke/SEE, as-treated set. 13
Table 7 Hazard ratios and 95% CI for composite endpoint of stroke/SEE/death 15
Table 8 Hazard ratios and 95% CI for stroke/SEE/PE/MI and vascular death 15
Table 9 Hazard Ratios (95% CI) for Stroke/SEE by medication use 21
Table 10 Placebo-Controlled Trials of Warfarin in Non-Valvular Atrial Fibrillation 22
Table 11 Comparisons on Demographic Variables, Clinical Characteristics, and Endpoints of Historical Warfarin AF Studies vs. RE-LY 23

List of Figures

Figure 3.1 Kaplan-Meier estimates of time to first stroke/SEE 11
Figure 3.2 Kaplan-Meier estimates of time to first stroke/SEE/death 14
Figure 3.3 The Upper Bound of Hazard Ratios for composite endpoint of stroke/SEE across trial calendar date 16
Figure 3.4 The Forest Plots of Hazard ratio and 95% CI for stroke/SEE comparing DE 150 to warfarin by countries 17
Figure 3.5 The Forest Plots of Hazard ratio and 95% CI for stroke/SEE comparing DE 110 to warfarin by countries 18
Figure 4.1 Hazard Ratios (95% CI) for stroke/SEE by Gender 19
Figure 4.2 Hazard Ratios (95% CI) for stroke/SEE by Age Groups 19
Figure 4.3 Hazard Ratios (95% CI) for stroke/SEE by Race 20
Figure 4.4 Hazard Ratios (95% CI) for stroke/SEE by Prior VKA Usage 20
Figure 4.5 Hazard Ratios (95% CI) for stroke/SEE by Stroke/SEE/TIA 21

1 EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

Overall, RE-LY demonstrated that both doses of dabigatran were non-inferior to warfarin and DE 150 was superior to warfarin for the primary (stroke/SEE) efficacy endpoints. Furthermore, the secondary (stroke/SEE/death and stroke/SEE/PE/MI/vascular death) efficacy endpoints also met the above claims numerically. However, sponsor did not specify the statistical testing rules and margins for these endpoints in the TSAP. Therefore, these findings can only be viewed as exploratory findings.

There was no discrepancy results found in any of the sensitivity analyses. Although, DE 150 did not show superiority for US subjects statistically, but it was still non-inferior to warfarin and the point estimate (hazard ratio) also less than 1.00. All the subgroup analyses performed in Section 4 were consistent with the primary efficacy results. Hence, RE-LY's finding is very robust. Furthermore, based on the reviewer's analysis on the impact of different end of trial dates, the dabigatran doses achieved the non-inferiority long before the end of trial date and DE 150 achieved superiority to warfarin more than one year before the end of trial date, see Figure 3.3.

1.2 Brief Overview of Clinical Study

RE-LY is a randomized, parallel group, active-controlled, non-inferiority trial of 2 blinded doses of Dabigatran Etexilate compared with open-label warfarin in patients with non-valvular AF. The trial was designed to evaluate whether 110 mg bid and 150 mg bid of Dabigatran Etexilate are non-inferior to adjusted dose warfarin in the prevention of stroke and systemic embolism in non-valvular AF patients with at least 1 additional risk factor for stroke. A total of 18,113 subjects (1:1:1) were randomized and the total number of subjects with adjudicated stroke/SEE was 513.

1.3 Statistical Issues and Findings

<u>The non-inferiority margin</u>

The proposed testing hypothesis for RE-LY was that whether either dabigatran doses (110 mg and 150 mg) were non-inferior to warfarin in reducing the incidences of Stroke/SEE. The non-inferiority margin of 1.46 for the hazard ratio in the sponsor's study report was derived based on the historical placebo controlled trials using the 95%-95% rule. This rule utilized the lower bound of the 95% confidence interval of the hazard ratio for warfarin versus placebo for the derivation of the non-inferiority margin, and the upper bound of the 95% confidence limit for dabigatran versus warfarin for the statistical test. The margin 1.46 used in the study design preserved at least 50% of warfarin's effect on the risk ratio scale using the lower bound of the 95% of the risk ratio of placebo over warfarin. However, a smaller margin of 1.38, derived to preserve the effect of warfarin on the Log scale, was recommended by a regulatory agency. In spite of this discrepancy on the margin, both dabigatran doses were non-inferior to warfarin based on the sponsor's efficacy findings.

<u>Summary of the historical trials and constancy assumption</u>

The effectiveness of warfarin has been studied both in placebo-controlled and active-controlled trials. There are six placebo-controlled studies of warfarin involved the patients with AF between 1989 and 1992. All these trials showed a consistent efficacy for warfarin in preventing stroke and other cardiovascular events, despite differences in their designs and patient populations. The primary outcomes of these studies are summarized in Table 10. Almost all of the trials showed significant reduction in the primary endpoint event by warfarin against placebo. Trial CAFA failed to show a significant benefit over placebo, but the estimated warfarin effect from this trial was consistent with those observed from the other trials.

Even if the historical studies are consistent, a critical consideration in deciding upon the NI margin derived from these studies is whether the constancy assumption is reasonable. To evaluate the plausibility of this constancy assumption, one might compare some features of the six placebo-controlled warfarin studies with the RE-LY study. There is considerable heterogeneity in the demographic characteristics of these studies. The draft guidance listed number of characteristics, such as a history of stroke or TIA, see Table 11. The most of characteristics are similar among the historical studies with RE-LY, but the history of stroke or TIA and CAD are much higher in RE-LY; see Table 11 on page 23 of this review.

Increase of sample size

The study was originally designed as an event driven trial. Based on an estimated yearly event rate of 1.6% and a two-year enrolment period and one-year follow up, a total of 15,000 subjects were planned to be randomized from approximately 800 centers. Due to rapid enrollment, 15,000 subjects were randomized in 1.5 years (18 months). Sponsor claimed that if the recruitment was stopped at that time, the last randomized subjects would have had to follow up for more than 1 year to achieve the planned total number of events, if the actual event rate was as expected. In addition, sponsor also claims that the actual event rate could be less than 1.6% based on other published studies. Therefore, sponsor decided to continue the recruitment as planned, which resulted a total of 18,113 subjects were randomized and the total number of subjects with adjudicated stroke/SEE was increased to 519. The above changes were added to protocol's second amendment on May of 2007. In order to validate the final primary efficacy results, both the sponsor and this reviewer had performed the sensitivity analysis for the first 450 adjudicated primary events. Based on all the analyses results, both doses of dabigatran have met the pre-specified non-inferior margin to warfarin to conclude that the two doses are effective for the stroke prevention in AF patients. Furthermore, DE 150 was superior to warfarin as well, see Table 4.

2 INTRODUCTION

2.1 Overview

Atrial Fibrillation is the most common sustained cardiac rhythm disturbance. The prevalence of paroxysmal or persistent AF is estimated at 0.4% of the general population, including up to 1% of all adults. The prevalence of AF increases with age. It occurs in less than 1% of those under 60 years of age but in more than 6% of those over 80 years of age. AF has significant morbidity, mortality, and economic cost, due to the occurrence of both hemodynamic impairment and thromboembolic events. The hemodynamic impairment and rhythm disturbances may be

symptomatic and can lead to a decrease in quality of life. However, most of the mortality and functional impairment associated with AF is due to the occurrence of ischemic stroke and systemic emboli. AF patients also have concomitant coronary artery disease, for which they should normally receive acetylsalicylic acid (ASA). However due to a higher rate of bleeding when anticoagulants and ASA are co-administered, one of these agents may either be withheld or dose-adjusted in such patients.

The vitamin K antagonists (VKAs, coumadins), typified by warfarin, are the most widely prescribed oral anticoagulants. In several adequate and well-controlled trials, warfarin decreased the risk of stroke/systemic thromboembolism by 68% versus placebo. This class of drugs when used in patients with AF also has shown to have a higher risk of bleeding at therapeutic doses than ASA alone. VKAs have a slow onset and offset of action, high inter- and intra-individual variability in their effective plasma concentrations, and have a high potential for food and drug interactions.

Dabigatran Etexilate is the orally bioavailable prodrug of Dabigatran, a novel thrombin inhibitor. Dabigatran Etexilate, a prodrug, does not have any antithrombin activity.

2.2 Data Sources

The sponsor's submitted data are stored in the following directory of the CDER's electronic document room: \\Cdsesub1\evsprod\NDA022512

3 STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

The following description is based on the sponsor's clinical study report. Any discrepancy between the study report and study protocol will be discussed in the section of statistical reviewer's comments.

3.1.1 RE-LY STUDY

RE-LY is a randomized, parallel group, active-controlled, non-inferiority trial of 2 blinded doses of Dabigatran Etexilate compared with open-label warfarin in patients with non-valvular AF. The trial was designed to evaluate whether 110 mg bid and 150 mg bid of Dabigatran Etexilate are non-inferior to adjusted dose warfarin (target INR of 2.0 to 3.0) in the prevention of stroke and systemic embolism in non-valvular AF patients with at least 1 additional risk factor for stroke.

Objectives

The primary objective is to demonstrate that the efficacy and safety of 2 blinded doses (110 mg bid and 150 mg bid) of Dabigatran Etexilate are non-inferior to adjusted dose warfarin (target INR 2-3) for the prevention of stroke and systemic embolism in subjects with non-valvular AF with at least 1 additional risk factor for stroke.

Study Design

This was a Prospective Randomized Open trial with Blinded outcome Evaluation (PROBE) study with 2 doses of Dabigatran Etexilate (110 mg bid, 150 mg bid) compared to adjusted warfarin therapy, INR 2.0-3.0. Approximately 6,000 subjects per treatment group were randomized over 2 years with a further year of follow-up to a common termination.

The trial was conducted from December 22, 2005 to March 15, 2009. There were 1,044 sites selected from 44 countries and 951 sites randomized at least 1 subject. The duration of treatment was expected to be a median of 20-24 months, with a minimum of 12 months' treatment after the last subject was randomized and a maximum treatment of approximately 3 years.

There were 5 protocol amendments written for this study. Amendment 1 mandated balanced randomization of warfarin-naïve and warfarin –experienced subjects at each site. In order to obtain balanced cohorts of both VKA-experienced and –naïve subjects, investigational sites were expected to recruit both types of subjects. With rapid recruitment of predominantly VKA-experienced subjects (80%) in the first 7 months of the trial, Amendment 1 (dated 31 Aug 2006) was implemented to ensure that balanced cohorts were recruited. The definition of VKA-naïve was expanded from 1 month to 2 months or less of lifetime VKA use. Amendment 2, dated 24 May 2007, increased the target sample size to 18,000 from originally proposed 15,000. The 15,000 patients were planned based on a two-year enrollment and one year of follow-up and a yearly event rate of 1.6%. Due to the faster enrollment, 15,000 patients will be randomized prior to the planned date. In order to maintain the statistical power in case of event rate < 1.6% within the original study time line, the enrollment should continue as planned. It is predicted that the number of patients randomized will be increased from 15,000 to 18,000. Amendment 3, 4 and 5 did not have any statistical issues.

The logistic of a double-blind study design employing warfarin, which is frequently monitored and dose-adjusted, compared with Dabigatran, which is neither monitored nor dose-adjusted, and are complex. A dummy INR monitoring system, with an algorithm for generating false INRs for Dabigatran subjects would need to be established, further complicating recruitment of both centers and subjects. This trial used the Prospective Randomized Open trial with Blinded Evaluation of outcomes (PROBE) design. A key element of the PROBE design was to use blinded adjudicators to reduce potential bias in the evaluation and classification of important study outcome events. The following measures were used to decrease open-label biases:

- Blinded Adjudication of events by at least 2 independent adjudicators
- Database and data handling assigned to an academic group independent from the sponsor
- Blinding of sponsor and trial management personnel to "by treatment" analyses during trial
- Oversight by DSMB
- CRF construction to elicit events based on investigations and other assessments performed by the site.

Efficacy Measures

The primary endpoint for this study is the incidence of stroke (including hemorrhagic) or non-Central Nervous System (CNS) systemic embolism, hereafter referred to as systemic embolism.

The secondary endpoints are:

- incidence of stroke (including hemorrhagic), systemic embolism, all death
- incidence of stroke (including hemorrhagic), systemic embolism, pulmonary embolism, acute myocardial infarction, or vascular deaths (includes deaths from bleeding)

There are two other efficacy endpoints:

- individual or composite occurrences of ischemic stroke (fatal and non-fatal), systemic embolism, pulmonary embolism, acute myocardial infarction, TIAs, vascular death (includes deaths from bleeding), all deaths, and hospitalizations
- Net Clinical Benefit (NCB) as measured by the composite of the clinical endpoint of stroke, systemic embolism, pulmonary embolism, acute myocardial infarction, all cause deaths, and major bleeds.

Statistical Hypotheses

The null hypothesis was that hazard ratio of Dabigatran vs. warfarin was larger than or equal to the specified non-inferiority margin $\delta = 1.46$. The alternative hypothesis was that the hazard ratio was less than 1.46. Since there were two comparisons of Dabigatran vs. warfarin, the Hochberg procedure was used to handle the multiple comparisons. To use the Hochberg procedure, the Dabigatran dose with the largest hazard ratio vs. warfarin were to be tested first for non-inferiority at $\alpha=0.025$ (one-sided) level. If the non-inferiority would be concluded from this comparison, then the non-inferiority vs. warfarin for both Dabigatran doses would be claimed. Otherwise, the non-inferiority for this dose would not be claimed and the other Dabigatran dose were to be compared to warfarin at $\alpha=0.0125$ (one-sided) level for non-inferiority.

As specified in the Trial Statistical Analysis Plan (TSAP), superiority testing was to be performed to compare Dabigatran to warfarin for the primary endpoint when the non-inferiority claim was established.

Efficacy Analysis

The primary analysis was performed by using the randomized set, which included all randomized subjects in the treatment groups to which they were randomized, regardless of whether the subjects took randomized study medication or not. The time to the occurrence of the primary endpoint event was computed as (event date – randomization date) +1. Subjects who did not have primary endpoint events during the trial period were considered to be censored. The time to censoring was computed as (study termination date – randomization date) + 1.
The yearly event rate for treatment group was computed as the total number of events that occurred in that treatment group divided by the total subject exposure in years (subject years) in that group. For a given subject, exposure was computed from the date of randomization to the date of study termination, using the randomized set.

The primary analyses include the following: yearly event rate summaries, Kaplan-Meier curves and Cox regression analyses. All secondary outcomes were analyzed using the Cox regression model with treatment as the factor in the model.

Sensitivity Analyses

An analysis of the primary endpoint including only the first 450 adjudicated primary endpoint events was performed as a sensitivity analysis since the originally planned number of events was 450. Subjects without primary events were censored at the onset date of the 450th primary event, or study termination date which ever occurred earlier.

Another analysis for the primary endpoint was performed by including all subjects randomized to dabigatran treatment and subjects randomized to warfarin who achieved good INR control, such as >= 65% of time INR in range 2-3 during the treatment period.

Overall, 8,542 (47%) subjects completed the trial without any interruption, 2,736 (15%) subjects permanently discontinued their study medication. Lastly, 6,762 subjects had a temporary interruption of study medication. Therefore, number of different on-treatment analyses by recoding event status and time to outcomes for those temporary discontinued subjects are included in this review. This review included three different recoding schemes: (1) censoring at first discontinuation of study medication, (2) censoring at last study medication date, and (3) censoring at 7 days after first discontinuation of study medication. The statistical analyses will be same as the primary efficacy analysis.

Sample Size Considerations

The RE-LY assumed a yearly event rate of 1.6% for both Dabigatran and warfarin, with 5,000 subjects per treatment group to be recruited in 2 years and followed up for 1 additional year to achieve 150 events per treatment group. Within these parameters, each comparison had approximately 90% power to conclude the non-inferiority of Dabigatran to warfarin at a one-sided α=0.025 level based on the derived non-inferiority margin of 1.46. With a total of 15,000 subjects randomized to the 2 Dabigatran doses and warfarin at a 1:1:1 ratio, to achieve a total of 450 events, using the Hochberg procedure to compare each Dabigatran dose to warfarin, the trial had approximately 84% power to conclude the non-inferiority of both Dabigatran doses to warfarin using the non-inferiority margin of 1.46.

A total of 15,000 subjects were recruited in less than 2 years (18 months). If the recruitment was stopped at that time, the last randomized subject would have had to be followed up for more than 1 year to achieve the planned total number of events, if the actual event rate was as expected. In addition, based on the results from other published studies, the actual event rate could be less than 1.6%. Because of these concerns, the operational committee decided to continue the recruitment as planned. As a result, a total of 18,113 subjects were randomized. It was expected that if the actual event rate was as planned, the statistical power would be increased.

3.1.1.1 Patient Disposition, Demographic and Baseline Characteristics

In general, there were no large differences among the three treatment groups in subject baseline demographic and disease characteristic information. Detailed baseline demographic and disease characteristics are presented in Table 1.

Table 1 Baseline Demographic Information

	DE 110 mg	DE 150mg	Warfarin	Total
Randomized [N]	6015	6076	6022	18,113
Age (mean, years)	71.4	71.5	71.6	71.5
Male (%)	64.3	63.2	63.3	63.6
Race: white (%)	70	70.2	69.8	70
Weight (mean, Kg)	82.9	82.4	82.6	82.6
VKA naïve (%)	50	49.8	51.4	50.4
Never on VKA (%)	31.1	31.4	32.7	31.7
CrCL (median, ml/min)	68.7	67.9	68.5	68.4
Systolic BP (mean, mmHg)	130.8	130.9	131.2	131
Diastolic BP (mean, mmHg)	77	77	77.1	77
AF type [N(%)]				
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 [N(%)]				
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)
Other	355(5.9)	362(6.0)	355(5.9)	1072(5.9)

3.1.1.2 Primary Efficacy Results

First of all, the results presented in this review were all this reviewer's own results. Furthermore, they also confirmed the sponsor's results. The primary objective in this study was to determine if Dabigatran was non-inferior to warfarin in reducing the occurrence of the composite endpoint, stroke/SEE. Comparisons between treatment groups for stroke/SEE were performed using a Cox regression analysis with treatment in the model. Descriptive statistics, such as event numbers and Kaplan-Meier plots, are also presented in Table 2.

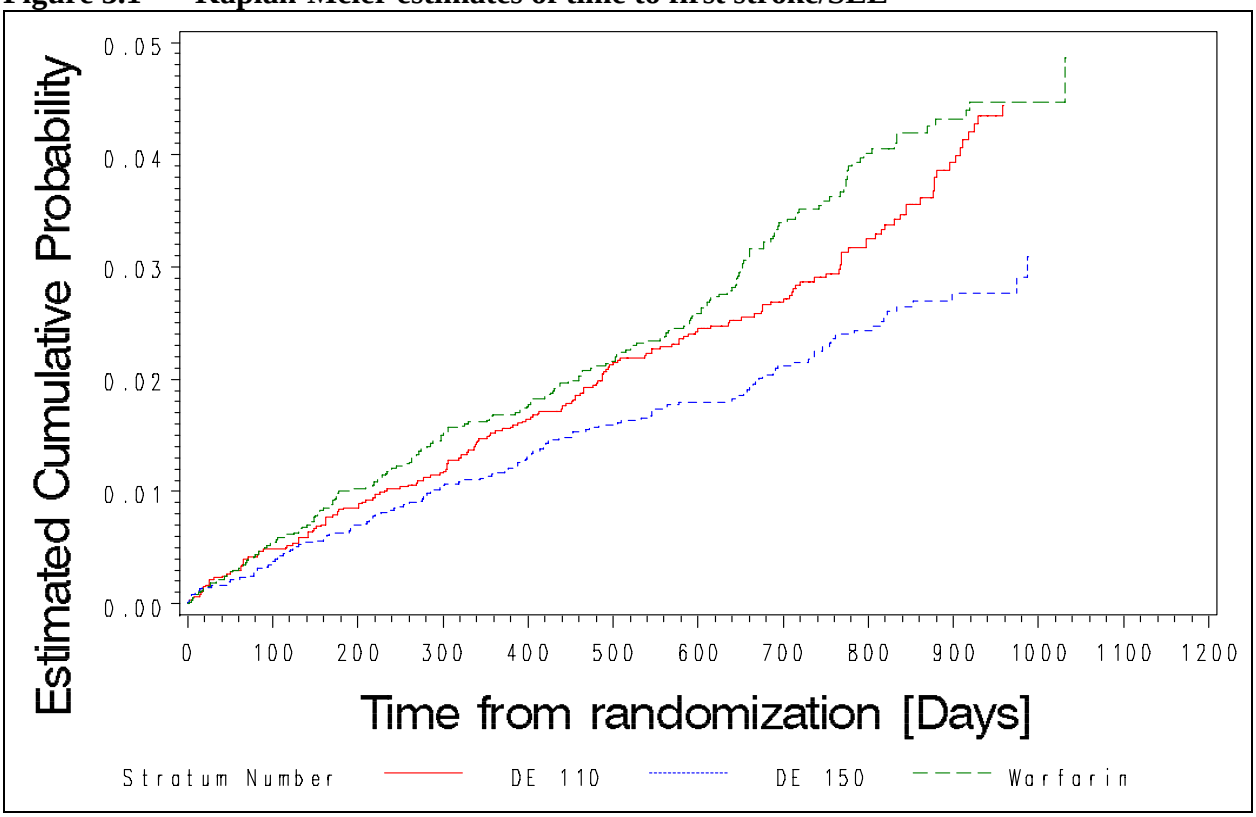
Table 2 Frequency for stroke/SEE in randomized set

	DE 110 mg	DE 150 mg	Warfarin
Subjects randomized	6015	6076	6022
Subjects with stroke/SEE	183	134	202
Stroke	183	132	194
Ischemic stroke	162	111	139
Haemorrhagic stroke	14	12	45
Stroke of uncertain	7	9	10
SEE	15	14	21

[Source: reviewer's results]

A total of 519 adjudicated first stroke/SEEs were observed during the trial: 183, 134 and 202 events in the DE 110, DE 150 and warfarin groups, respectively (Table 2) The Kaplan-Meier estimates are shown in Figure 3.1.

Figure 3.1 Kaplan-Meier estimates of time to first stroke/SEE



[Source: Reviewer's Results]

Non-inferiority of both dabigatran doses compared to warfarin was demonstrated. The hazard ratio for stroke/SEE of DE 110 over warfarin was 0.90, with the 95% confidence limits (CI) of (0.74, 1.10). The upper bound of the 95% CI is below 1.46, the protocol specified margin, for both doses. Relative risk reductions for stroke/SEE by DE 110 and DE 150 were 10% and 35%, respectively, in comparison to warfarin. Furthermore, DE 150 was superior to warfarin for the

primary endpoint of stroke/SEE. The hazard ratio of DE 150 over warfarin was 0.65, with the 95% CI of (0.52, 0.81). The upper bound of the 95% CI is below 1.00, See Table 3.

Table 3 Hazard ratios and CIs for stroke/SEE, randomized set.

	DE 110 mg vs. Warfarin	DE 150 mg vs. Warfarin
#Events/N	183/6015 vs. 202 /6022	134/6076 vs. 202/6022
Hazard ratio (SE)	0.90 (0.09)	0.65 (0.07)
95% CI	0.74, 1.10	0.52, 0.81
P-value for NI using 1.46	0.0001	0.0001
P-value for superiority	0.2943	0.0001

[Source: Reviewer's results]

3.1.1.3 Sensitivity analyses for stroke/SEE

Sensitivity analyses were performed for the primary endpoint in order to provide evidence that the primary analysis is robust. The following sensitivity analyses are presented in this section:

1. analyses of the first 450 adjudicated events;
2. analyses of all dabigatran and warfarin subjects with INR in 2-3 ≥65% of the time and <65% of the time;
3. analyses of as-treated subjects.

<u>Analysis of the first 450 adjudicated events</u>

The original targeted number of events for stroke/SEE in this study was 450. At the end of the study, 519 adjudicated stroke/SEEs were reported. The analysis including the first 450 events was performed as a sensitivity analysis. The 450th adjudicated stroke/SEE occurred on October 30, 2008. Subjects without a stroke/SEE were considered censored on this date for purposes of this analysis.

Table 4 Hazard ratios and CIs for stroke/SEE randomized set, data cutoff at the event onset date of the 450th adjudicated event

	DE 110 mg vs. Warfarin	DE 150 mg vs. Warfarin
#Events/N	159/6015 vs. 170/6022	121/6076 vs. 170/6022
Hazard ratio	0.936	0.70
95% CI	0.75, 1.16	0.56, 0.89

[Source: Reviewer's results]

As in the primary analysis, both doses of dabigatran were non-inferior to warfarin, and DE 150 mg was superior to warfarin, see Table 4.

<u>Analyses by INR control</u>

The subjects on warfarin had their INR level measured throughout the whole trial and the mean percent of time of INR in 2-3 were computed for each warfarin subject as well. Hence, the results of the sensitivity analyses of all dabigatran and warfarin subjects with INR in 2-3 ≥ 65% of the time and < 65% of the time for the primary endpoint in provided in Table 5.

Table 5 Hazard ratios and 95% CI for stroke/SEE by INR control for warfarin

Mean % of the time of INR in range 2-3 ≥ 65%		
	DE 110 mg vs. Warfarin	DE 150 mg vs. Warfarin
#Events/N	183/6015 vs. 89/3195	134/6076 vs. 89/3195
Hazard ratio	1.12	0.81
95% CI	0.87, 1.44	0.62, 1.05
Mean % of the time of INR in range 2-3 < 65%		
	DE 110 mg vs. Warfarin	DE 150 mg vs. Warfarin
#Events/N	183/6015 vs. 113/2827	134/6076 vs. 113/2827
Hazard ratio	0.73	0.53
95% CI	0.58, 0.92	0.41, 0.67

[Source: Reviewer's results]

Results of the above sensitive analysis showed that the non-inferiority of both dabigatran doses compared to warfarin for stroke/SEE is maintained compared to well-controlled warfarin subjects when using a NI margin of 1.46. Superiority of both dabigatran doses compared to warfarin is demonstrated when dabigatran subjects are compared to subjects on warfarin whose mean percent of time of INR in 2-3 was <65% since the upper bound of both hazard ratio comparisons are below 1.00.

On-Treatment Analysis

During the further examination of the sponsor's datasets, the reviewer has noticed that around 13,151 subjects had a temporary interruption of study medication among all three treatment groups during the course of the trial. Some of them went back in a few short periods or longer periods. And others never went back to their assigned treatment.

Table 6 Hazard ratios and CIs for stroke/SEE, as-treated set.

Censoring Scheme	**DE 110 vs warfarin**		**DE 150 vs warfarin**	
	HR (95% CI)	p-value*	HR (95% CI)	p-value*
Censoring at first discontinuation of study medication (temporary or permanent)	0.86 (0.59, 1.27)	0.45	0.56 (0.40, 0.86)	0.009
Censoring at last study medication date	0.70 (0.53, 0.92)	0.01	0.45 (0.32, 0.61)	<.0001
Censoring at 7 days after first discontinuation of study medication (temporary or permanent)	0.85 (0.64, 1.13)	0.273	0.62 (0.46,0.85)	0.0028

[Source: Reviewer's results. *p-value is for superiority]

The reviewer, hence, conducted the following as-treatment analyses by re-code the time to censoring: (1) censoring at first discontinuation of study medication, (2) censoring at last study medication date, and (3) censoring at 7 days after first discontinuation of study medication. The detailed recoding mechanism for analysis (1) is described as the following: the data is re-coded based on their first discontinuation date (FDdate). For the censored subjects, if their FDdate occurred prior to their study termination date, then the time to censoring will be recoded as FDdate – Randomization date +1. For the event subjects, if their FDdate occurred prior to their event date, then the time to event will be recoded as FDdate – Randomization date +1 and the events will be changed to the censors. The recoding mechanism for analyses (2) and (3) would

be same as (1). Based on the findings in Table 6, the results are consistent with the primary efficacy analysis.

3.1.1.4 Secondary Efficacy Analysis

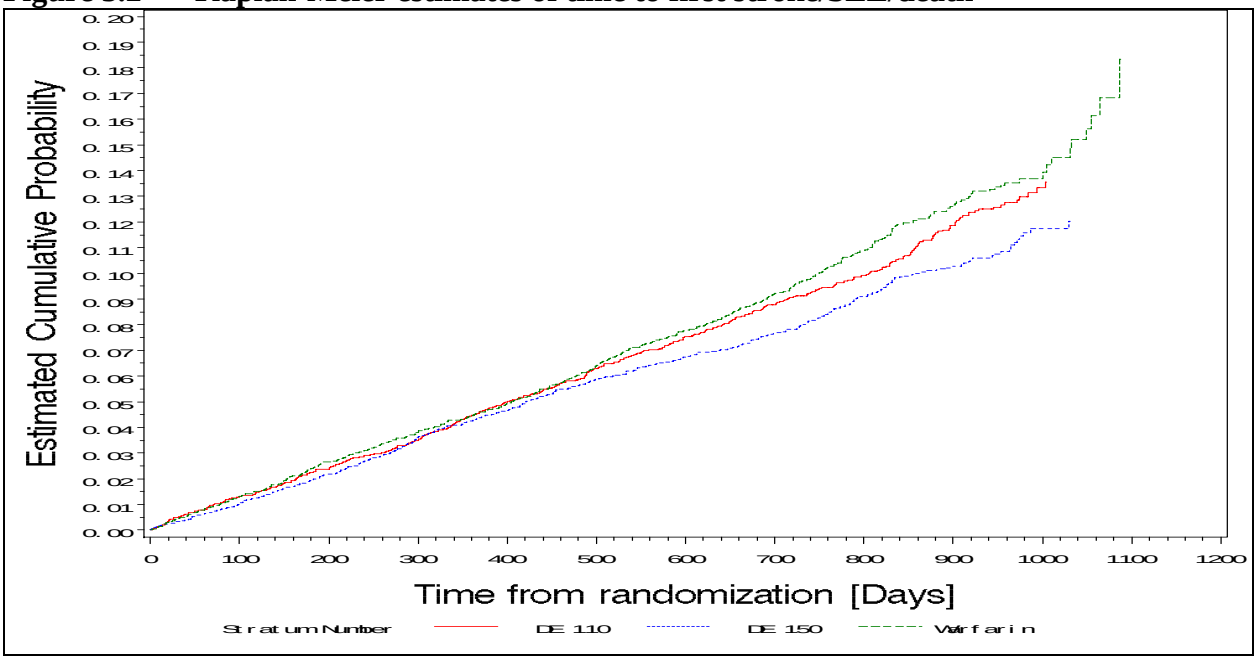
There were two secondary endpoints were specified in the protocol: 1) composite of stroke, SEE and all cause death, and 2) composite of stroke, SEE, PE, MI and vascular death.

Analysis of stroke, SEE, and all cause death

A total 1,710 stroke/SEEs/all cause deaths were observed during the trial: 577, 520 and 613 from the DE 110, DE 150 and the warfarin groups, respectively. The yearly event rate for the composite endpoint was the lowest in the DE 150 group (4.85%, 4.32% and 5.20%) in the DE 110, DE 150 and warfarin groups, respectively).

The Kaplan-Meier estimate for stroke/SEE/death shows the separation among the three curves as 500 days after the date of the randomization, with the DE150 group starting to be lower than the warfarin curve. DE 150 then has the lowest occurrence rate of death, with DE 110 also consistently below warfarin after about 1 year and through the end of the study, see Figure 3.2.

Figure 3.2 Kaplan-Meier estimates of time to first stroke/SEE/death



[Source: reviewer's result]

The risk reduction for the DE 110 group in stroke/SEE/death was 7% in comparison to warfarin, which was not statistically significant. The relative risk reduction for the DE 150 group was 17%, which was significant (p-value =0.0015) (Table 7).

Table 7 Hazard ratios and 95% CI for composite endpoint of stroke/SEE/death

	DE 110 mg vs. Warfarin	DE 150 mg vs. Warfarin
#Events/N	575/6015 vs. 609/6022	518/6076 vs. 609/6022
Hazard ratio (SE)	0.93 (0.05)	0.83 (0.05)
95% CI	0.83, 1.05	0.74, 0.93
P-value	0.2206	0.0015

[Source: reviewer's results]

Analysis of stroke, SEE, PE, MI and vascular death

For the other secondary composite endpoint (stroke/SEE/PE/MI/vascular death), results followed the same pattern as composite endpoints stroke/SEE and stroke/SEE/death. The event rates for DE 110 and warfarin were similar, while the event rate in the DE 150 was lower. A total 1,435 such composite endpoints were observed during the trial: 496, 435 and 504 from the DE 110, DE 150 and the warfarin groups, respectively. DE 150 had a statistically significant reduction in reducing the risk of the stroke/SEE/PE/MI/vascular death composite endpoint when compared to warfarin (relative risk reduction of 16%, p-value 0.0096) (Table 8). DE 110 was comparable to warfarin for this endpoint.

Table 8 Hazard ratios and 95% CI for stroke/SEE/PE/MI and vascular death

	DE 110 mg vs. Warfarin	DE 150 mg vs. Warfarin
#Events/N	493/6015 vs. 496/6022	433/6076 vs. 496/6022
Hazard ratio (SE)	0.98 (0.06)	0.84 (0.05)
95% CI	0.86, 1.10	0.74, 0.96
P-value	0.6972	0.0096

[Source: reviewer's results]

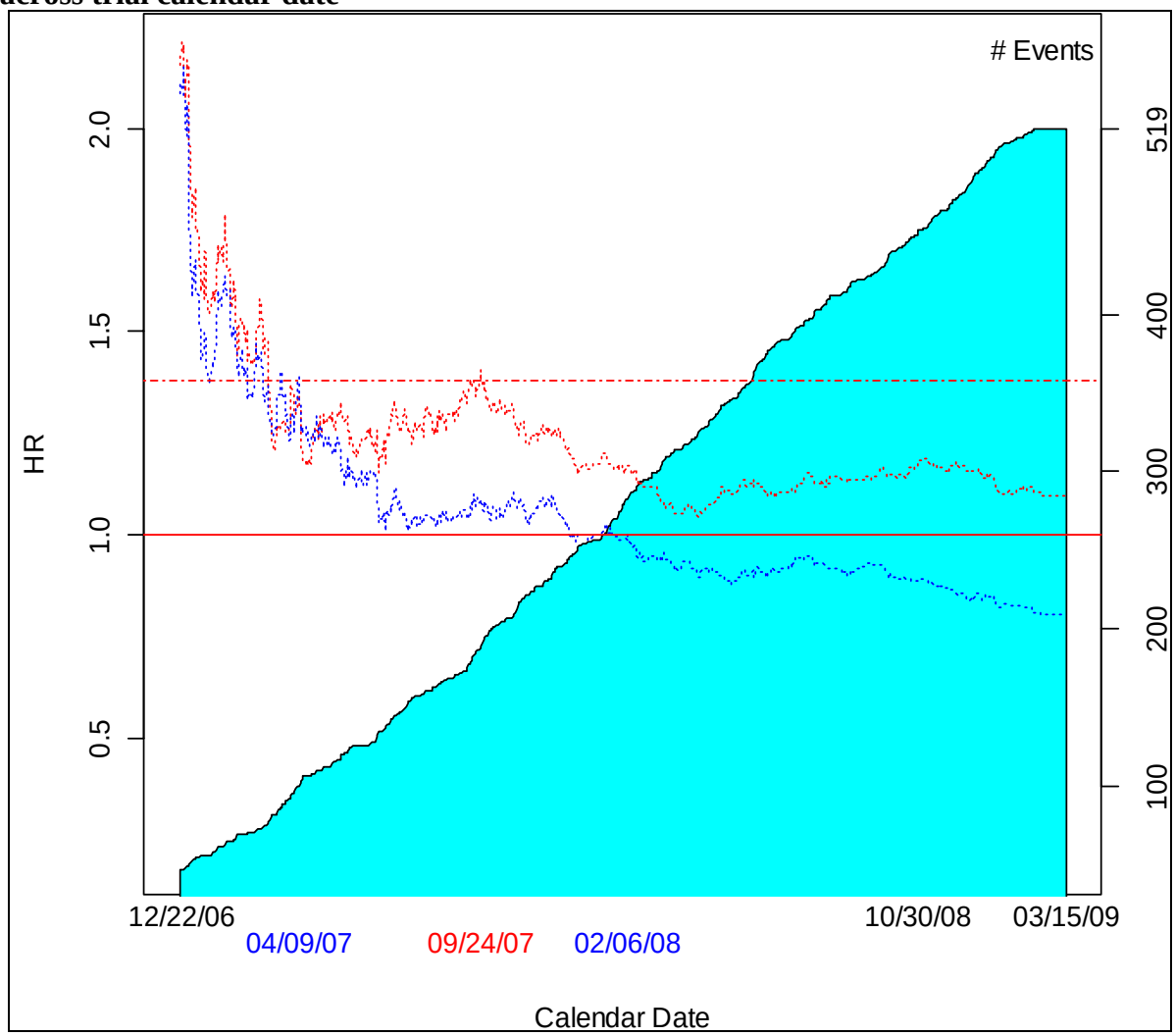
3.1.1.5 Reviewer's Results

Analysis on the Impact of Different End of Trial Dates

Both dabigatran doses achieved non-inferiority and DE 150 achieved superiority in relationship to warfarin with extremely significant statistical evidences (p-values are well less than 0.05). It would be very useful to find out how early those findings were established during the course of the trial. Figure 3.3 shows the upper 95% confidence bounds for the primary endpoint as a function of calendar time of the study. In this figure, I changed the event (censor) status and time to event information as if the current calendar time is assumed be the end of trial date starting from 12/22/2006 to 03/15/2009 (actual trial ending date). The original Cox regression analysis with treatment in the model was performed for each day to 03/15/2009. The red curve is the upper bound of hazard ratio of DE 100 mg over warfarin, and the blue curve is the upper bound of hazard ratio of DE 150 mg over warfarin. The dates on the x-axis correspond to a few important milestone dates. 12/22/2006 was arbitrarily chosen at one year after the initiation of the trial. 04/09/2007 was last time the upper bound of DE 150 mg stayed above NI margin of 1.38. 09/24/2007 was last time the upper bound of DE 100 mg stayed above NI margin of 1.38.

02/06/2008 was last time the upper bound of DE 150 mg stayed above superiority margin of 1.00. 10/30/2008 was the date that 450th adjudicated event had occurred. The blue background shows the cumulative number of events. The red dash horizontal line is the non-inferiority margin of 1.38, and the red solid horizontal line is the hazard ratio of 1.0.

Figure 3.3 The Upper Bound of Hazard Ratios for composite endpoint of stroke/SEE across trial calendar date



[Source: Reviewer's Results]

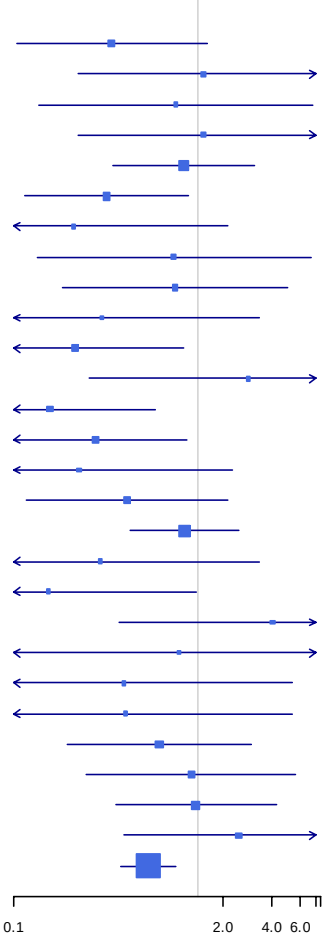
There are several interesting findings in Figure 3.3 should be noted. First of all, the efficacy of both dabigatran doses are very robust, the non-inferior findings were established long before the end of trial. Secondly, DE 150 mg achieved the superiority over warfarin more than one year before the end of trial. Finally, if the sponsor did not increase the originally proposed sample size from 15,000 to 18,000, the trial would still be able to demonstrate the non-inferiority claim over warfarin. When the 450th event had occurred on 10/30/2008, the study already established the overwhelming statistical evidence for the efficacy claims of the primary analysis.

<u>Analysis on the Impact of Individual Country</u>

The study was conducted in 44 countries. The number of patients per country ranged from 13 to 5,383. Among these countries, dabigatran doses were numerically non-inferior to warfarin in the vast majority of countries (see Figure 3.4 and Figure 3.5).

Figure 3.4 The Forest Plots of Hazard ratio and 95% CI for stroke/SEE comparing DE 150 to warfarin by countries

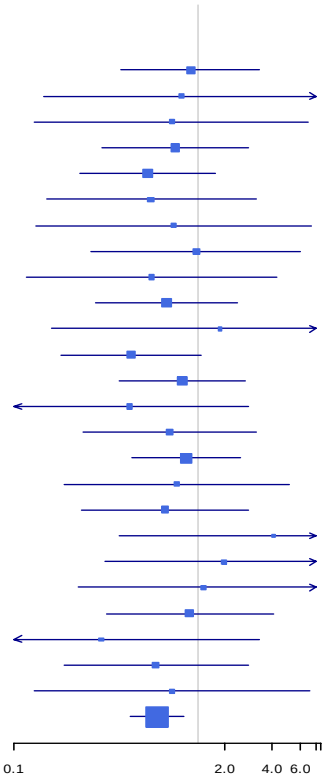
Country	#events/N (DE150)	#events/N (warfarin)	HR	(95% CI)
Argentina	3/179	7/172	0.408	(0.1055 , 1.578)
Australia	3/73	2/71	1.498	(0.2500 , 8.969)
Brazil	2/84	2/84	1.017	(0.1432 , 7.220)
Bulgaria	3/119	2/122	1.513	(0.2528 , 9.057)
Canada	8/385	7/379	1.137	(0.4121 , 3.135)
China, Peoples Republic of	4/181	10/180	0.378	(0.1184 , 1.205)
Czech Republic	1/117	4/114	0.236	(0.0264 , 2.113)
Denmark	2/80	2/83	0.993	(0.1398 , 7.053)
Finland	3/88	3/89	1.005	(0.2027 , 4.978)
France	1/59	3/60	0.352	(0.0366 , 3.380)
Germany	2/219	8/221	0.242	(0.0513 , 1.137)
Hong Kong	3/30	1/30	2.849	(0.2962 , 27.395)
India	2/194	11/192	0.169	(0.0374 , 0.761)
Israel	3/229	9/229	0.322	(0.0871 , 1.189)
Japan	1/111	4/108	0.254	(0.0284 , 2.271)
Malaysia	3/63	5/59	0.51	(0.1212 , 2.149)
Netherlands	14/420	12/423	1.156	(0.5345 , 2.499)
Norway	1/37	3/41	0.346	(0.0359 , 3.328)
Philippines	1/53	6/52	0.164	(0.0198 , 1.365)
Poland	4/162	1/162	4.051	(0.4528 , 36.250)
Romania	1/16	1/15	1.061	(0.0660 , 17.048)
Russia	1/101	2/99	0.483	(0.0438 , 5.335)
Slovakia	1/52	2/51	0.492	(0.0446 , 5.422)
South Korea	4/111	5/114	0.802	(0.2152 , 2.986)
Sweden	4/95	3/93	1.268	(0.2837 , 5.667)
Taiwan	7/119	5/119	1.357	(0.4308 , 4.278)
United Kingdom	5/113	2/111	2.488	(0.4827 , 12.827)
United States	42/1815	60/1788	0.685	(0.4620 , 1.017)



[Source: Reviewer's Results]

Figure 3.5 The Forest Plots of Hazard ratio and 95% CI for stroke/SEE comparing DE 110 to warfarin by countries

Country	#events/N (DE110)	#events/N (warfarin)	HR	(95% CI)
Argentina	9/179	7/172	1.242	(0.4625 , 3.34)
Australia	2/65	2/71	1.079	(0.1519 , 7.66)
Bulgaria	2/122	2/122	0.944	(0.1329 , 6.70)
Canada	7/386	7/379	0.991	(0.3475 , 2.82)
China, Peoples Republic of	7/180	10/180	0.669	(0.2545 , 1.76)
Czech Republic	3/119	4/114	0.707	(0.1582 , 3.16)
Denmark	2/84	2/83	0.97	(0.1366 , 6.88)
Finland	4/88	3/89	1.34	(0.3000 , 5.99)
France	2/58	3/60	0.706	(0.1179 , 4.22)
Germany	7/219	8/221	0.876	(0.3177 , 2.42)
Hong Kong	2/30	1/30	1.891	(0.1713 , 20.86)
India	6/192	11/192	0.532	(0.1966 , 1.44)
Israel	10/231	9/229	1.093	(0.4443 , 2.69)
Japan	2/107	4/108	0.52	(0.0952 , 2.84)
Malaysia	5/63	5/59	0.922	(0.2665 , 3.19)
Netherlands	14/423	12/423	1.163	(0.5378 , 2.51)
Norway	3/37	3/41	1.012	(0.2038 , 5.02)
Philippines	5/52	6/52	0.858	(0.2619 , 2.81)
Poland	4/161	1/162	4.048	(0.4524 , 36.22)
Russia	4/100	2/99	1.987	(0.3639 , 10.85)
Slovakia	3/53	2/51	1.5	(0.2507 , 8.98)
South Korea	6/111	5/114	1.225	(0.3739 , 4.02)
Sweden	1/89	3/93	0.344	(0.0358 , 3.30)
Taiwan	4/117	5/119	0.752	(0.2017 , 2.80)
United Kingdom	2/113	2/111	0.948	(0.1335 , 6.73)
United States	46/1780	60/1788	0.765	(0.5213 , 1.12)



[Source: Reviewer's Results]

The point estimate (hazard ratio) in the most of countries is below the non-inferiority margin of 1.38. Furthermore, the upper bounds of hazard ratio were well below the margin in United States for both dabigatran doses.

3.2 Evaluation of Safety

Safety is not evaluated in this review. Please see the clinical review.

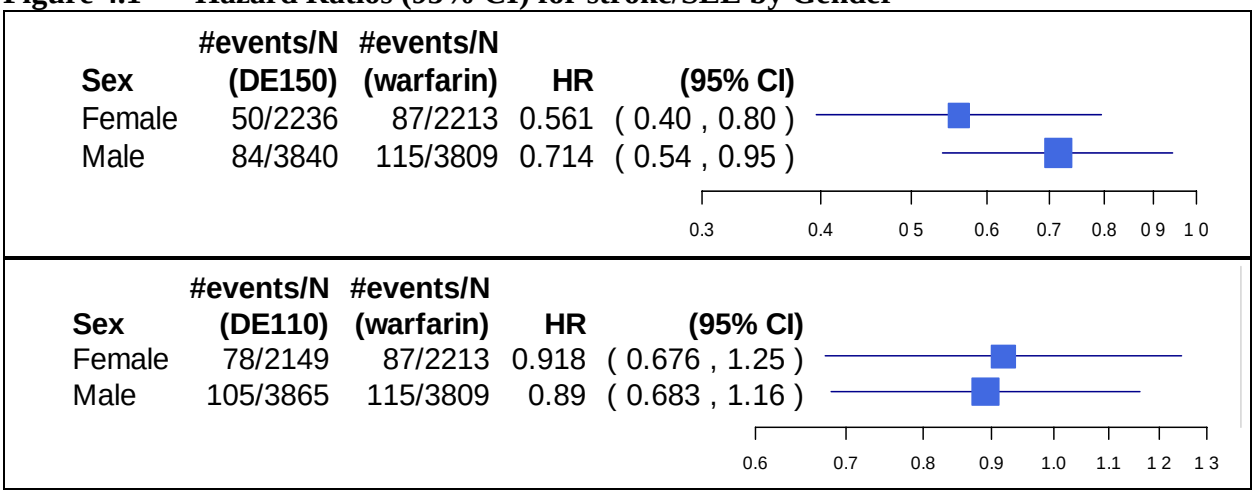
4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Age and Race group

4.1.1 GENDER

There were no obvious differences in hazard ratios for the primary endpoint across either Gender group. Both groups had favorable non-inferior results towards dabigatran doses when compared to warfarin. The DE 150mg was superior to warfarin in both female and male, see Figure 4.1.

Figure 4.1 Hazard Ratios (95% CI) for stroke/SEE by Gender

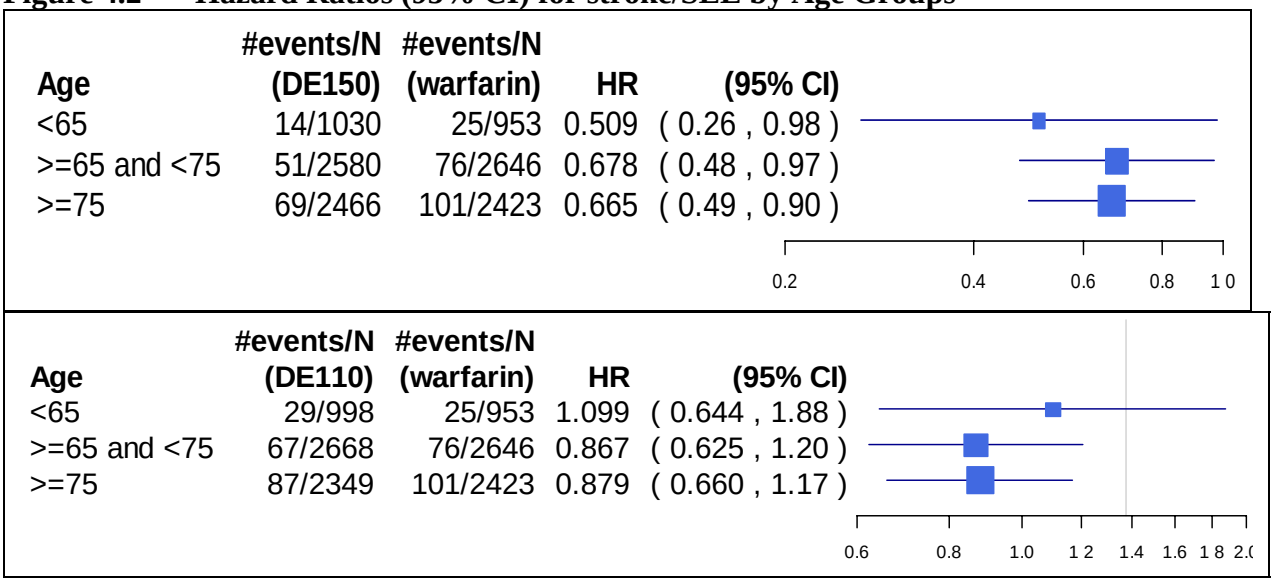


[Source: Reviewer's results]

4.1.2 AGE

The age is categorized into the following three groups: < 65, 65-75, and ≥75. The rates of stroke/SEE increased with age across all three treatment groups. Among the six comparisons in the Figure 4.2, only DE 110 had a hazard ratio greater than 1 over warfarin in the younger than 65 years of age group. The rest of groups had consistent results as the primary analysis results.

Figure 4.2 Hazard Ratios (95% CI) for stroke/SEE by Age Groups



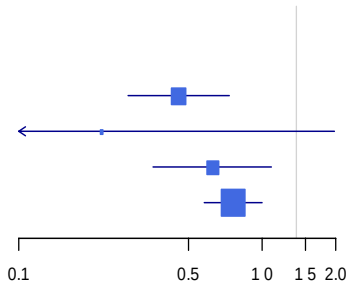
[Source: Reviewer's results]

4.1.3 RACE

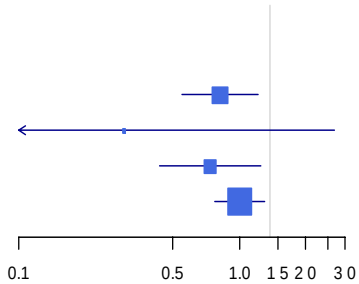
Whites dominated the numbers of subjects. There were no obvious differences in hazard ratios for the primary endpoint observed across different Race groups, except that for Blacks both DE groups had relatively low hazard ratios compared to warfarin. This is due to the fact there are fewer than 70 black subjects in each group.

Figure 4.3 Hazard Ratios (95% CI) for stroke/SEE by Race

Race	#events/N (DE150)	#events/N (warfarin)	HR	(95% CI)
Asian	25/965	52/955	0.453	(0.2808 , 0.73)
Black	1/57	4/67	0.218	(0.0241 , 1.97)
Other	20/786	32/797	0.622	(0.3556 , 1.09)
White	88/4268	114/4203	0.757	(0.5735 , 1.00)



Race	#events/N (DE110)	#events/N (warfarin)	HR	(95% CI)
Asian	44/955	52/955	0.815	(0.5456 , 1.22)
Black	1/52	4/67	0.3	(0.0334 , 2.69)
Other	24/799	32/797	0.736	(0.4336 , 1.25)
White	114/4208	114/4203	0.997	(0.7689 , 1.29)



[Source: Reviewer's results]

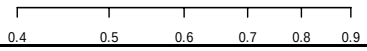
4.2 Other Subgroup Populations

4.2.1 PRIOR VKA USE

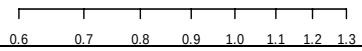
Warfarin, the most widely used VKA, was chosen as the active control. Therefore, it is important to find out whether Dabigatran has any different effects depend on the patients' prior VKA usage.

Figure 4.4 Hazard Ratios (95% CI) for stroke/SEE by Prior VKA Usage

Prior VKA Use	#events/N (DE150)	#events/N (warfarin)	HR	(95% CI)
Naived	61/3028	97/3093	0.634	(0.460 , 0.873)
Experienced	73/3047	105/2929	0.661	(0.491 , 0.892)



Prior VKA Use	#events/N (DE110)	#events/N (warfarin)	HR	(95% CI)
Naived	89/3005	97/3093	0.935	(0.701 , 1.25)
Experienced	94/3008	105/2929	0.868	(0.657 , 1.15)



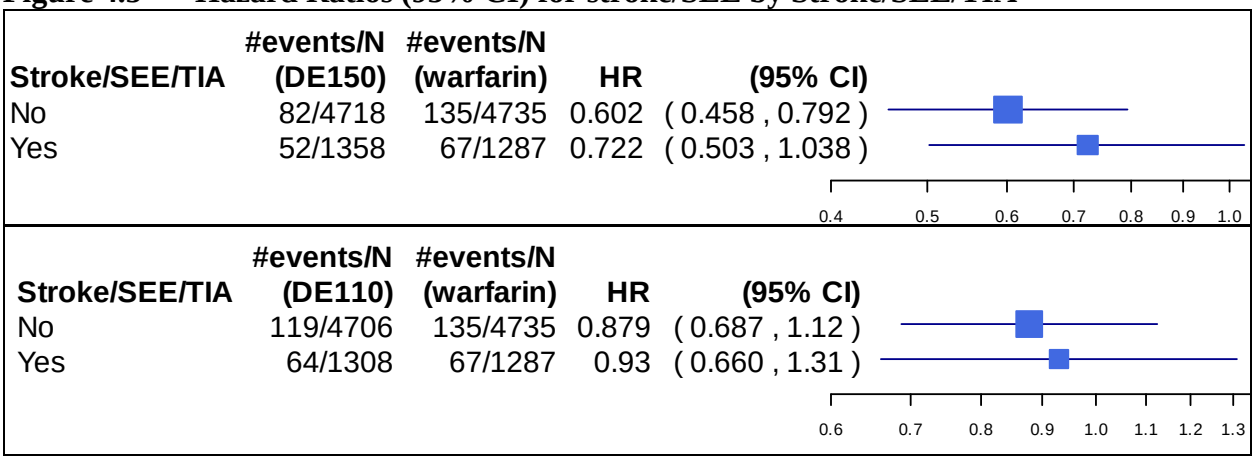
[Source: Reviewer's Results]

Based on Figure 4.4, the hazard ratio of stroke/SEE on DE 110 over warfarin did not rule out 1.00 regardless of VKA use, so they had similar event rates for this primary endpoint. On the other hand, DE 150 seemed numerically superior to warfarin regardless of VKA use.

4.2.2 History of Stroke/SEE/TIA

The majority of subjects never had any episodes of Stroke/SEE/TIA in all treatment groups. Both Dabigatran doses had lower hazard ratio over warfarin in this subgroup. Furthermore, DE 150 was numerically superior to warfarin in this subgroup. Among the subjects who ever had history of Stroke/SEE/TIA, DE 110 seems similar to warfarin in the Stroke/SEE event rates. DE 150 nearly demonstrated superiority over warfarin in this subgroup, see Figure 4.5.

Figure 4.5 Hazard Ratios (95% CI) for stroke/SEE by Stroke/SEE/TIA



[Source: Reviewer's Results]

4.2.3 Subgroup analysis for baseline Medication use

The treatment effects of both DE 110 and 150 were generally consistent across all subgroups defined by baseline medication use in comparison to warfarin. In general, DE 110 was comparable to warfarin and DE 150 was numerically superior to warfarin for most of the subgroups, see Table 9.

Table 9 Hazard Ratios (95% CI) for Stroke/SEE by medication use

	DE 110 mg vs. Warfarin	**DE 150 mg vs. Warfarin**
	Hazard Ratio (95% CI)	Hazard Ratio (95% CI)
ASA		
Never used	0.92 (0.71, 1.20)	0.64 (0.48, 0.86)
Used at least once	0.87 (0.64, 1.18)	0.67 (0.48, 0.93)
Clopidogrel		
Never used	0.95 (0.77, 1.17)	0.66 (0.52, 0.83)
Used at least once	0.38 (0.16, 0.91)	0.57 (0.27, 1.20)
ASA+Clopidogrel		
Never used	0.96 (0.78, 1.17)	0.67 (0.48, 0.86)
Used at least once	0.08 (0.01, 0.58)	0.31 (0.10, 0.93)
Amiodarone		
Never used	0.94 (0.77, 1.16)	0.68 (0.54, 0.85)
Used at least once	0.47 (0.21, 1.04)	0.35 (0.15, 0.83)
Verapamil		
Never used	0.94 (0.76, 1.16)	0.67 (0.54, 0.84)

Used at least once	0.46 (0.20, 1.06)	0.40 (0.17, 0.96)
Diltiazem		
Never used	0.93 (0.76, 1.15)	0.67 (0.53, 0.84)
Used at least once	0.60 (0.29, 1.23)	0.46 (0.21, 1.02)
Statin		
Never used	1.00 (0.77, 1.31)	0.56 (0.41, 0.76)
Used at least once	0.78 (0.58, 1.06)	0.75 (0.55, 1.02)

[Source: Reviewer's Results]

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

The non-inferiority margin

The proposed testing hypothesis for RE-LY was that whether either dabigatran doses (110 mg and 150 mg) were non-inferior to warfarin in reducing the incidences of Stroke/SEE. The non-inferiority margin of 1.46 for the hazard ratio in the sponsor's study report was derived based on the historical placebo controlled trials using the 95%-95% rule. This rule utilized the lower bound of the 95% confidence interval of the hazard ratio for warfarin versus placebo for the derivation of the non-inferiority margin, and the upper bound of the 95% confidence limit for dabigatran versus warfarin for the statistical test. The margin 1.46 used in the study design preserved at least 50% of warfarin's effect on the risk ratio scale using the lower bound of the 95% of the risk ratio of placebo over warfarin. However, a smaller margin of 1.38, derived to preserve the effect of warfarin on the Log scale, was recommended by a regulatory agency. In spite of this discrepancy on the margin, both dabigatran doses were non-inferior to warfarin based on the sponsor's efficacy findings.

Summary of the historical trials and constancy assumption

The effectiveness of warfarin has been studied both in placebo-controlled and active-controlled trials. There are six placebo-controlled studies of warfarin involved the patients with AF between 1989 and 1992. All these trials showed a consistent efficacy for warfarin in preventing stroke and other cardiovascular events, despite differences in their designs and patient populations. The primary outcomes of these studies are summarized in Table 10. Almost all of the trials showed significant reduction in the primary endpoint event by warfarin against placebo. Trial CAFA failed to show a significant benefit over placebo, but the estimated warfarin effect from this trial was consistent with those observed from the other trials.

Table 10 Placebo-Controlled Trials of Warfarin in Non-Valvular Atrial Fibrillation

Study	Summary	Events/Patient Years		Risk Ratio (95% CI)
		Warfarin	Placebo	
AFASAK	open label. 1.2 yr follow-up	9/413 = 2.18%	21/398 = 5.28%	0.41 (0.19, 0.89)
BAATAF	open label. 2.2 yr follow-up	3/487 = 0.62%	13/435 = 2.99%	0.21 (0.06, 0.72)
EAFT	open label. 2.3 yr follow-up patients with recent TIA	21/507 = 4.14%	54/405 = 13.3%	0.31 (0.19, 0.51)
CAFA	double blind. 1.3 yr follow-up	7/237 = 2.95%	11/241 = 4.56%	0.65 (0.26, 1.64)
SPAF I	open label. 1.3 yr follow-up	8/260 = 3.08%	20/244 = 8.20%	0.38 (0.17, 0.84)
SPINAF	double blind. 1.7 yr follow-up	9/489 = 1.84%	24/483 = 4.97%	0.37 (0.17, 0.79)

[Source: FDA Non-inferiority draft guidance Table 1]

Even if the historical studies are consistent, a critical consideration in deciding upon the NI margin derived from these studies is whether the constancy assumption is reasonable. To evaluate the plausibility of this constancy assumption, one might compare some features of the six placebo-controlled warfarin studies with the RE-LY study. There is considerable heterogeneity in the demographic characteristics of these studies. The draft guidance listed number of characteristics, such as a history of stroke or TIA, see Table 11. The most of characteristics are similar among the historical studies with RE-LY, but the history of stroke or TIA and CAD are much higher in RE-LY.

Table 11 Comparisons on Demographic Variables, Clinical Characteristics, and Endpoints of Historical Warfarin AF Studies vs. RE-LY

	AFASAK	BAATAF	CAFA	SPAF	VA	EAFT	RE-LY
Age years (mean)	73	69	68	65	67	71	71
Sex (%) Male	53%	75%	76%	74%	100%	59%	59%
h/o stroke or TIA (%)	6%	3%	3%	8%	0%	100%	20%
h/o HTN (%)	32%	51%	43%	49%	55%	43%	NA
≥65 years old & CAD (%)	8%	10-16%	12-15%	7%	17%	7%	24.2%
>65 years old & DM (%)*	7-10%	14–16%	10-14%	13%	17%	12%	19.3%
h/o LV dysfunction (%)*	50%	24-28%	20-23%	9%	31%	8%	10.7%
Mean BP at BL (mm Hg)	NA	NA	NA	130/78	NA	145/84	131/77
Target INR	2.8-4.2	1.5-2.7	2-3	2-4.5	1.4-2.8	2.5-4.0	2-3
Primary endpoint	Stroke, TIA, systemic embolism	Ischemic stroke	Ischemic stroke and systemic embolism	Ischemic stroke and systemic embolism	Ischemic stroke	Vascular death, NF MI, stroke, systemic embolism	Stroke and SEE

Increase of sample size

The study was originally designed as an event driven trial. Based on an estimated yearly event rate of 1.6% and a two-year enrolment period and one-year follow up, a total of 15,000 subjects were planned to be randomized from approximately 800 centers. Due to rapid enrollment, 15,000 subjects were randomized in 1.5 years (18 months). Sponsor claimed that if the recruitment was stopped at that time, the last randomized subjects would have had to follow up for more than 1 year to achieve the planned total number of events, if the actual event rate was as expected. In addition, sponsor also claims that the actual event rate could be less than 1.6% based on other published studies. Therefore, sponsor decided to continue the recruitment as planned, which resulted a total of 18,113 subjects were randomized and the total number of subjects with adjudicated stroke/SEE was increased to 519. The above changes were added to protocol's second amendment on May of 2007. In order to validate the final primary efficacy results, both the sponsor and this reviewer had performed the sensitivity analysis for the first 450 adjudicated primary events. Based on all the analyses results, both doses of dabigatran have met the pre-

specified non-inferior margin to warfarin to conclude that the two doses are effective for the stroke prevention in AF patients. Furthermore, DE 150 was superior to warfarin as well, see Table 4.

5.2 Conclusions and Recommendations

Overall, RE-LY demonstrated that both doses of dabigatran were non-inferior to warfarin and DE 150 was superior to warfarin for the primary (stroke/SEE) efficacy endpoints. Furthermore, the secondary (stroke/SEE/death and stroke/SEE/PE/MI/vascular death) efficacy endpoints also met the above claims numerically. However, sponsor did not specify the statistical testing rules and margins for these endpoints in the TSAP. Therefore, these findings can only be viewed as exploratory findings.

There was no discrepancy results found in any of the sensitivity analyses. Although, DE 150 did not show superiority for US subjects statistically, but it was still non-inferior to warfarin and the point estimate (hazard ratio) also less than 1.00. All the subgroup analyses performed in Section 4 were consistent with the primary efficacy results. Hence, RE-LY's finding is very robust. Furthermore, based on the reviewer's analysis on the impact of different end of trial dates, the dabigatran doses achieved the non-inferiority long before the end of trial date and DE 150 achieved superiority to warfarin more than one year before the end of trial date, see Figure 3.3.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22512	ORIG-1	BOEHRINGER INGELHEIM PHARMACEUTICALS INC	PRADAXA (DABIGATRAN ETEXILATE MESYLATE)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

STEVE G BAI
07/20/2010

HSIEN MING J J HUNG
07/20/2010