CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
22-512

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

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
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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_____
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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 $\geq$ 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 10^{th} to 90^{th} 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 10^{th} to 90^{th} 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 (b) (4) product used in the RE-LY trial and the (b) (4) 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

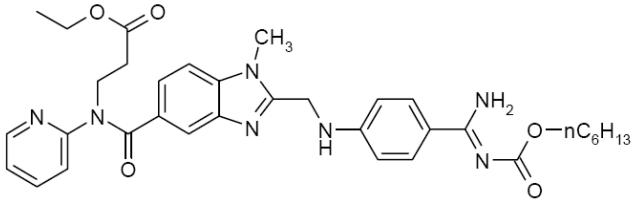
3.1 General Attributes

3.1.1 History of Regulatory Development

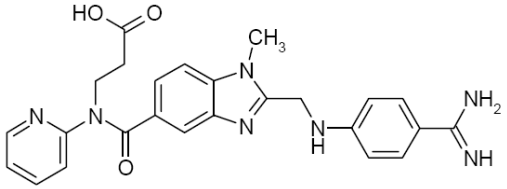
Dabigatran is a synthetic, non-peptide, competitive, oral direct thrombin inhibitor (oral DTI), that specifically and reversibly inhibits thrombin, the final enzyme in the coagulation cascade. Dabigatran etexilate is the oral pro-drug of the active moiety dabigatran and does not possess any anticoagulant 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 ± 0.1 (benzimidazol moiety) pKa_2 = 6.7 ± 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.

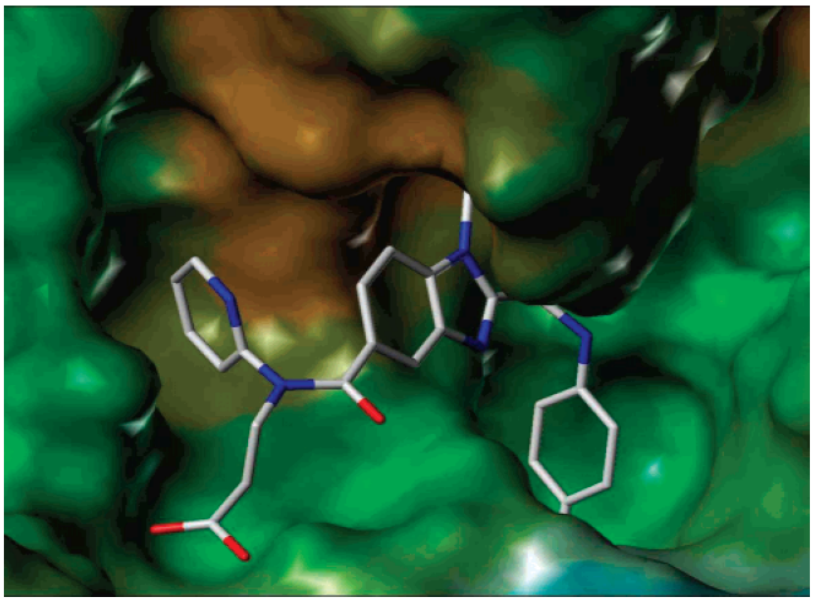


Figure 1. X-ray crystal structure of BIBR953 in complex with thrombin in a surface representation. The lipophilic potential is mapped on the protein surface.

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%.

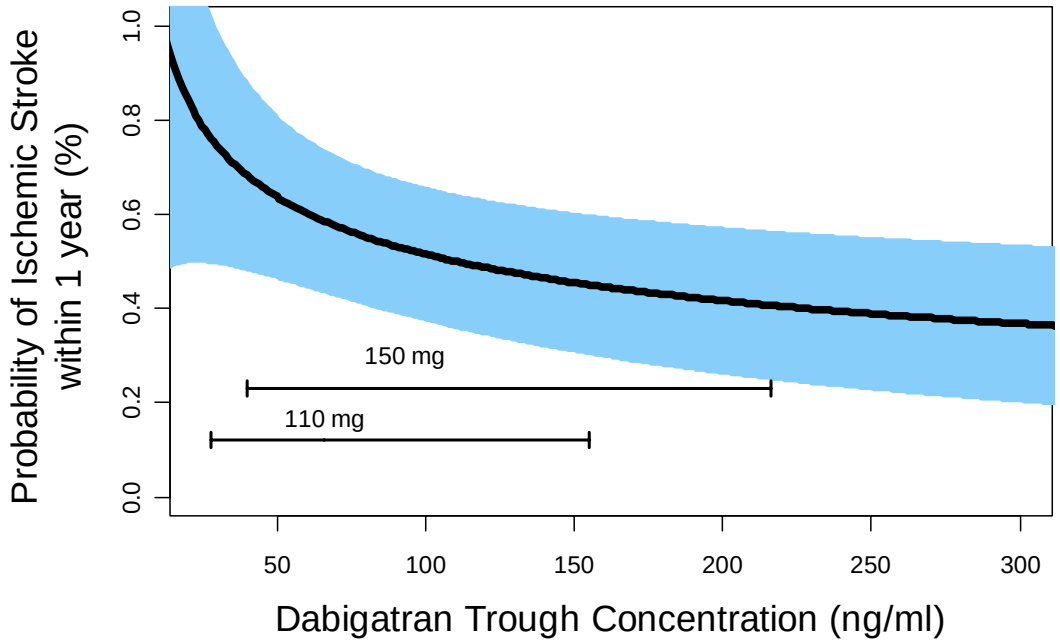


Figure 2. Probability of ischemic stroke within 1 year vs. dabigatran pre-dose concentration. The blue shaded region represents the standard error. The bars on the bottom on the plot region represent the 10th to 90th percentiles of observed dabigatran pre-dose concentrations in the RE-LY trial.

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%.

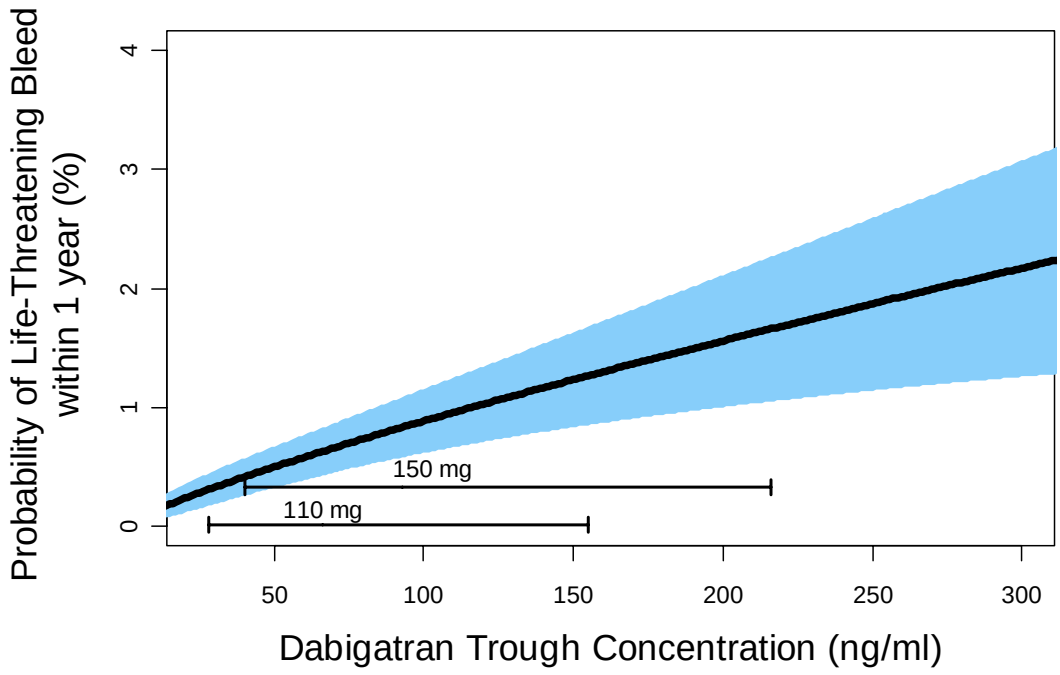


Figure 3. Probability of a major bleed within 1 year vs. dabigatran pre-dose concentration. The blue shaded region represents the standard error. The bars on the bottom on the plot region represent the 10th to 90th percentiles of observed dabigatran pre-dose concentrations in the RE-LY trial.

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.

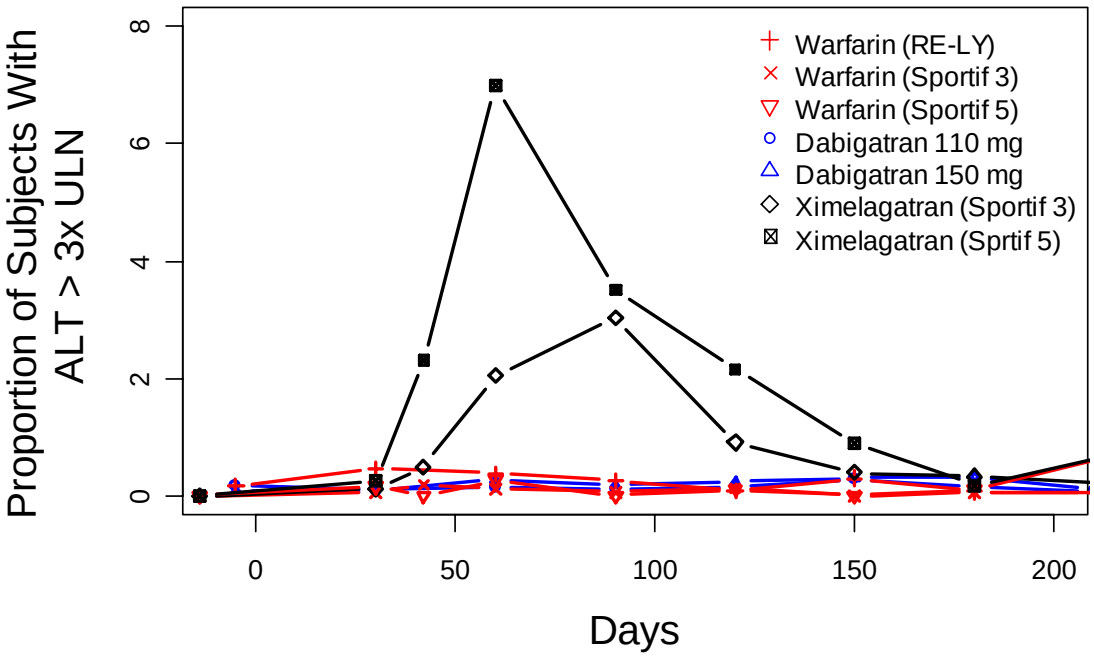


Figure 4. Time course of ALT > 3x ULN for warfarin, ximelagtran and dabigatran in the Sportif and RELY trials.

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.

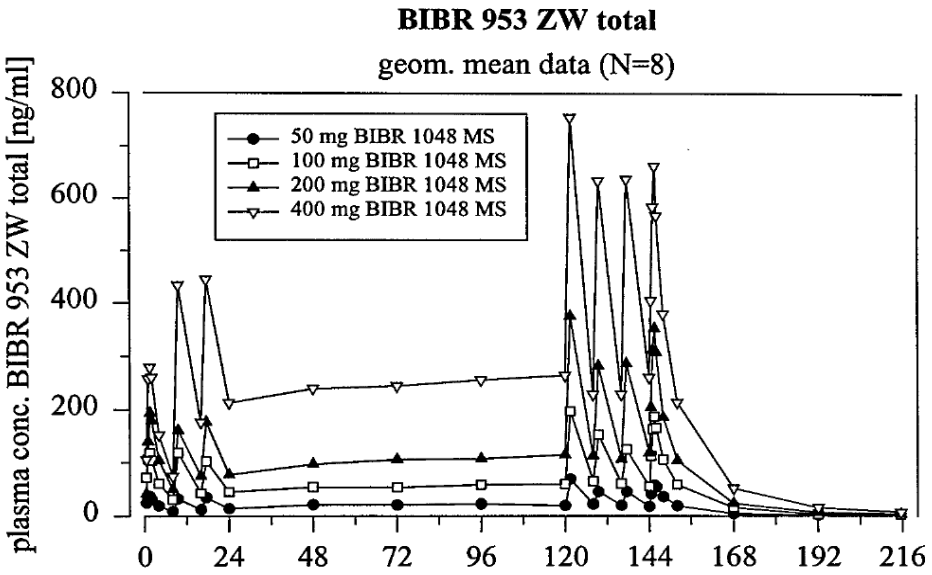


Figure. 5. Geometric mean total dabigatran plasma concentration vs. time (hrs)

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.

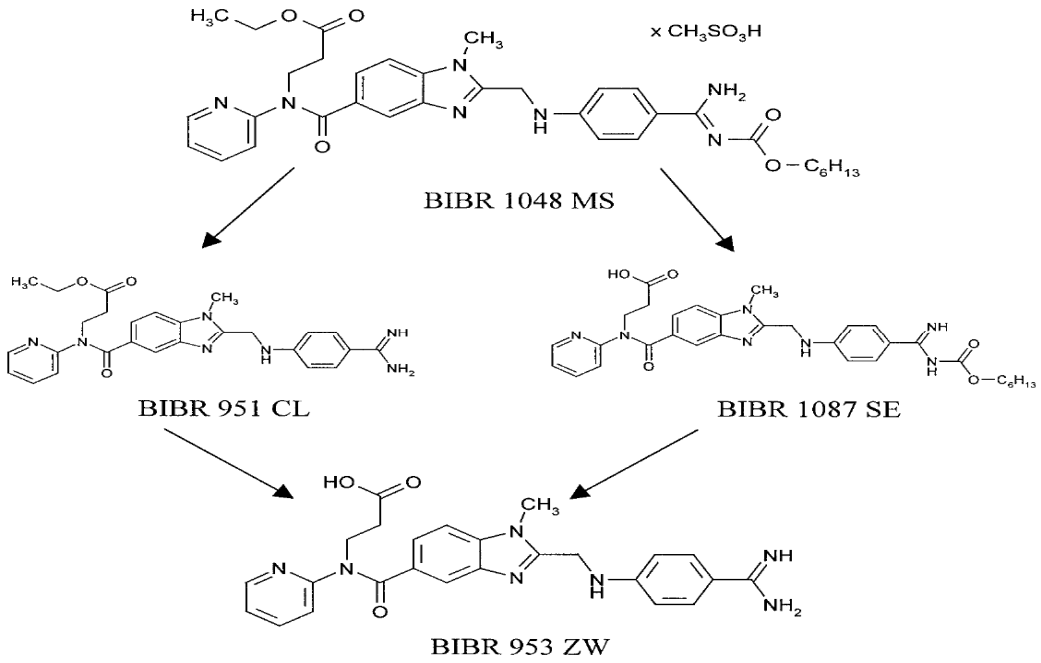
3.2.11 Does the mass balance study suggest renal or hepatic as the major route of elimination?

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.

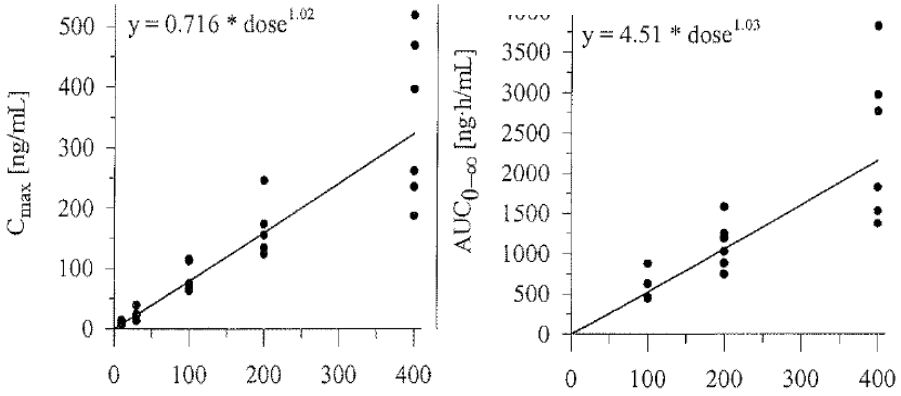


Figure 6. Dose proportionality of total dabigatran Cmax and AUCinf after the single doses of BIBR1048MS

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.

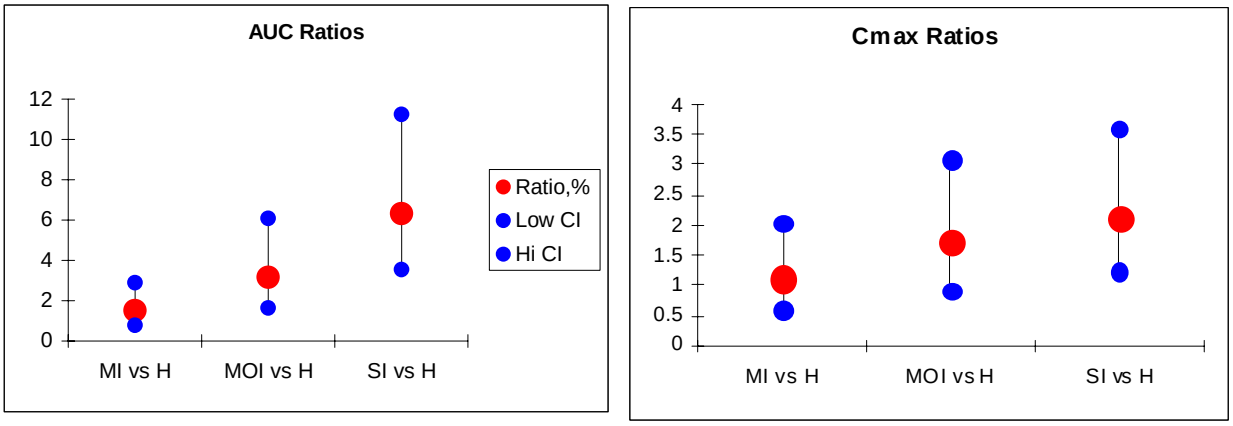


Figure 7. Comparison of the geometric mean ratios for AUC and Cmax (mean and 90%CI) in subjects with renal impairment vs. healthy subjects

Although excretion was not completed for SI subjects (over 24 hours), the data for HC, MI & MOI groups demonstrate that the relationship is linear.

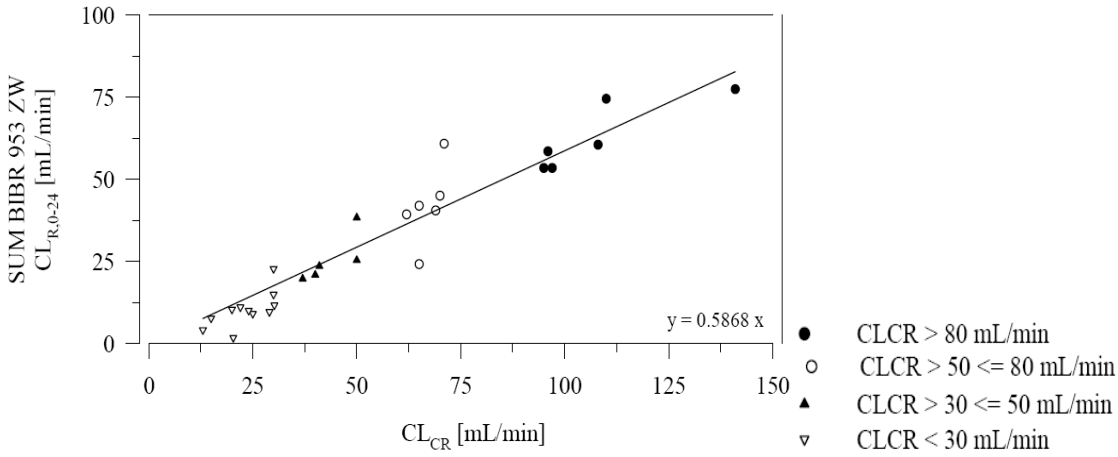


Figure 8. Correlation between individual values of total dabigatran renal clearance (0-24) and creatinine clearance

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).

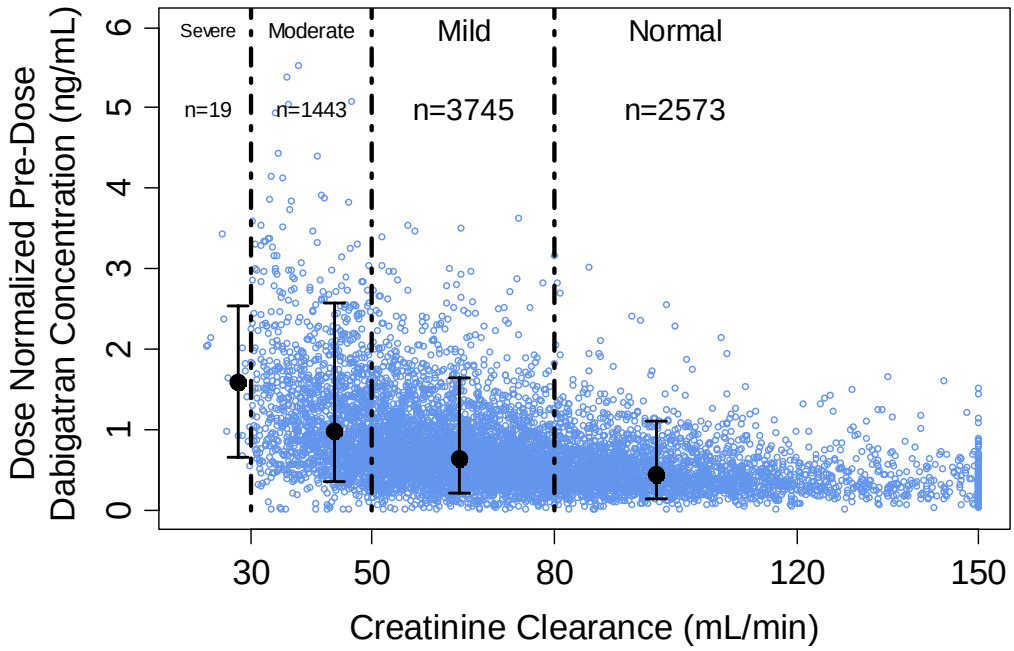


Figure 9. Dose-normalized pre-dose dabigatran concentration vs. creatinine clearance in RE-LY.

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.

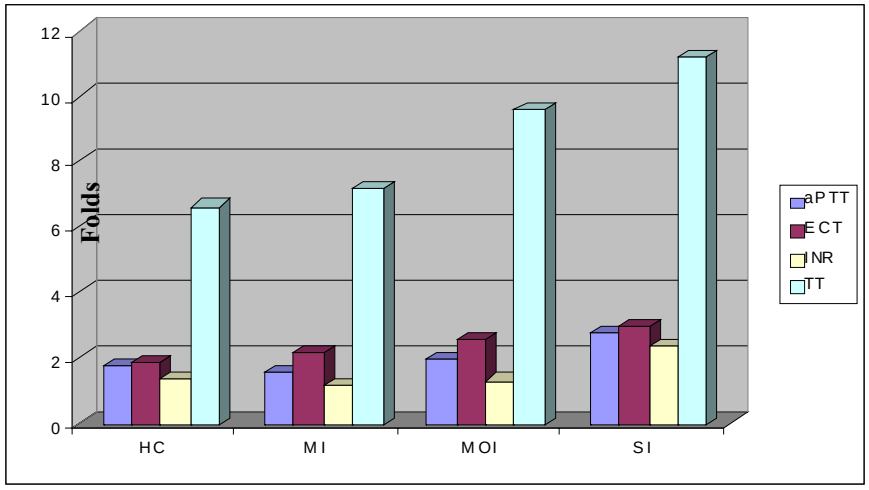


Figure 10. Baseline corrected mean maximum prolongation of blood coagulation parameters (aPTT, ECT, INR, and TT)

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.

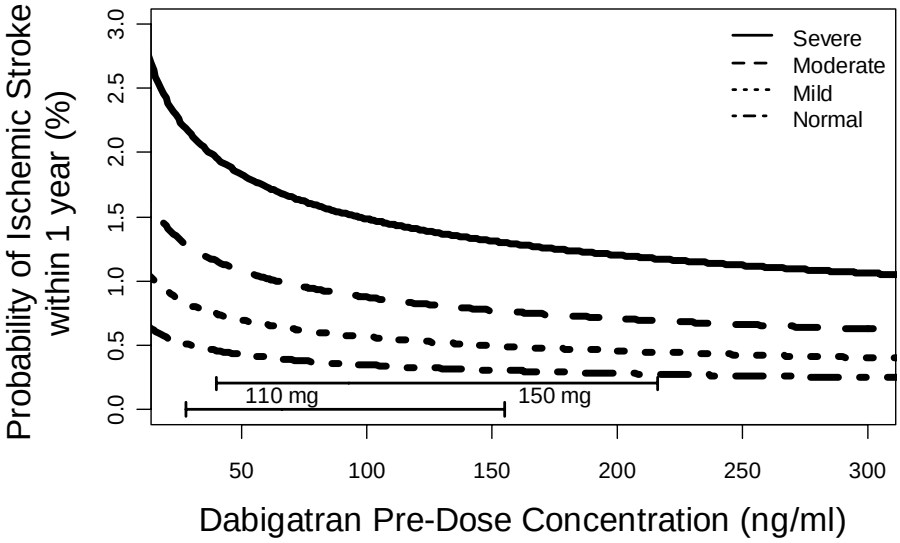


Figure 11: Probability of ischemic stroke with 1 year vs. dabigatran pre-dose concentration in a patient with no history of stroke/TIA by creatinine clearance category.

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.

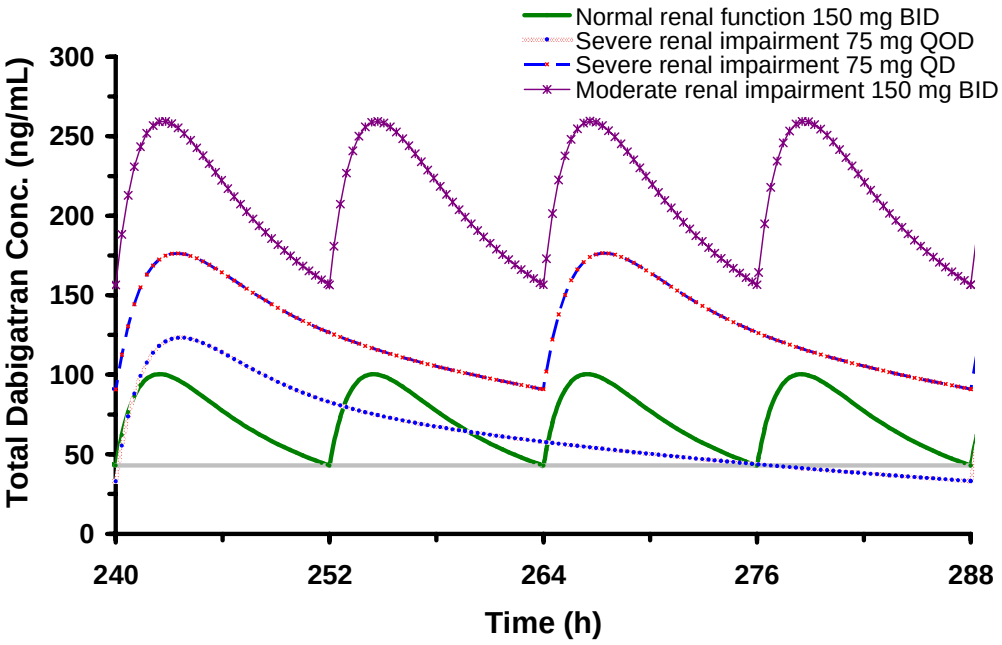


Figure 12: Simulated mean steady state total dabigatran plasma concentration for subjects with normal renal function and moderate renal impaired administered 150 mg BID and severe renal impaired patients administered 75 mg QD and 75 mg every other day.

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.

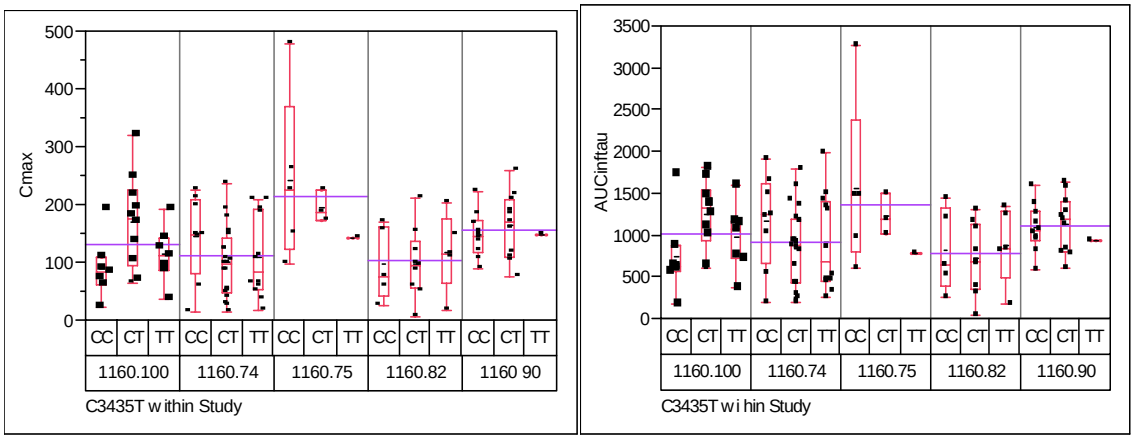


Figure 13. Total dabigatran exposure by *ABCB1* 3435C>T genotype in healthy subject drug interaction studies (monotherapy phases) AUC0-∞ is presented for single dose studies (1160.74, 1160.82, 1160.100); AUC0-τ and Cmax,ss are presented for multiple dose studies (1160.75, 1160.90). Horizontal blue lines 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.

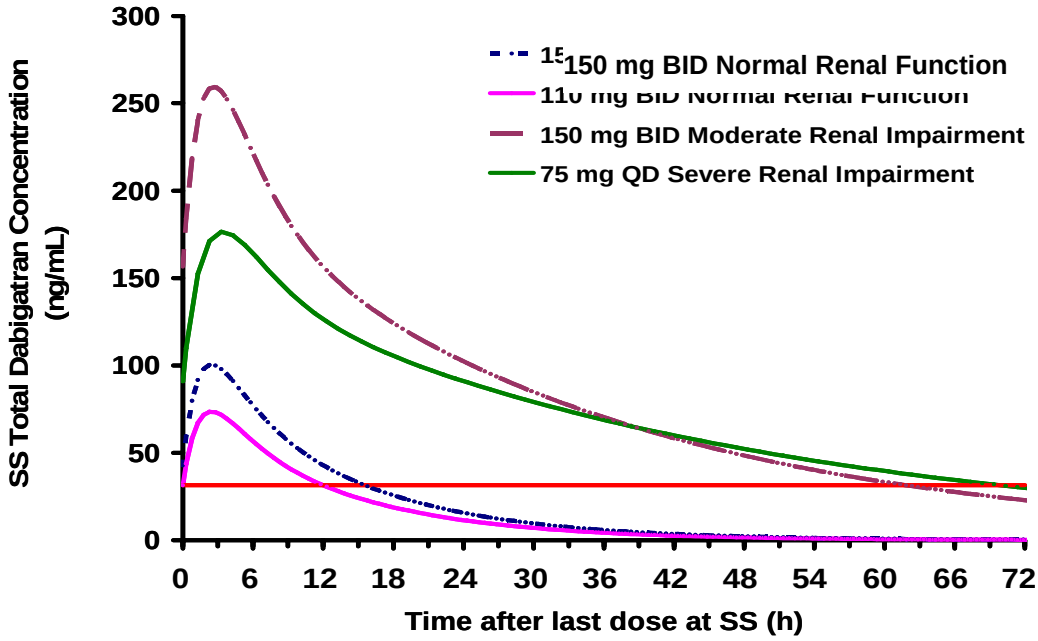


Figure 14: Simulated mean steady state total dabigatran plasma concentration following last dose for subjects with normal renal function and moderate renal impaired administered 150 mg BID and severe renal impaired patients administered 75 mg QD.

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)

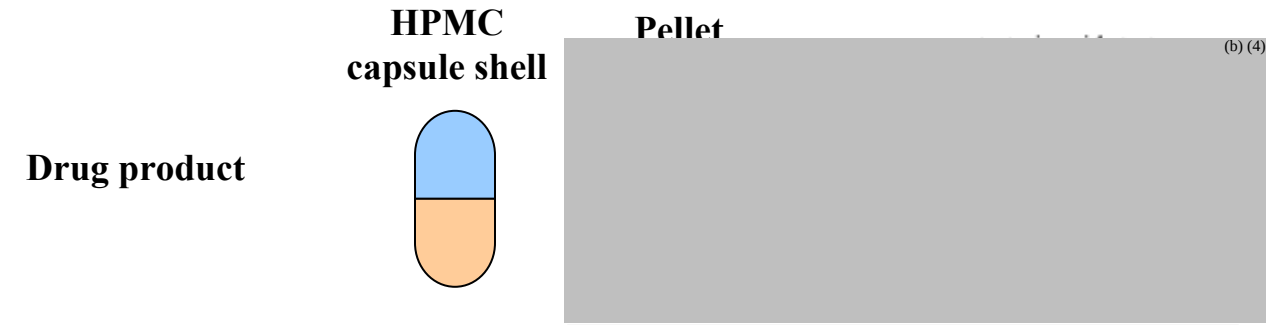


Figure 9: Final marketing image of dabigatran etexilate capsules

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			
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.

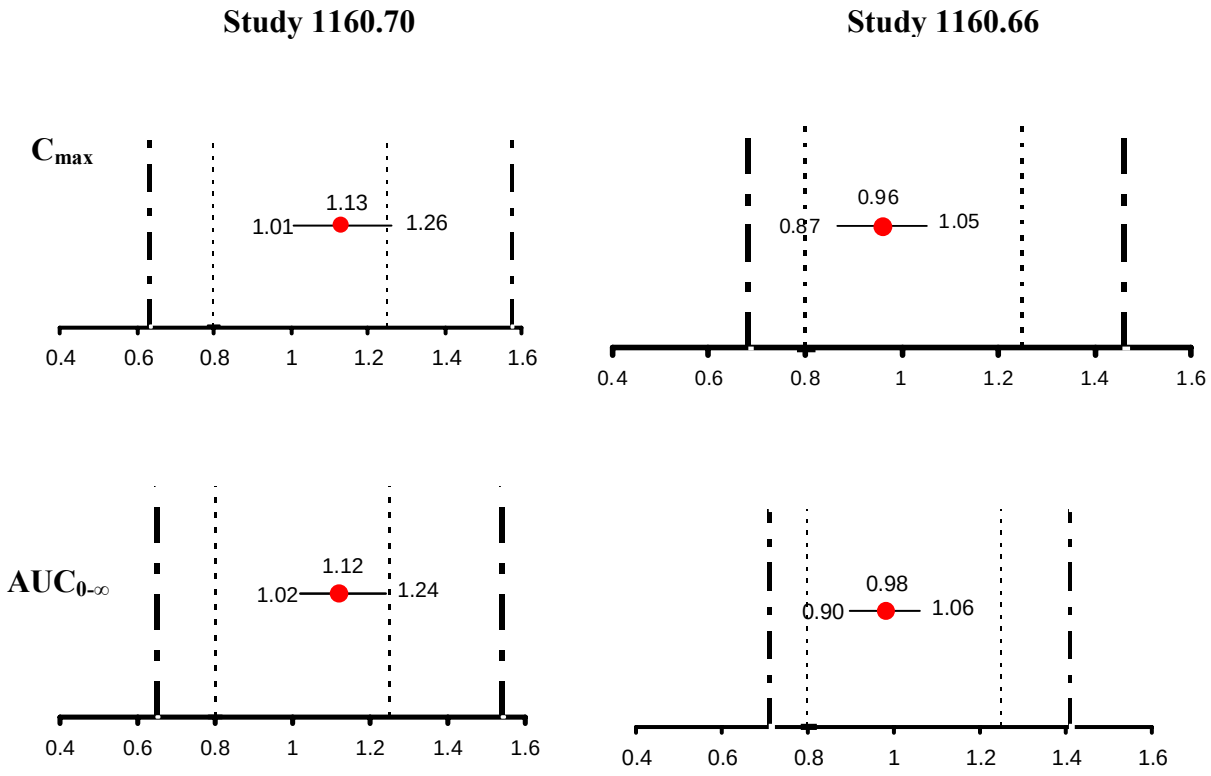


Figure 15: X-axis represents the geometric mean ratios. The fine and bold broken vertical lines represent the unscaled and scaled average bioequivalence limits. Data is represented as geometric mean ratio of the PK metrics (C_{max}, $AUC_{0-\infty}$) with 90% CI around the point estimate.

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).

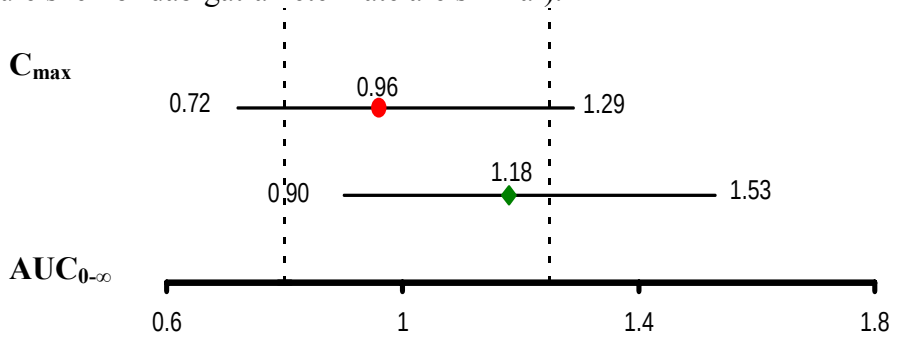


Figure 16 : Effect of a high fat meal on total dabigatran exposure. X-axis represents the geometric mean ratios. The fine broken vertical lines represent 80-125% limits. Data is represented as geometric mean ratio of the PK metrics (C_{max}, $AUC_{0-\infty}$) with 90% CI around the point estimate.

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).

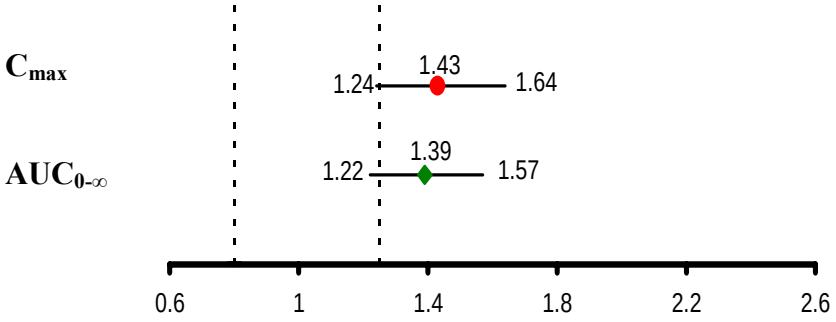


Figure 17: Relative bioavailability of total dabigatran when administered as pellets when compared to pellets in capsules. X-axis represents the geometric mean ratios. The fine broken vertical lines represent 80-125% limits. Data is represented as

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
09/01/2010
This review (originally signed on 8/17/2010) is resubmitted in order to include the signature of the Division Director

PETER H HINDERLING
09/02/2010

SUDHARSHAN HARIHARAN
09/02/2010
Note: On page 30 Section 3.4.1 line 3, the sentence should read "...corresponding to 110 mg BID..."

KEVIN M KRUDYS
09/07/2010

PRAVIN R JADHAV
09/07/2010

MICHAEL A PACANOWSKI
09/07/2010

ISSAM ZINEH
09/07/2010

RAJANIKANTH MADABUSHI
09/08/2010
Concur

MEHUL U MEHTA

09/08/2010

ONDQA (Biopharmaceutics) Review Addendum

NDA:	22-512 (000)
Submission Date:	08/10/10
Product:	Dabigatran etexilate mesylate Capsules (75, 110 and 150 mg)
Trade Name:	Pradaxa
Type of Submission:	Original Submission
Sponsor:	Boehringer Ingelheim (BI)
Reviewer:	Tapash K. Ghosh, Ph.D.

Background: This NDA is for a new molecular entity, dabigatran etexilate mesylate, an oral direct thrombin inhibitor for the indication of stroke prevention in atrial fibrillation.

FDA Request:

A teleconference was held August 3, 2010 between FDA and Boehringer Ingelheim to discuss the dissolution specification for dabigatran etexilate capsules. During this teleconference, FDA requested a dissolution specification of Q= (b) (4) *in 30 minutes.*

Subsequent to the teleconference (email of August 5, 2010), FDA requested BI to provide the following information to facilitate future discussions related to this topic:

1. *Provide the number of batches that pass Stage 1, Stage 2, and Stage 3, respectively; provide the number of batches that fail (OOS).*
2. *Do the capsules with very low dissolution values at 30 minutes pass at 45 minutes?*
3. *Clarify how you are handling these failures in view of the proposed 2-year expiration dating.*

BI provided additional information in response to the FDA's comments to the teleconference, to better clarify their analysis of the large data set of dissolution values that have been collected on dabigatran etexilate capsules. (This analysis was provided in BI's response to question #17 of FDA's June 29, 2010 Request for Information submitted July 15, 2010)

Dissolution data were obtained on 12 individual capsules for each timepoint during stability storage from registration stability batches. An assessment of the dissolution data for the nine primary stability batches in the original capsule colors and the three commitment batches in changed capsule colors is provided. Table 1 below shows a summary of the dissolution OOS frequency for all nine primary stability and three commitment stability batches,

Table 1 **Summary of the distribution of individual dissolution values in primary stability and commitment stability batch studies**

Batch (strength)	Packaging material	Storage condition	Q=(b) (4) at 30 minutes	Q=(b) (4) at 45 minutes
			Rate of Occurrence*	Rate of Occurrence*
709203 (75 mg)	PP bottle or 6ct alu/alu blister	25°C/60% r.h. or 40°C/75% r.h.	(b) (4)	
709204 (75 mg)	PP bottle or 6ct alu/alu blister	25°C/60% r.h. or 40°C/75% r.h.		
709205 (75 mg)	PP bottle or 6ct alu/alu blister	25°C/60% r.h. or 40°C/75% r.h.		
709000 (110 mg)	PP bottle or 6ct alu/alu blister	25°C/60% r.h. or 40°C/75% r.h.		
709001 (110 mg)	PP bottle or 6ct alu/alu blister	25°C/60% r.h. or 40°C/75% r.h.		
709002 (110 mg)	PP bottle or 6ct alu/alu blister	25°C/60% r.h. or 40°C/75% r.h.		
708724 (150 mg)	PP bottle or 6ct alu/alu blister	25°C/60% r.h. or 40°C/75% r.h.		
708725 (150 mg)	PP bottle or 6ct alu/alu blister	25°C/60% r.h. or 40°C/75% r.h.		
708726 (150 mg)	PP bottle or 6ct alu/alu blister	25°C/60% r.h. or 40°C/75% r.h.		
002703 (110 mg)	PP bottle or 6ct alu/alu blister	25°C/60% r.h. or 40°C/75% r.h.		
002704 (110 mg)	PP bottle or 6ct alu/alu blister	25°C/60% r.h. or 40°C/75% r.h.		
002705 (110 mg)	PP bottle or 6ct alu/alu blister	25°C/60% r.h. or 40°C/75% r.h.		
Summary of all registration stability values			**4 OOS out of (b) (4) = 0.2%**	**1 OOS out of (b) (4) = 0.05%**

* Only the criteria for individual dissolution values is assessed.

There were four individual values (b) (4) dissolved (=OOS) at the 30 minutes time point of the FDA proposed specification, and there was one value (b) (4) dissolved (=OOS) at the 45 minutes time point of the BI proposed specification. The data show a similar pattern for individual dissolution data below the (b) (4) and (b) (4) dissolved thresholds. Note that these individual OOS values occur in four (4) out of the twelve (12) registration batches in two packaging materials. The OOS results were observed at 25°C/(b) (4) r.h. and 40°C/(b) (4) r.h, and show that the occurence is not linked to the storage condition.

Based on that, BI believes that the proposed dissolution specification of Q = (b) (4) at the 45 minutes time point is justified and also reflects the dissolution of the pivotal clinical phase III study batches. BI would like to ask the FDA to reconsider their request for the Q = (b) (4) dissolved at 30 minutes specification.

In lieu of FDA's acceptance of this 45 minutes time point specification, BI proposes an alternative path towards an acceptable dissolution specification. In this proposal we will introduce an additional specification of Q = (b) (4) for the mean value only at 30 minutes. This additional specification would address the desire for tight control of the mean dissolution value at 30 minutes for all capsules tested at 45 minutes, with no individual value specification at 30 minutes, as shown below.

Time: 45 minutes; Q = (b) (4)	
Stage 1 (n=6):	No individual value is less than Q (b) (4)
Stage 2 (n=12):	The average value is equal to or greater than Q.
	No individual value is less than Q (b) (4)
Stage 3 (n=24):	The average value is equal to or greater than Q.
	Not more than 2 individual values are less than Q (b) (4)
	and none is less than Q (b) (4)

Time: 30 minutes	
Requirement:	The average value is equal to or greater than (b) (4) dissolved.
(n= capsules tested at 45 minutes)	

The above proposal involves collecting dissolution data at both the 30 minute and the 45 minute time point at the time of release and at all stability time points. BI would monitor the entire data set to confirm that no change in drug product quality occurs.

Discussion: Upon review of the raw individual dissolution data for each capsule from each batch at individual time points along with Dr. Prafull Shiromani and Dr. Kasturi Srinivasachar of ONDQA, no specific trend in OOS occurrence was observed. The OOS data appeared sporadic and the sponsor is advised to investigate further the root-cause of this sporadic OOS occurrence. Therefore, judging from the low percentage of OOS both at the 30 minute and 45 minute time points, the Agency still recommends a dissolution specification of ***Q =*** (b) (4) ***in 30 minutes.***

Recommendations:

- *The sponsor's justification of the dissolution methodology including use of size-adjusted basket beyond 6 months for 150 mg tablet is acceptable. However, the reviewer recommends a dissolution specification of* ***Q =*** (b) (4) ***in 30 minutes*** *using the following methodology:*

Apparatus:	USP Apparatus 1 (basket) for 75 (b) (4) USP Apparatus 1(basket with adjusted diameter, 24.5 mm) for 150 mg
Agitation:	100 rpm
Medium:	900 mL 0.01M HCl (pH 2.0)
Temperature:	37°C
Sampling time:	30 minutes
Determination:	Spectrophotometric at 325 nm.

- *The above specification (Q = (b) (4) in 30 minutes) will be granted as an interim specification for one year and during this period, the sponsor is recommended to collect dissolution data from all commercial batches at both 30 minute and 45 minute time points. After the one year time period the final dissolution specification will be set based on the collected data.*

- *The OOS data appeared sporadic and the sponsor is advised to investigate further the root-cause of this sporadic OOS occurrence.*

Tapash K. Ghosh, Ph. D.
Biopharmaceutics Primary Reviewer
Office of New Drugs Quality Assessment

FT Initialed by Patrick Marroum, Ph. D. _____

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/

TAPASH K GHOSH
08/24/2010

PATRICK J MARROUM
08/25/2010

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

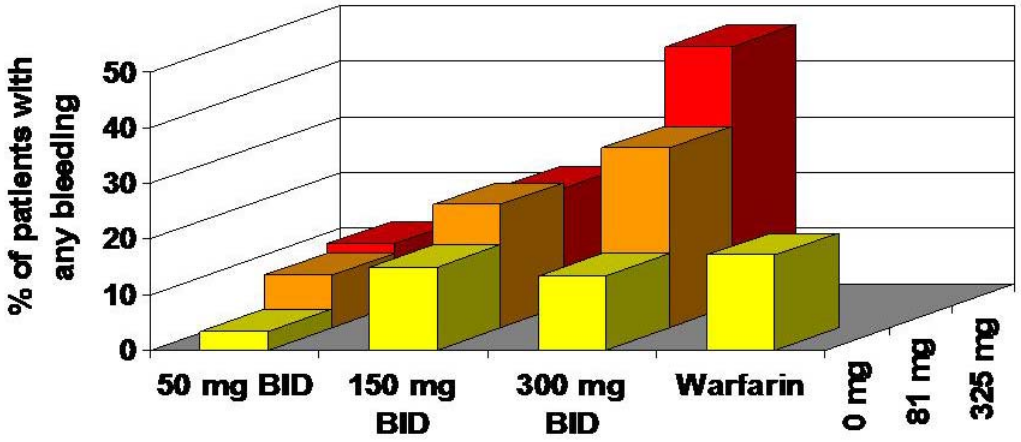
Dabigatran etexilate is a prodrug of dabigatran, a competitive, reversible direct thrombin inhibitor being developed for the prevention of stroke, non-CNS systemic embolism and reduction of vascular mortality in subjects with non-valvular atrial fibrillation. The proposed dose is 150 mg twice daily. 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

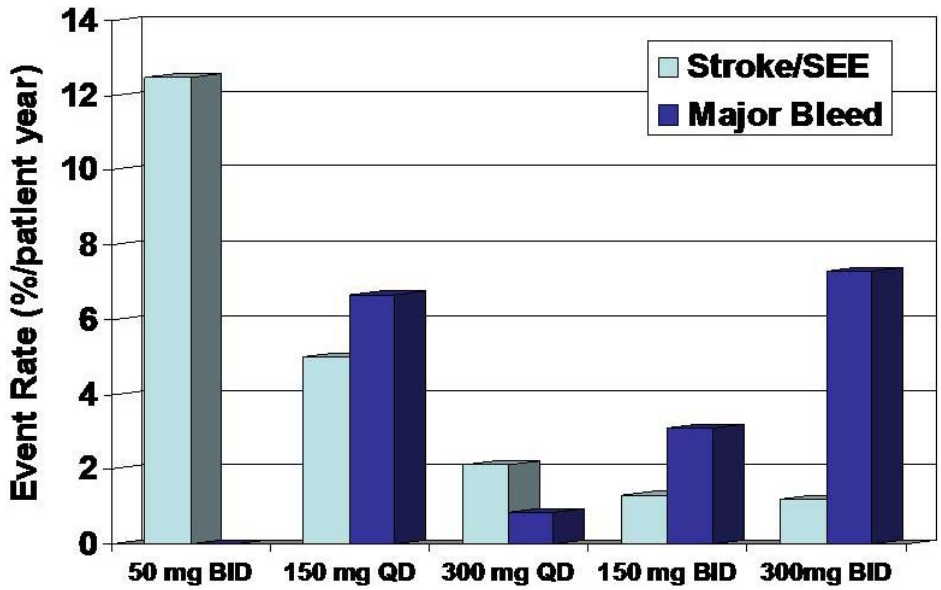
The dose ranging PETRO study randomized 502 subjects with chronic atrial fibrillation to 12 weeks treatment of 50, 150 or 300 mg dabigatran twice daily combined with 0, 81 or 325 mg aspirin in a factorial design with an additional arm of subjects treated with warfarin adjusted to INR 2 to 3. In the absence 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

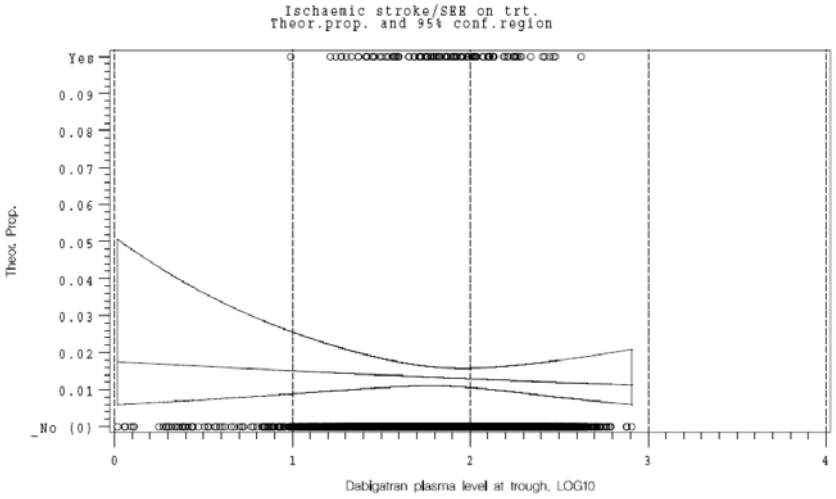
Source data: Table 15.6.3: 1
Prim.: primary endpoint (stroke, systemic embolism)
Sec.1: secondary endpoint 1 (stroke, systemic embolism, all death)
Sec.2: secondary endpoint 2 (stroke, systemic embolism, pulmonary embolism, myocardial infarction, vascular deaths)
(+): with event on treatment, (-): without 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

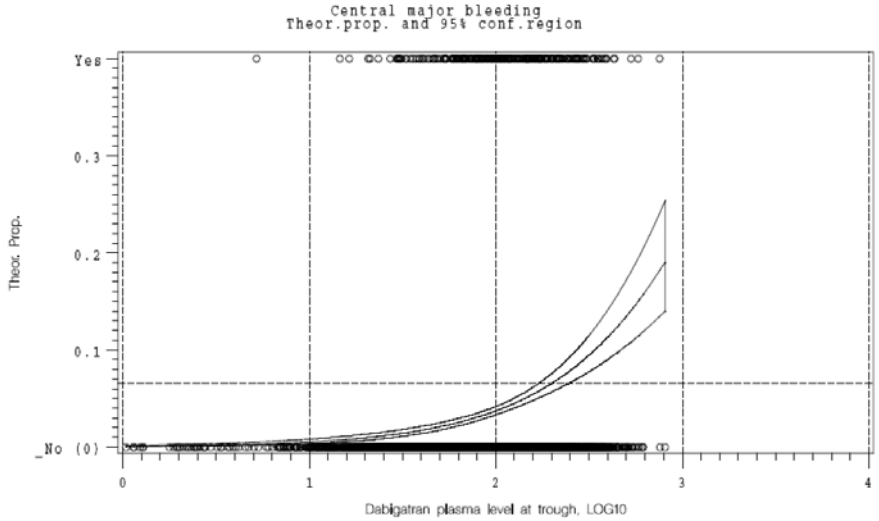


Source: Clinical Overview P-33, Figure 2.5.3.4.5: 3

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

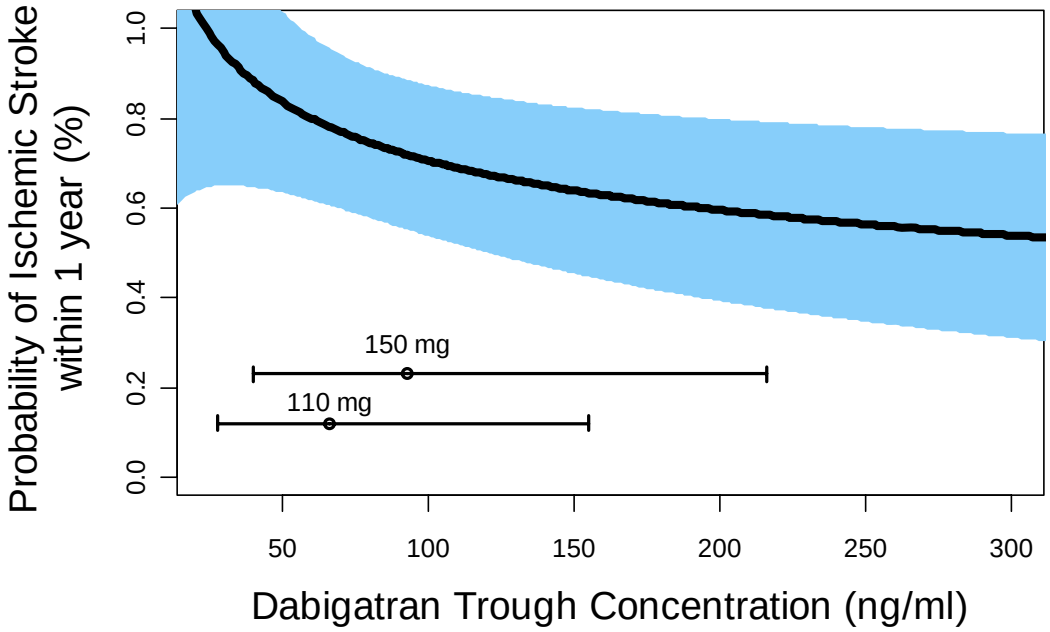
The exposure-efficacy analysis identified age, weight, history of stroke/TIA, diabetes mellitus and age ≥ 65 years and trough dabigatran concentration as significant risk factors. The parameter describing the relationship between dabigatran concentration and ischemic stroke was of marginal significance ($p=0.056$) 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

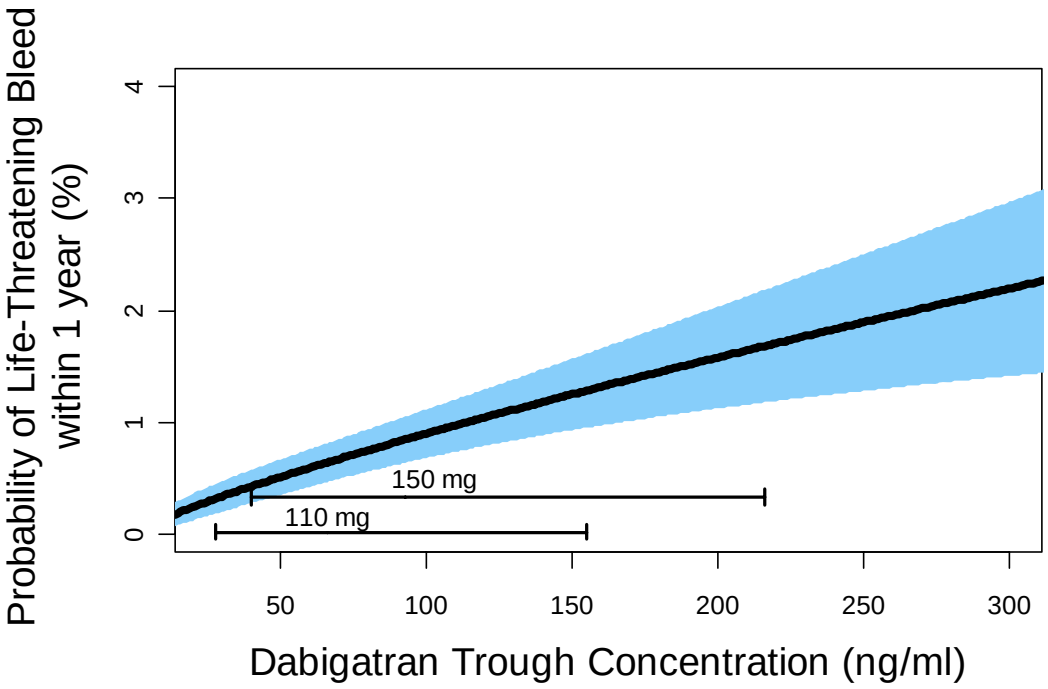
The exposure-efficacy analysis identified age, sex, trough dabigatran concentration, history of stroke/TIA and coronary artery disease and age ≥ 65 years as significant risk factors. These results are similar to the analysis conducted by the sponsor. Aspirin use was not identified as a significant covariate 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

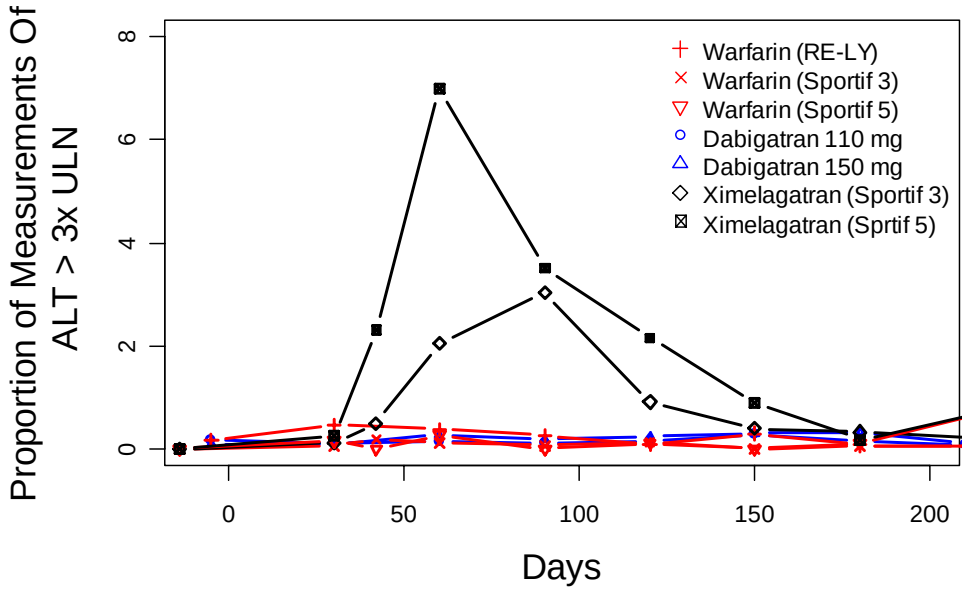


Figure 8: Time course of AST > 3x ULN for warfarin, ximelagatran and dabigatran in the Sportif and RE-LY trials

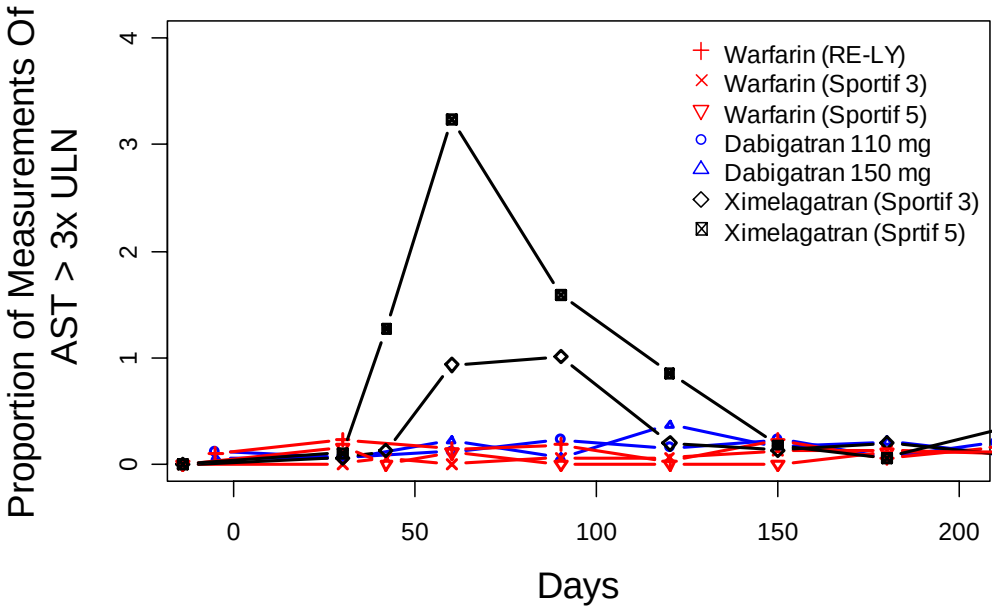
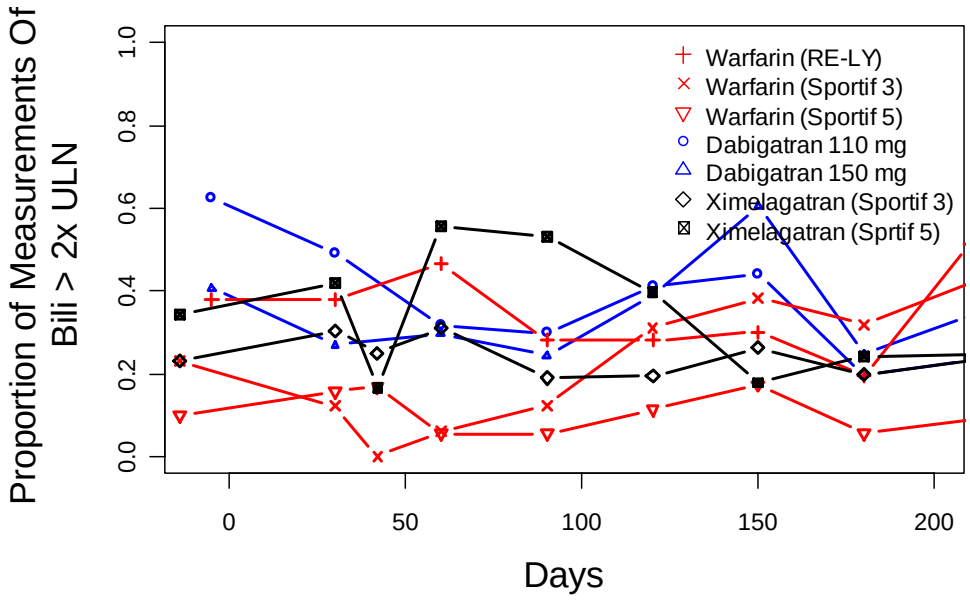


Figure 9: Time course of Bilirubin > 2x ULN for warfarin, ximelagatran and dabigatran in the Sportif and RE-LY trials



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)

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/s/

KEVIN M KRUDYS
08/24/2010

PRAVIN R JADHAV
08/24/2010

ONDQA (Biopharmaceutics) Review

NDA:	22-512 (000)
Submission Date:	04/19/2010; 04/28/10
Product:	Dabigatran etexilate mesylate Capsules (75, 110 and 150 mg)
Trade Name:	Pradaxa
Type of Submission:	Original Submission
Sponsor:	Boehringer Ingelheim
Reviewer:	Tapash K. Ghosh, Ph.D.

Background: This NDA is for a new molecular entity, dabigatran etexilate mesylate, an oral direct thrombin inhibitor for the indication of stroke prevention in atrial fibrillation. Dabigatran etexilate mesilate is the prodrug of the pharmacodynamically active principle dabigatran (BIBR 953 ZW) which is a thrombin blocking agent. The applicant selected dabigatran etexilate mesilate for oral treatment due to the limited oral availability of BIBR 953 ZW. Dabigatran etexilate mesilate (BIBR 1048 MS) is converted into the active moiety BIBR 953 ZW in vivo via esterases.

Dabigatran etexilate mesilate has low solubility and high intrinsic passive permeability characteristics. Based on the physicochemical and biopharmaceutical properties of dabigatran etexilate mesilate and the clinical requirements for a reliable drug release, a multilayer pellet approach was selected as the formulation principle. Active ingredient layered pellets including tartaric acid as (b) (4) filled into hard capsules were developed as the dosage form.

Capsules were developed containing dabigatran etexilate mesilate with strengths between 25 mg and 175 mg, calculated to the corresponding amount of free base. The overall manufacturing process of dabigatran etexilate capsules was developed in two phases, the (b) (4) drug product manufacturing process involving (b) (4) for (b) (4) of the active ingredient pellets and its optimization resulting in the (b) (4) drug product manufacturing process involving a (b) (4) process for (b) (4) of the active ingredient pellets. The latter is proposed for market supply.

Four dosages of the dabigatran etexilate mesylate HPMC capsules, 50 mg, 75 mg, 110 mg and 150 mg, were used in clinical trials. However, this application seeks approval of 110 mg and 150 mg strengths only.

This review will focus on the dissolution methodology and specification, impact of capsule shell color change for 110 mg capsules (Amendment # 0054) and the influence of the drug product manufacturing process change from the (b) (4) to the (b) (4) on the dissolution results.

Recommendations:

- *The sponsor's justification of the dissolution methodology including use of size-adjusted basket beyond 6 months for 150 mg tablet is acceptable. However, the reviewer recommends a dissolution specification of* ***Q =*** (b) (4) ***in 30 minutes*** *using the following methodology:*

Apparatus:	(b) (4) USP Apparatus 1(basket with adjusted dia, 24.5 mm) for 150 mg
Agitation:	100 rpm
Medium:	900 mL 0.01M HCl (pH 2.0)
Temperature:	37°C
Sampling time:	30 minutes
Determination:	Spectrophotometric at 325 nm.

- *Changes in the drug product manufacturing process has no impact on the dissolution profile.*

(b) (4)

Tapash K. Ghosh, Ph. D.
Biopharmaceutics Primary Reviewer
Office of New Drugs Quality Assessment

FT Initialed by Patrick Marroum, Ph. D. _____

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Table 1 Qualitative and Quantitative Composition of Dabigatran Etexilate Capsules, 150 mg / Capsule

Ingredient	[mg / capsule]	Function	Reference to Standards
(b) (4)			
Purified water [1]			USP
Acacia			NF
Tartaric acid, (b) (4)			NF
			NF and company standard [2]
			NF and company standard [2]
			USP
Hypromellose (b) (4)			USP
Dimethicone			NF
Talc			USP
(b) (4)			
			USP
Hydroxypropyl cellulose			NF
Dabigatran etexilate mesilate [4]			Company standard
(b) (4)			USP
			USP
			(b) (4)
Total Weight	**522.4**		

A suitable dissolution method including acceptance criteria for use in the quality control of immediate release Dabigatran etexilate capsules has been developed. The variables investigated included:

- pH-dependent solubility of Dabigatran etexilate mesilate (BIBR 1048 MS),
- dissolution profiles of Dabigatran etexilate capsules in media covering a pH range from 1.0 to 6.8,
- stirring speed and apparatus,
- solution state stability of the drug substance, and
- the discriminatory power of the selected conditions towards drug product differences associated with manufacturing variables and storage conditions.

For capsule size 0 product the effect of modified basket size was also investigated.

The investigation was performed for different dosage strengths ranging from 50 to 150 mg used during clinical development, covering the 75, 110 and 150 mg dosage strengths intended for commercial supply. The data base on which the proposed dissolution specification of Dabigatran etexilate capsules is established are clinically acceptable batches, including the batches used in clinical studies, and the primary stability batches.

DISSOLUTION METHOD DEVELOPMENT

Selection of Dissolution Medium:

The key property impacting the selection of the dissolution medium is the pH-dependent solubility of the drug substance. The solution state stability of the drug substance as a function of the pH was also taken into consideration.

Solubility of BIBR 1048 MS : The solubility profile of BIBR 1048 MS in aqueous media is strongly pH dependent and typical for a basic drug with rather high solubility in acidic media and very poor solubility in neutral and basic media from pH 6.5 upwards (Table 2). BIBR 1048 MS reveals pKa values of 4.0 (pKa_1) and 6.7 (pKa_2). A saturated solution of the drug substance in pure water was found to have a solubility of 1.8 mg/mL and an intrinsic pH of (b) (4). Figure 2 shows the pH-dependent aqueous solubility of dabigatran etexilate mesilate.

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

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/s/

TAPASH K GHOSH
06/18/2010

PATRICK J MARROUM
06/18/2010