

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-512

CROSS DISCIPLINE TEAM LEADER REVIEW



MEMORANDUM
DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

DATE: October 6, 2010

FROM: Abraham Karkowsky, M.D., Ph.D., Group Leader, Division of Cardiovascular and Renal Products, HFD-110.

TO: Dr. Robert Temple, Director, ODE-1.

SUBJECT: Approval recommendation of NDA 22512 (dabigatran etexilate) at a dose of 150 mg BID to decrease the risk of strokes and systemic embolic events in non-valvular atrial fibrillation patients. Sponsor: Boehringer Ingelheim.

Dabigatran etexilate methylsulfonate (DEM) is a pro-drug for the active moiety dabigatran. Dabigatran etexilate (DE) is the prodrug equivalent without including the weight of the methylsulfonate salt. The doses which are referred to in this document are dabigatran etexilate equivalent, as the free base and not the DEM salt. Dabigatran is a reversible direct thrombin-inhibitor. DEM should be approved to decrease the risk of strokes and possibly also of systemic embolic events (SEE) in a population at risk for these events because they have either paroxysmal, persistent or permanent non-valvular atrial fibrillation (AF).

I am basing this recommendation on the efficacy demonstrated by the RE-LY (Randomized Evaluation of Long term anticoagulant therapY) trial.

The 150 mg BID dosing regimen is clearly effective and should be approved, based on the decreased risk of strokes relative to warfarin. The 110 mg BID dose is more problematic. This dose was shown with either the non-inferiority margin (M2) as proposed by the sponsor (upper boundary of Hazard ratio as proposed by the sponsor of 1.46) or the M2 proposed by the FDA (upper boundary of Hazard of 1.38), to rule out the upper boundary of either of these margins. The risk of strokes in the 150 mg BID dose group, both hemorrhagic and ischemic strokes, was less than that of the 110 mg BID dose. So why approve a "less" effective treatment?

Attendant with the greater efficacy of DE 150 BID is a greater risk of bleeding than DE 110 mg BID dose. The consequence of the bleeding, however, is usually transient and only infrequently results in mortality or permanent disability. Bleeding, however, is visible to the patient, whereas prevention of strokes is not, and the presence of bleeding would create a disincentive for the patient to continue on therapy. Based on the far greater benefit to the patient of preventing a stroke than inducing a bleed, the 150 mg BID should be the preferred dose over the 110 mg BID dose.

Is there any reason to approve the 110 mg BID dose? Perhaps the lower dose could be approved if there was a population for which *a priori*, the risk of bleeding is so great, and/or the consequence of those bleeds so dire, that the risk of sustaining a stroke makes the risk benefit for the lower dose acceptable. No such population has yet been described.

The oldest population > 75 had greater bleeding rates than those less than 75 but also had an increase in stroke prevention. The population > 80 years old had few individuals to ascertain whether the risk-benefit ratio is sufficiently altered to recommend a lower dose.

Other populations where the lower dose could potentially be useful are among those subjects who are treated with either single or dual anti-platelet therapy. There is insufficient evidence from the RE-LY population that the risk to benefit relationship is sufficiently altered that a low dose would be an acceptable choice in that population. Lastly, there are subjects who have had major or life threatening bleeds on the DE 150 mg dose. Even in this population that has defined itself as having increased risk of bleeding, there is no empirical information from the RE-LY study that the utilization of a lower dose would be rational. In summary, the ability to utilize a lower dose of DE is tantalizing, nevertheless, whether its use in any population is a reasonable alternative is unclear.

The pharmaco-metric team at the FDA, in analyzing the data from the RE-LY study and derived a model which relates the concentration of dabigatran to the two dynamic effects of concern. The model assesses the relationship between trough concentration and yearly risk having an ischemic stroke. A second relationship was also modeled between the trough concentrations of dabigatran and the yearly risk of sustaining a major bleed. These relationships are shown as Figure 14 later in this memo.

There is a very rapid upward inflection of the risk of ischemic stroke at the lower concentrations of DE. The major risk of approving the lower dose of DE is that some fraction of population who are treated with the lower DE dose would have concentrations which fall in the less than effective range. A substantial fraction of those patients who are treated with the lower dose of DE would fall in the range of concentrations where there is overlapping effect with the high dose group. The patients with relatively high concentrations would be well treated even with the lower DE dose. These patients would however, be at lower risk for having the higher concentrations which predispose to bleeding risk. The balance of increased risk of sustaining a stroke versus increased risk of having a major bleed would be approaching the reasonable trade-off range for those patients who develop reasonable concentrations of dabigatran even when treated with the lower DE dose. In summary, if assurances are available that the lower dose for an individual generates adequate dabigatran concentration, the use of the lower dose although not optimal may be acceptable.

For those who are treated with the lower 110 mg BID of DE either dabigatran concentrations or the dynamic effect of DE should be measured to assure that the specific patient has adequate concentrations or that the effect of inhibiting clotting is sufficient. With respect to DE's effect, the preferred dynamic measurement is the ECT (ecarin clotting time). The aPTT is also acceptable to assure a reasonable degree of anticoagulation with DE.

Until a reasonable population that would benefit by the 110 mg dose of DE dose is clarified and/or an adequate algorithm is defined to assure that no population is inadequately anti-coagulated, the 150 mg BID dose should be approved now. Approval of the 110 mg BID dose should be delayed until it can be appropriately used.

Despite the apparent overall superiority of DE to warfarin at the 150 mg BID dose in the population as a whole, the population who were well controlled with warfarin had the equivalent risk of having a stroke or fatal event as those treated with dabigatran. (b) (4)



The submitted label is being edited currently. The label should clarify the population who benefit as non-valvular atrial fibrillation patients. Should the two doses of dabigatran be approved a REMS strategy needs to be in place to educate physicians when it is reasonable to utilize the lower dose of dabigatran and how the effect of that dose should be monitored.

Dabigatran appears to provoke fetal loss in Han Wistar rats when they are gavage fed DE at doses of 0 to 200 mg/kg through implantation and in a second study from days 6 through day 16. When Himalayan rabbits were administered DE from gestation days 6 through 18 there were also total number of resorptions, the number of early resorptions and the resorption rate was numerically higher and greater than the lab normals for these animals. The NOAEL dose for rabbits was 70 mg/kg.

Despite the temptation to employ dabigatran, a convenient oral anti-coagulant, for the treatment of pregnant women with DVTs, the off-label use of DE in this population should be discouraged.

I am somewhat surprised with the large dose response effect of the 150 mg BID dose compared to the 110 mg BID dose. In log terms the doses are very similar ($\log_{10}150 = 2.18$; $\log_{10}110 = 2.04$). The difference in log dose is approximately 6%.

The best estimate that I can ascertain for the IC_{50} for dabigatran in inhibiting either soluble or clot-bound thrombin is approximately 200 nM, somewhat higher than the concentrations generated at trough of approximately 140nM for the 150 mg BID dose. Peak concentrations for this dose are approximately 400 nM. Thus, the concentrations of dabigatran which are effective in the RE-LY study fall in the mid-range of the dose effect response curves. This range of the curve is frequently described by a log dose response relationship. The small differences of log dose (6%) make the large dose effect response in the RE-LY study surprising.

The concentration of dabigatran rapidly decays during the dosing interval. The peak concentration of dabigatran when DE, as a single dose, is taken fasted is at about 2 hours (studyU04-1459); when DE is taken with a high-fat meal, there is a delay in absorption with concentrations of dabigatran at 2 hours after the dose, not that different from trough values. C_{max} values under fed conditions are delayed till approximately 4 hours after the dose. The

peak measurements during the clinical trials were taken at 2 hours, corresponding to peak concentrations for those who took the drug fasted but captured some low to intermediate values, closer to those of trough, for those who took DE fed. The inter-dosing interval concentration measurements (close to but not quite the trough measurements when taken fed) show reasonable proximity of the fasting measurements to those measurements when the drug is taken fed. The C_{max}/C_{min} concentrations, based on these simulations are approximately 3 to 4 when DE is taken fasted and approximately 2.5 when taken fed. These fairly large excursions in concentrations during the dosing interval are suggestive that a sustained release formulation would have been useful.

The following reviews by FDA were consulted in composition of this memo. In addition, information gleaned from the Cardio-Renal Product Advisory Committee deliberations as well as the sponsor's submissions were also considered in composing this memo:

- ◆ Joint efficacy and safety review by Aliza Thompson, M.D., (efficacy) and Bach N. Beasley, PharmD., (safety), dated August 25, 2010.
- ◆ Addendum to clinical review by Bach N. Beasley, PharmD., dated September 2, 2010.
- ◆ Review of Chemistry, Manufacturing and Controls by Charles Jewell Ph.D., and Prafull Shiromani Ph.D., dated June 29, 2010.
- ◆ Issues for the inspection team by Prafull Shiromani, Ph.D., dated July 8, 2010 through July 15, 2010.
- ◆ Considerations for inspection by Charles F. Jewell, Ph.D., (drug substance reviewer), dated July 9, 2010.
- ◆ Environmental Assessment by Raanan A. Bloom, Ph.D., dated July 16, 2010.
- ◆ Inspection of site of Nabil Charle Morcos, M.D., Ph.D., with an accompanying letter by Tejashris Purohit-Sheth, dated July 27, 2010 (voluntary action indicated).
- ◆ Inspection of site of Dr. Wilson, M.D., with an accompanying letter by Tejashris Purohit-Sheth, dated July 27, 2010 (voluntary action indicated).
- ◆ Pharmaco-metric Review by Kevin Krudys, Ph.D., dated August 24, 2010
- ◆ ONDQA (Biopharmaceutic) Review by Tapash K. Ghosh, Ph.D. dated August 24, 2010.
- ◆ Review of Chemistry, Manufacturing and Controls by Charles Jewell, Ph.D. (Drug Substance) and Prafull Shiromani, Ph.D., (drug product), dated September 7 through September 15, 2010.
- ◆ Statistical Review and Evaluation of Carcinogenicity Study by Steve Thomson, dated March 8, 2010.
- ◆ Proprietary Name Review by Judy Park, Ph.D., Safety Evaluator, dated May 10, 2010.
- ◆ Hepatic effects of dabigatran etexilate by John R. Senior, M.D., dated September 8, 2010.
- ◆ Clinical Pharmacology Review by Elena V Mishina, Ph.D., Peter Hinderling, M.D., Sudharshan Hariharan, Ph.D., Kevin Krudys, Ph.D., and Mike Pacanowski, PharmD, M.P.H., dated September, 2010 through September 7, 2010.
- ◆ Statistical Review and Evaluation by Steven Bai, Ph.D., dated July 20, 2010.
- ◆ Pharmacology/Toxicology NDA Review and Evaluation by Patricia P. Harlow, Ph.D., dated September 13, 2010.

General issues:

Trade name:

DMEPA found the name Pradaxa® acceptable and not easily confused with other products, only if more than one dose is approved. The presence of more than one dose would require that the prescription have a dose written after the name. If only one dose is approved the name would not be accompanied by the dose level and confusion could occur with Prenexa a prenatal vitamin. Since the DMEPA evaluation was performed more than 90 days ago, a reassessment of the trade name is in order.

Adequacy of data:

In the original submission, the clinical reviewers found easily detected errors in the database supplied by the sponsor when they compared the information there to the information contained in the supplied CRF. The errors that they detected, for example, had number of transfusions that were not credible (92 units of blood) and INR values and warfarin dose levels that were clearly transposed. Because of the concern that these errors should have been detected, the reviewers did not consider the database as reliable and a REFUSE TO FILE letter was issued on 12 February 2010.

In response to the refuse to file letter, the sponsor instituted a quality recheck of the data, particularly for those events pertinent either to the assessment of stroke/systemic embolism or those related to significant bleeds. The algorithm employed by the sponsor included plausibility checks of in-range for laboratory values, cross case report form consistency checks, that is whether the value on two different case report forms which collected the same data were the same, and accuracy of the OCR (optical character reader). All SAE narratives were also reviewed for potential endpoint events.

The results of these data checks were screened by unblinded reviewers (Tier 1 reviewers). If the Tier 1 reviewer had any concern, the particular data point or event was elevated to be further assessed by an unblinded Tier 2 reviewer. If any event were plausibly reflected one of the endpoint efficacy or safety events, and had not yet been submitted for adjudication, the study sites would submit these CRFs for adjudication. A total of 111 events were submitted for adjudication 31: 39: 41 which resulted in the inclusion of 22: 29: 29 events in the DE 110: DE 150: warfarin groups, respectively. In addition, ECG data were reviewed for evidence of silent myocardial infarctions. The results added 11: 8: 9 events in the DE110: DE 150: warfarin groups, respectively.

The clinical reviewers were concerned that the decision to elevate an event for adjudication was based on open-label information. Furthermore, the decision to elevate an event was made based on the available CRFs and not the raw data i.e. hospital discharge summaries. The use of open-label assessments by both the Tier 1 and Tier 2 reviewers, coupled with the assessments being based on descriptions supplied by unblinded individual investigator (to warfarin versus DE), detracts from the confidence in the results of the study. Given, however, the large numbers of events which would be needed to alter the study's conclusions, the reviewers thought the process was acceptable. I agree.

The clinical supply formulation and the to-be marketed formulation of the 150 mg dose were assessed for equivalence in study 1160.70. The ratio of C_{max} comparing the formulations to be marketed to the clinical trial formulation demonstrated a C_{max} ratio of 1.13 (90% CI 1.01 to 1.26), and an $AUC_{0-\infty}$ ratio of 1.12 (90% CI 1.02 to 1.24). Although the upper confidence interval for C_{max} to define equivalence slightly exceeded the generally accepted upper confidence interval of 1.25, the clinical pharmacology reviewers considered the formulations sufficiently equivalent. I would point out that the lower confidence intervals for both C_{max} and AUC, rule out equivalence i.e. a value of 1.0. Nevertheless, there is some indication that the efficacy may be slightly improved at slightly higher doses. As such, the to-be-marketed formulation is acceptable.

The market formulation consists of small pellets [REDACTED] (b) (4)

[REDACTED] The requisite amount of dabigatran etexilate mesylate pellets is then filled into a hard shell capsule. The bioavailability of drug if the pellets are ingested outside of the capsule is not bioequivalent to the capsule itself. The formulation should not therefore, be opened and sprinkled on a food vehicle for ingestion.

There are two polymorphic forms of DEM. When each polymorph is incorporated as a single entity, they have equivalent dissolution profiles over a range of pHs and are bioequivalent.

In summary, the formulation that is to be marketed differed slightly from the formulation that was studied in the RE-LY study. The results of the to-be marketed formulation indicate that it provides slightly greater C_{max} and exposure than the studied formulation.

Clinical Pharmacology:

Dabigatran etexilate mesylate (BIBR 1048 MS) is itself not active as an inhibitor of thrombin activity. Dabigatran (BIBR 953 ZW), which is the active thrombin inhibitor is generated by the action of hydrolysis on the two acyl-centers sequentially to generate active drug. The figure below shows the pathway from DEM to dabigatran.

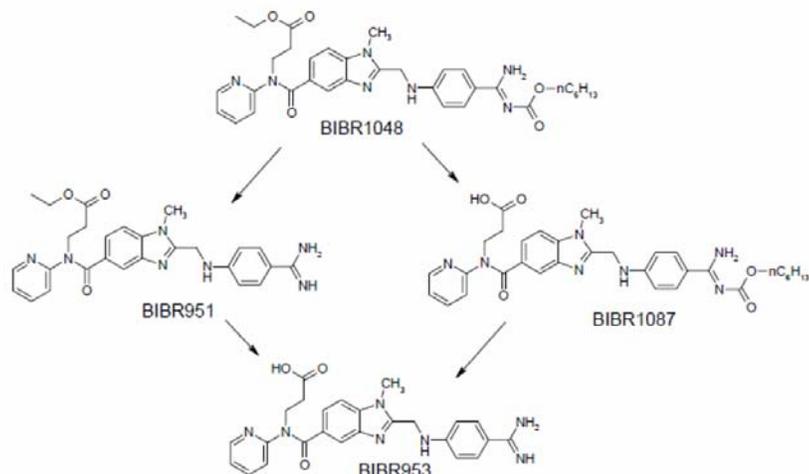


Figure 2: Structure of dabigatran etexilate, the two partially hydrolyzed products and the completely hydrolyzed dabigatran

The solubility of DEM is markedly dependant on pH. At a pH of 1 (0.01 N HCl) the solubility of DEM is approximately 40 mg/ml. At a pH of 6 the solubility is approximately 4 log units less (approximately 0.005 mg/ml).

Dabigatran from DEM is poorly bioavailable, with an estimated bioavailability of approximately 3-7%. Active dabigatran rapidly is observed in plasma two hours after the drug is administered in the fasting state. Peak concentrations are observed at approximately 2 hours. When it is administered after a fed (high fat) meal there is a delay of dabigatran in plasma for 2 hours. Concentrations at 2 hours post dose are relatively low. Peak concentrations are generally observed at approximately 4 hours. Simulated data for dabigatran concentrations when the prodrug is taken consistently with and without food is shown below. The data were derived from a single dose study (study U04-1459), with the concentrations modeled to steady state. The excursion of concentrations during the dosing interval when DEM is taken fasted is approximately a factor of 3-4. When it is taken fed, the excursion during the dosing interval is approximately a factor of 2.5. There is no information as to the consequence of a meal other than high fat meal on the kinetic profile of dabigatran.

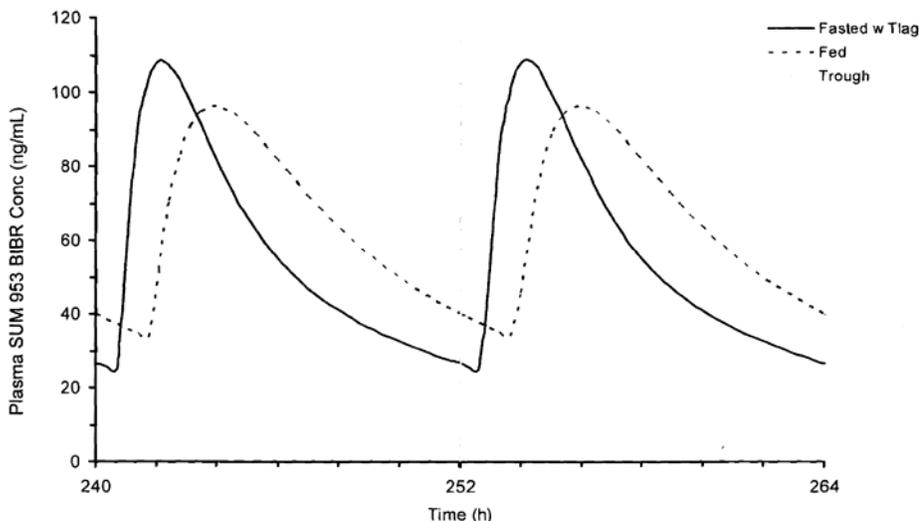


Figure 3: Simulated curves of concentration of dabigatran based on single dose fed versus fasted study.

Dabigatran is widely distributed with a volume of distribution ranging from 50-70 L. Protein binding was approximately 35% and independent of the concentration of dabigatran in the concentration range of 50-500 ng/ml.

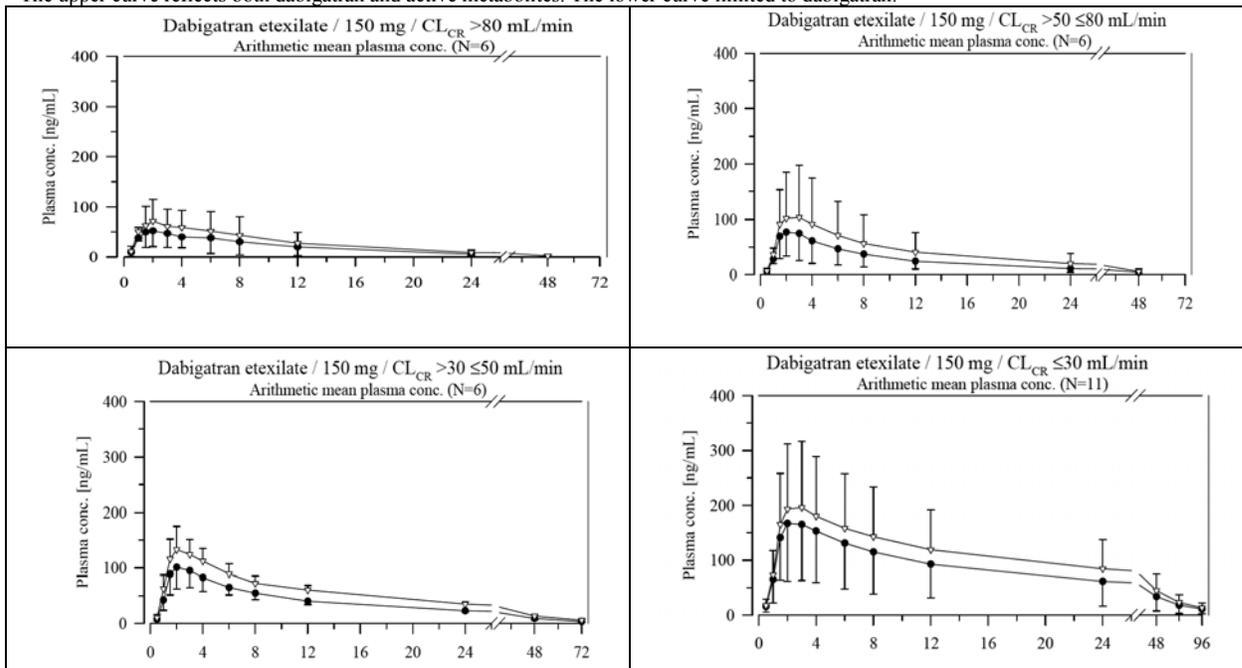
DE is hydrolyzed by ester hydrolysis (the specific esterases are not stated). It is conjugated with glucuronic acid to form 1-O-acyl glucuronide. The glucuronide can rearrange on the same site of dabigatran to form other glucuronides. The glucuronides of dabigatran may have some activity but the shape of the dose-response curves for these glucuronides are not well described.

Dabigatran is not a substrate or inhibitor of CYP enzymes. Dabigatran, however, is a substrate for the efflux transporter P-gp.

Dabigatran is primarily excreted renally. Subjects with progressively worsening renal function had increases both in concentration and also variability mean \pm SD (Study 1160.23).

Figure 4: Single dose curves for dabigatran with SD for subjects with different degrees of renal dysfunction.

The upper curve reflects both dabigatran and active metabolites. The lower curve limited to dabigatran.



With respect to drug-drug interactions there is an effect of P-gp inhibitors on the pharmacokinetic parameters of DE. The effects are shown in Table 1 (Table 3 of the clinical pharmacology review). The largest effect is those when DE is administered with either single or multiple doses of ketoconazole. The effect of the co-administration of DE with P-gp inhibitors is markedly dependent on the timing of the administration of the inhibitor with DE, and can substantially increase both the AUC and C_{max} of active dabigatran. These effects are shown in the table below.

Table 1: Effect of drugs and time on administration on the AUC and Cmax of dabigatran**Table 3 Impact of Other Drugs on Exposure to Dabigatran**

| Other Drugs | BIBR 1048 MS | | Δ Time ^a | Rel. Exposure to Dabigatran in Presence of Other Drug | |
|--------------------------|------------------------|---------------------|----------------------------|---|------------------------|
| | Dose, mg | Dose, mg | | 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) |
| Ketoconazole | 240 ER | 150 | 0 | 171 (134-217) | 191 (147-248) |
| | 400 | 150 | 0 | 238 (217-261) | 235 (205-270) |
| Quinidine 1 ^c | 400 qd | 150 | 0 | 253 (233-275) | 249 (223-279) |
| | 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) |
| | 600 qd | 150 | -0.5 ^h | 33 (27-41) | 35 (27-44) |
| Rifampicin | | 150 | -7.5 ^h | 82 (65-104) | 81 (65-102) |
| | | 150 | -14.5 ^h | 86 (68-109) | 82 (63-106) |
| | 500 | 150 | -1 | 91 (62-132) | 87 (58-131) |
| Clarithromycin | 500 bid | 150 | -1 | 119 (90-158) | 115 (84-157) |
| | 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

DE did not substantially increase the concentrations of other P-gp substrates (Table 4 of clinical pharmacology review, not shown here).

Pharmacokinetic-pharmacodynamic modeling of concentrations of dabigatran to efficacy (probability of sustaining an ischemic stroke) and to safety (probability of sustaining a life threatening bleed) will be described after the results of the RE-LY study has been described.

The relationship between concentrations of dabigatran and various parameters that describe the inhibition of clotting is shown below. The ECT (ecarin clotting time) has the most appropriate slope, responsiveness and variance when compared to dabigatran concentrations. This assay, however, may not be readily available. The aPTT or thrombin time seems acceptable alternatives.

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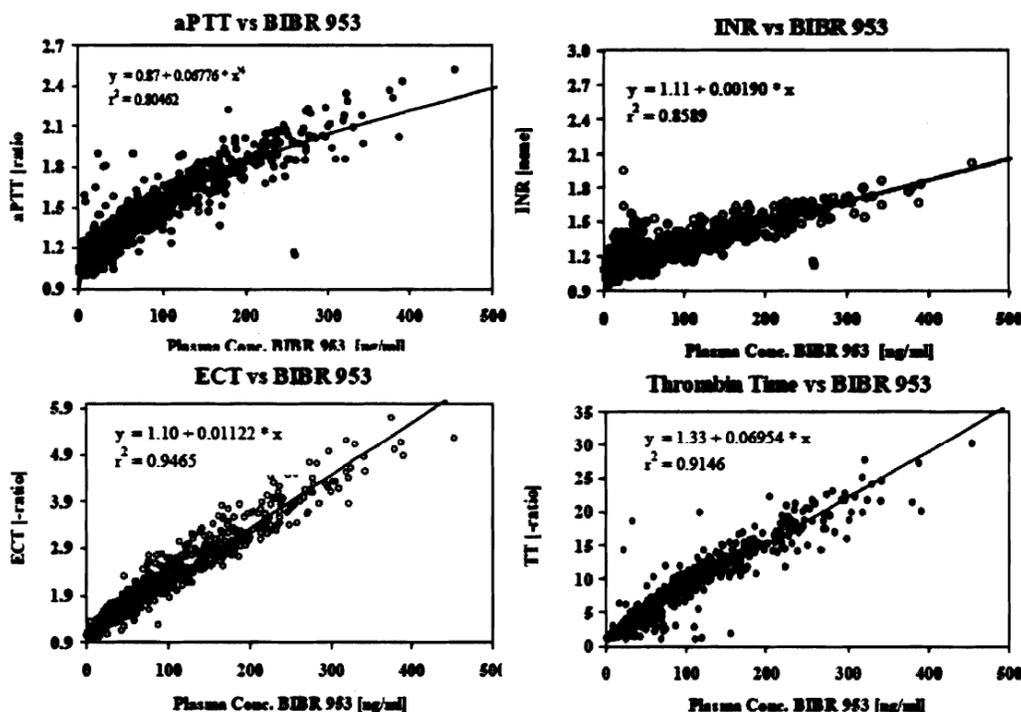


Figure 3. Relationship between dabigatran (BIBR 953) concentration and aPTT, ECT, Thrombin time, and INR

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

Figure 5: Concentration of dabigatran and various measurements of clotting parameters

Pharmacology:

In humans the concentrations generated at trough for a 150 mg BID dose of DE are approximately 90 ng/ml (RE-LY study). This concentration corresponds to a concentration of approximately 140 nM. The peak value for dabigatran is approximately 3-4 times higher or approximately 420 nM (based on the modeled data from the fed and fasted study). Dabigatran is a competitive reversible inhibitor of thrombin. It inhibits thrombin activity in soluble as well as clot bound thrombin in *ex vivo* studies, when the blood from 4 volunteers was tested. The IC_{50} for clot bound and fluid phase thrombin was 254 and 186 nM, respectively (when the assay for activity was the generation of (b) (4)). Using a chromogenic short peptide (S-2238) as substrate for thrombin, the K_i for dabigatran is approximately 4.5 nM¹.

In repeated dose studies in rats (13 weeks) and rhesus monkeys (52 weeks), nearly all the pathological observations can be attributed to excessive pharmacodynamic effects of dabigatran. Observations included decreases in red cell number parameters as well as evidence of hemorrhage and hemosiderosis (in the thymus of rats). Triglycerides were also noted to be

¹ Wiene W, Stassen J, Priepe H, Riew UJ, Huel N. In-vitro profile of ex-vivo anticoagulant activity of the direct thrombin inhibitor dabigatran and its orally active prodrug, dabigatran etexilate. *Thromb Haemost* 2007; 98: 155-162.

elevated in the high dose female rhesus monkey group. The NOAEL dose was 200 mg/kg for rats and 36 mg/kg for rhesus monkeys.

Two-year carcinogenicity studies were carried out in mice and rats. Minutes from the executive CAC dated February 16, 2010 indicate that there was no evidence of carcinogenic potential for dabigatran. There were observations of testicular and ovarian neoplasia in the rat carcinogenicity studies. The pair-wise trend test, however, did not attain the thresholds required to classify these observations as positive and related to drug. There were also increases in bronchoalveolar adenocarcinoma (female) and pleomorphic and the combination of benign, malignant fibrosarcomas and malignant sarcomas (males) but the incidence was within the historical range and did not attain threshold required to classify these tumors as drug related.

DE, with and without metabolic transformation, was not genotoxic or induced excessive revertants in the usual bacterial strains. Neither DE nor active drug induced excessive micronucleus formation. The seven CMC-specified impurities when spiked with DE also did not show up as positive in the revertant or micronucleus formation assays.

Treatment of Han Wistar male and female rats with doses of up to 200 mg/kg with DEM when started at 29 days (male) and 15 days (female) prior to mating and continued through time of implantation (day 6) resulted in a decrease in the mean number of implantations as well as and the number of viable fetuses. Dr. Harlow concluded that the NOAEL dose for embryo-toxicity was 15 mg/kg.

When female Han Wistar rats were administered DE at doses from 0-200 mg/kg from gestation day 7 (post implantation) to gestation day 16 (post organogenesis), with sacrifice at day 22, there was evidence of an increased resorption rate and a decrease in the mean number of viable fetuses in the high mid dose group. Because of an increase in mortality among the dams of the high dose group, the decreased numbers of viable fetuses in that group is not readily interpretable. The resorption rate in the mid-dose group, was higher than the control group (13.1% versus 7.7%), which although not significantly different did fall outside historical control values. Most of these resorptions were early and occurred without evidence of development of fetal tissues.

Clinical:

Efficacy for dabigatran for decreasing the risk of strokes and systemic emboli in patients with non-valvular atrial fibrillation rests on the results of the RE-LY study. This study was an open-label warfarin comparison to two closely spaced and blinded doses of dabigatran, either 110 mg BID or 150 mg BID. There were 44 countries and 951 sites which participated in enrolling patients. Endpoints were to be adjudicated in a blinded manner by at least two assessors for the occurrence of stroke and SEE and to categorize the strokes as ischemic or hemorrhagic. Major bleeds were also adjudicated and further classified as to whether the bleeds were life threatening.

Subjects with non-valvular atrial fibrillation and at least one additional risk factor for stroke were eligible to enroll in RE-LY. The risk factors include previous ischemic stroke or

TIA; previous systemic embolism; evidence of heart failure (left ventricular ejection fraction of < 40% or NYHA class II or greater); age ≥ 75 years; age ≥ 65 with either diabetes mellitus, coronary artery disease [previous myocardial infarction, positive stress exercise test, positive nuclear perfusion study, prior CABG or PCI or an angiogram showing $\geq 75\%$ stenosis in a major coronary artery]; or hypertension.

Major exclusion criteria included: prosthetic valve or hemodynamically significant valvular disease; recent stroke; conditions associated with excessive risk of bleeding (e.g. major recent surgery or planned surgery, history of bleed into vital area or GI hemorrhage, bleeding diathesis, recent treatment with fibrinolytics); contraindication to warfarin; liver disease; and anemia.

The primary endpoint of the study was stroke (including hemorrhagic) and systemic embolism. Systemic embolism was a documented event that consisted of an occlusion of the extremities or any major organ.

There were two secondary endpoints:

- ◆ Incidence of stroke, systemic embolism and all cause death.
- ◆ Incidence of stroke, systemic embolism, pulmonary embolism, myocardial infarction, vascular death (including bleeding deaths).

Other endpoints:

- ◆ Individual or composite occurrences of ischemic stroke (both fatal and nonfatal), systemic embolism, pulmonary embolism, acute myocardial infarctions, TIAs, vascular deaths (including deaths from bleeding), all deaths and hospitalizations.
- ◆ Net clinical benefit as measured by the composite of the clinical endpoint of stroke, systemic embolism, pulmonary embolism, acute myocardial infarction, all cause death and major bleeds.

Statistical:

The primary hypothesis was that dabigatran at either dose was non-inferior to warfarin. The non-inferiority margin of 1.46 as proposed by the sponsor was based on the historical placebo-controlled trials and employed a 95%/95% rule. This calculation employed the lower 95% confidence interval of the hazard ratio of warfarin compared to placebo as derived from a series of 6 trials carried out in the late 1980s and early 1990s (M1). Once this lower CI for the hazard ratio was obtained, 50% of that effect was to be maintained (M2). The Hazard ratio comparing dabigatran to warfarin was to rule out the M2 margin with a 95% confidence interval. The sponsor using a linear scale arrives at a value for the non-inferiority margin of 1.46. The FDA applied the same calculations but employed a log scale. The appropriate non-inferiority margin by that calculation was 1.38.

The primary analysis included the following: yearly event rate summaries, Kaplan-Meier curves and Cox regression analysis. All secondary outcomes were analyzed using a Cox regression model with treatment as a factor.

Since two doses were compared to warfarin, the Hochberg procedure was used to protect alpha. This process utilizes the least convincing of the alpha values, and if the one-sided p-value was $\alpha < 0.025$ both therapies was considered as significant. If the p-value of the assessment is $\alpha > 0.25$, the next therapy is tested at an $\alpha < 0.0125$. There was no α -sparing strategy described for the secondary and other endpoints both considering the number of such endpoints and the two doses.

There were five amendments to the study. Amendment #1 altered the enrollment conditions to assure that there were approximately 50% of those who enrolled were considered as vitamin K naïve patients (defined originally as treated with the antagonists for ≤ 30 days but changed with amendment #1 to < 2 months).

The second amendment increased the subject number for 15,000 to 18,000 subjects due to the more rapid than anticipated enrollment of subjects. The other three amendments dealt with decreasing the frequency of monitoring liver function tests, altering the use of P-gp inhibitors and altering the algorithm for the holding of dabigatran prior to surgery.

The study eventually enrolled 18,113 patients with nonvalvular atrial fibrillation divided equally among the three treatments DE 110 BID: DE 150 BID: warfarin. Some baseline demographic parameters are shown in Table 2.

Table 2: Baseline characteristics RE-LY study

| Characteristic | DE 110 N=6015 | DE 150 N=6076 | Warfarin N=6022 |
|---------------------------|------------------|------------------|--------------------|
| Male | 3865 (64%) | 3840 (63%) | 3809 (63%) |
| Age mean | 71 | 71 | 72 |
| <65 | 998 (17%) | 1030 (17%) | 953 (16%) |
| ≥ 65 to < 75 | 2668 (44%) | 2580 (43%) | 2646 (44%) |
| ≥ 75 | 2349 (39%) | 2466 (41%) | 2423 (40%) |
| AF type | | | |
| Paroxysmal | 1929 (32%) | 1978 (33%) | 2036 (34%) |
| Permanent | 2132 (35%) | 2188 (36%) | 2055 (34%) |
| Persistent | 1950 (32%) | 1909 (31%) | 1930 (32%) |
| VKA naive | 3005 (50%) | 3028 (50%) | 3093 (51%) |
| Risk factors | | | |
| History of stroke | 761 (13%) | 756 (13%) | 756 (13%) |
| History of TIA | 548 (9%) | 587 (10%) | 528 (10%) |
| History of stroke/TIA/SEE | 1308 (22%) | 1358 (22%) | 1287 (21%) |
| History of hypertension | 4738 (79%) | 4795 (79%) | 4750 (79%) |
| History of diabetes | 1409 (23%) | 1402 (23%) | 1410 (23%) |
| History of heart failure | 1937 (32%) | 1934 (32%) | 1922 (32%) |
| History of MI | 1008 (17%) | 1029 (17%) | 968 (16%) |
| History of CAD | 1661 (28%) | 1710 (28%) | 1633 (28%) |
| NYHA class | | | |
| NYHA I | 295 (5%) | 292 (5%) | 297 (5%) |
| NYHA II | 1225 (20%) | 1198 (20%) | 1222 (20%) |
| NYHA III | 386 (6%) | 401 (6%) | 353 (6%) |
| NYHA IV | 30 (< 1%) | 41 (1%) | 48 (1%) |
| CHADS2 score | | | |
| 0 | 151 (3%) | 146 (2%) | 155 (3%) |
| 1 | 1809 (30%) | 1815 (30%) | 1707 (28%) |
| 2 | 2088 (35%) | 2136 (35%) | 2229 (37%) |
| 3+ | 1966 (33%) | 1979 (33%) | 1931 (32%) |
| Creatinine clearance | | | |
| ≥ 30 to < 50 | 1136 (19%) | 1156 (19%) | 1051 (18%) |
| ≥ 50 to < 80 | 2714 (45%) | 2777 (46%) | 2806 (47%) |
| ≥ 80 | 1899 (32%) | 1882 (31%) | 1877 (31%) |

Missing data may prevent columns from adding to 100%.

The populations were reasonably balanced. This was an elderly population. The etiology of the AF was balanced between persistent, permanent and paroxysmal. Approximately 1/3 had CHADS2 scores of 3 or greater. Approximately 36% of those enrolled in this study were enrolled in USA and Canadian sites (this last piece of information was not from this table).

The disposition of subjects during the course of the study is shown in Table 3. Subjects who discontinued were to be followed till the end of the study.

Table 3: Disposition of subjects in the RE-LY studies

| | DE 110 BID | DE 150 BID | Warfarin |
|---|------------|------------|------------|
| Randomized | 6015 | 6076 | 6022 |
| Treated | 5983 | 6059 | 5998 |
| Completed study | 5765 (96%) | 5808 (96%) | 5748 (96%) |
| On medication | 4610 (77%) | 4625 (76%) | 4848 (81%) |
| Stopped medication | 1155 (19%) | 1183 (20%) | 900 (15%) |
| Premature discontinuation | 218 (4%) | 251 (4%) | 250 (4%) |
| Mean ± SD duration of exposure (months) | 20.5 ± 9.6 | 20.3 ± 9.8 | 21.3 ± 8.8 |

There were more DE subjects, at either dose, who stopped medication prematurely. The nature of the transfer medication which these patients were switched to is unclear. The duration of exposure to warfarin was approximately 4% greater than either DE dose.

The number stroke/SEE in the randomized set (as first event) is shown below.

Table 4: Efficacy outcome events for RE-LY study

| | Dabigatran 110 | Dabigatran 150 | Warfarin |
|--------------------|----------------|----------------|----------|
| N treated | 5983 | 6059 | 5988 |
| N with stroke/SEE | 183 | 134 | 202 |
| Stroke | 171 | 122 | 186 |
| Ischemic stroke | 152 | 103 | 134 |
| Hemorrhagic stroke | 14 | 12 | 45 |
| Uncertain | 5 | 7 | 7 |
| SEE | 15 | 13 | 21 |

The numbers don't add up since more than one event may have been observed.

The Kaplan-Meier estimate of time to first stroke/SEE event by treatment arm is shown in Figure 6.

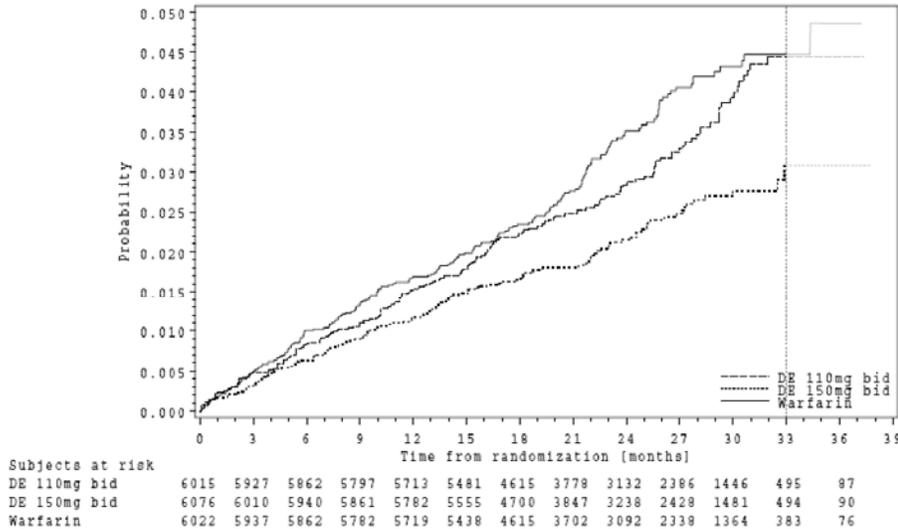


Figure 6.3: 1 Kaplan-Meier Estimate of Time to First Stroke/SEE

Source: NDA Amendment; Figure 15.2.1.1: 1

Figure 6: Kaplan-Meier curves for stroke and SEE events in the RE-LY study.

The Hazard Ratios compared to warfarin for the two DE doses is shown in Table 5:

Table 5: Hazard ratios and p-values for the primary endpoint of the RE-LY study

| | DE 110 versus warfarin | DE 150 versus warfarin |
|------------------------------------|--------------------------|--------------------------|
| # events/N | 183/6015 versus 202/6022 | 134/6076 versus 202/6022 |
| Hazard ratio (SE) [95% CI] | 0.90 (0.09)[0.74, 1.10] | 0.65 (0.07) [0.52, 0.81] |
| p-value for non-inferiority (1.38) | <0.0001 | <0.0001 |
| p-value for superiority | 0.29 | 0.0001 |

For the primary endpoint both doses of dabigatran satisfy the more conservative non-inferiority margin as proposed by the FDA. For the primary endpoint the DE 150 mg BID dose was superior to warfarin.

When reported, the Rankin scores for those who had strokes at 3-6 months after the event are shown in Table 6.

Table 6: Rankin score for the strokes in the RE-LY trial

| | DE 110 | DE 150 | Warfarin |
|---|--------|--------|----------|
| # of strokes | 171 | 122 | 186 |
| Missing | 10 | 4 | 11 |
| Rankin 0 | 21 | 21 | 21 |
| Rankin 1 | 31 | 24 | 35 |
| Rankin 2 | 20 | 12 | 22 |
| Rankin 3 | 18 | 6 | 17 |
| Rankin 4 | 16 | 9 | 14 |
| Rankin 5 | 8 | 4 | 8 |
| Rankin 6 | 47 | 42 | 58 |
| Data derived from Table 31 of the medical review. The Rankin scale is an outcome scale for performance post stroke and ranges from 0 (asymptomatic) to 6 (death). Scores of ≥ 3 are suggestive of substantial morbidity. | | | |

Approximately 30% of the strokes were fatal. Approximately 30% were Rankin score of ≤ 2 , meaningful but not debilitating.

The relationship to baseline characteristics is shown in the Figure 7. The right side Forest plot is the HR of DE 110 and the left side is the HR of DE 150 both compared to warfarin for the primary endpoint based on several baseline demographic characteristics.

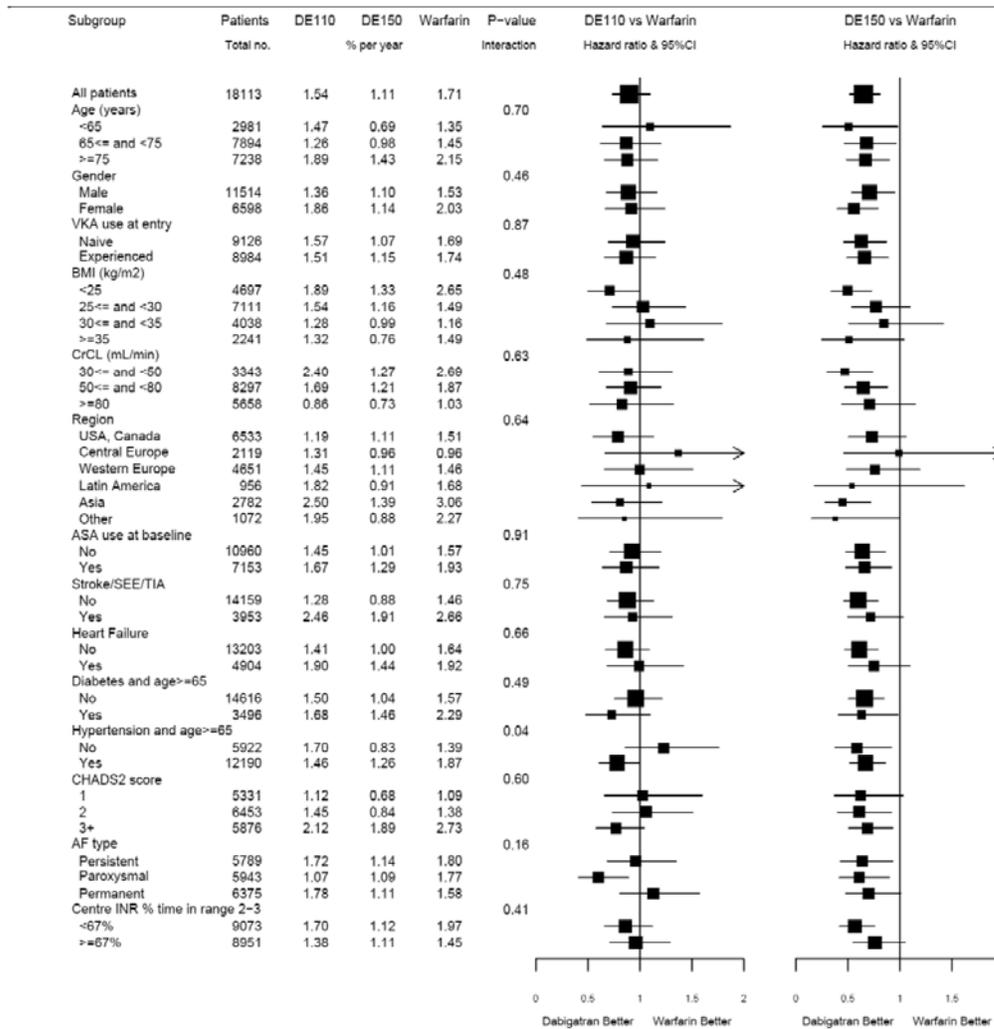


Figure 7. Stroke/SEE hazard ratios by baseline characteristics

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

Figure 7: Hazard ratio for the primary endpoint of the RE-LY Trial based on baseline demographics

Compared to warfarin, both the DE 150 and DE 110 doses appear to have a consistent effect based on baseline characteristics. The only observation of additional interest is that in the effect of renal dysfunction actually shows an increase in the benefit as the renal function decreases. The decrease in renal function creates higher exposure to dabigatran. The observation here suggests that even higher doses of DE might have provided additional benefit.

With respect to the secondary endpoint of first stroke/SEE /death the Kaplan-Meier curves are shown as Figure 8:

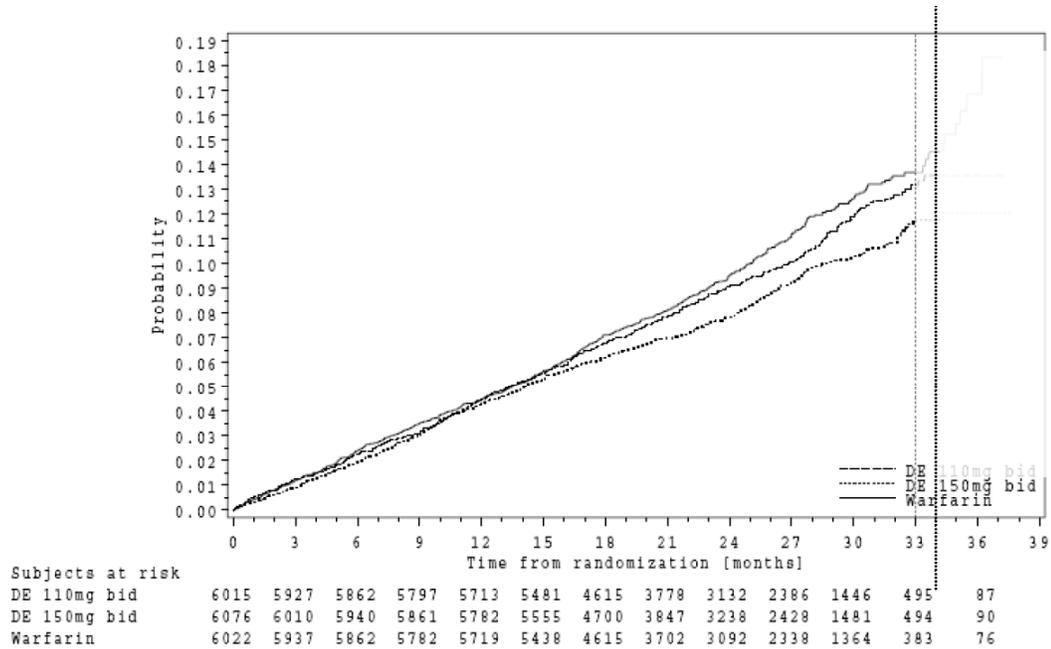


Figure 6.4.1: 1 Kaplan-Meier Estimates of Time to First Stroke/SEE/Death

Source: NDA Amendment; Figure 15.2.2.1: 1

Figure 8: Kaplan-Meier curves for the first occurrence of stroke/SEE or death, RE-LY trial

The Hazard ratios for the two secondary endpoints are strongly driven by the primary endpoint. The HR is shown as Tables 7 and 8. A separate analysis of mortality is shown as Table 9.

Table 7: Hazard ratios and 95% CI for the composite endpoint of stroke/SEE/death

| | DE 110 versus warfarin | DE 150 versus warfarin |
|--------------------------|--------------------------|--------------------------|
| # events/N | 575/6015 versus 609/6022 | 518/6076 versus 609/6022 |
| Hazard ratio (SE)[95%CI] | 0.93 (0.05)[0.83,1.05] | 0.83 (0.05)[0.74,0.93] |
| P-value for superiority | 0.2 | 0.0015 |

Table 8: Hazard ratios and 95% CI for stroke/SEE/PE/MI/vascular death

| | DE 110 versus warfarin | DE 150 versus warfarin |
|--------------------------|--------------------------|--------------------------|
| # events/N | 493/6015 versus 496/6022 | 433/6076 versus 496/6022 |
| Hazard ratio (SE)[95%CI] | 0.98 (0.06)[0.86,1.10] | 0.84 (0.05)[0.74,0.96] |
| P-value for superiority | 0.2 | 0.01 |

Table 9: Hazard ratios for mortality

| | Dabigatran 110 versus warfarin | | Dabigatran 150 versus warfarin | |
|------------------|--------------------------------|----------|--------------------------------|----------|
| | HR (95% CI) | p-value* | HR (95% CI) | p-value* |
| According to SAP | 0.91 (0.8, 1.03) | 0.13 | 0.88 (0.78, 1.0) | 0.052 |

*Not corrected for multiple doses

The above assessments do not account for comparisons versus two dose groups. Nevertheless, the effect of both doses of DE for the composite endpoints mirror the overall primary endpoint's results. This is not surprising for the majority of the events in either secondary are strongly driven by the same events in the primary analysis.

In considering mortality alone, applying the Hochberg method, neither dose has a significant positive effect on mortality. Both doses readily satisfy the non-inferiority margins which were set.

Yearly event rate (%) for the individual events of stroke, SEE, PE, MI, vascular death and all cause death are shown below. Not all events favor DE doses. MIs and PE favor warfarin and diminish the 0.6 events/year of stroke prevention.

Table 10: Specific events during the RE-LY trial (yearly event rates % of population)

| | DE 110 | DE 150 | Warfarin |
|------------------------|------------|------------|------------|
| Subject year follow up | 11,899 | 12,033 | 11,794 |
| Stroke | 171 (1.4%) | 122 (1.0%) | 186 (1.6%) |
| SEE | 15 (0.1%) | 13 (0.1%) | 21 (0.2%) |
| PE | 14 (0.1%) | 18 (0.2%) | 12 (0.1%) |
| MI (excl silent MI) | 87 (0.7%) | 89 (0.7%) | 66 (0.6%) |
| Silent MI | 11 (0.1%) | 8 (0.1%) | 9 (0.1%) |
| Vascular mortality | 289 (2.4%) | 274 (2.3%) | 317 (2.7%) |
| All cause mortality | 446 (3.7%) | 438 (3.6%) | 487 (4.1%) |

The efficacy results of the RE-LY study are robust. The time course of the upper confidence interval for the p-values is shown in Figure 9 (from Dr. Bai's review). The upper confidence interval for DE 150 BID dose group persists below the non-inferiority margin after approximately 100 events have accrued and dropped below a HR of 1.0 after 260 events. The lower dose dropped below the non-inferiority margin after approximately 200 events accrued and remained there throughout the trial. The increase in study size (based on amendment #2) did not alter the conclusion of the study's results.

Figure 3.3 The Upper Bound of Hazard Ratios for composite endpoint of stroke/SEE across trial calendar date

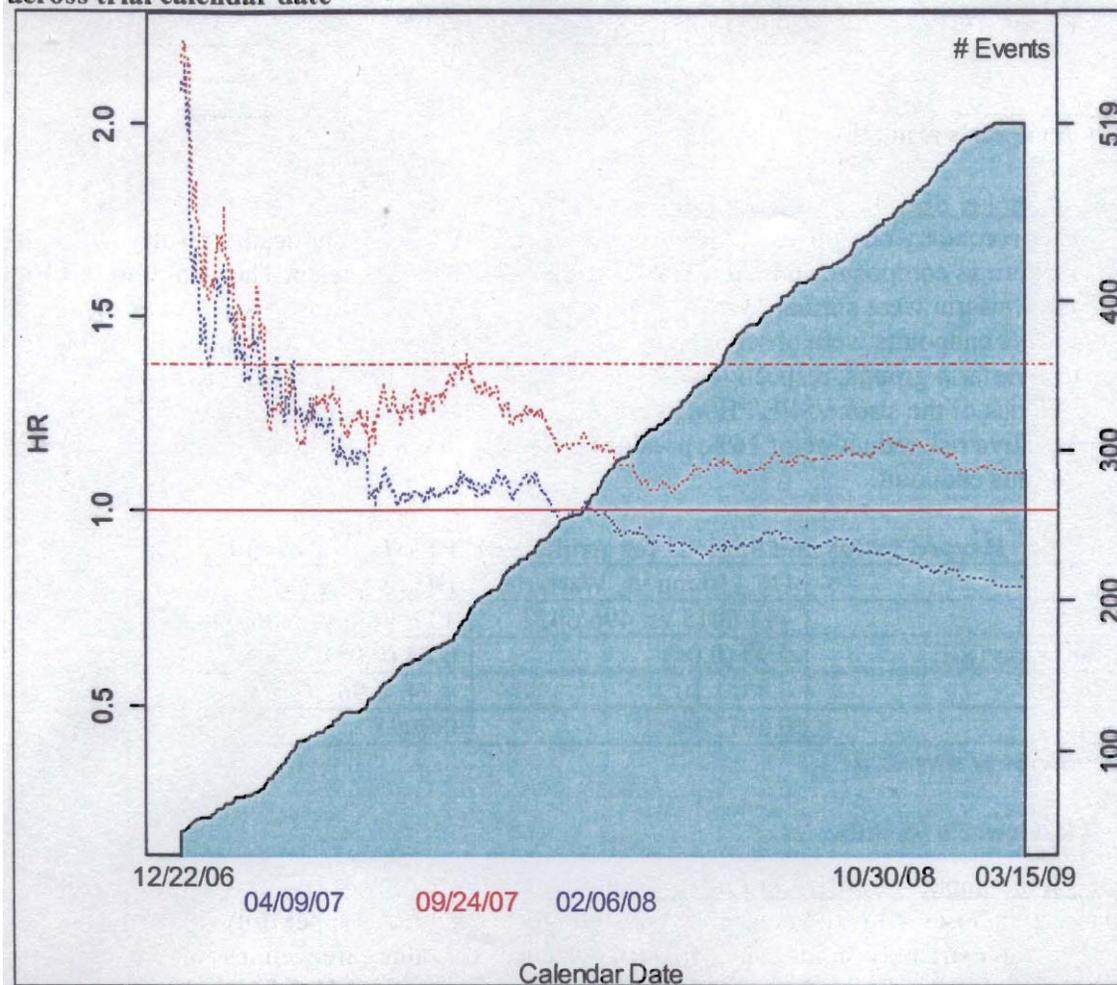


Figure 9: Hazard ratio throughout the RE-LY trial.

Source: Dr. Bai's review

Calendar time X-axis versus Hazard ratio with CI of 1.38 and 1.0 demarcated. Right Y-axis is the number of accrued events. The shaded curve reflects the cumulative events.

Issues:

The clinical reviewers noted their concerns regarding the interpretation of an open-label comparison of warfarin to Dabigatran. The double-blind comparison of the DE 150 to DE 110 is, however, supportive of efficacy since these comparisons were blinded.

When warfarin was compared in an open label fashion to ximelagatran in the Sportif III study in a similar population as those enrolled in the RE-LY study, ximelagatran was numerically superior to warfarin. When the same drug was compared to warfarin in a double-blind study, Sportif V, warfarin was numerically superior to ximelagatran. It is unclear if the reason why there were such discrepant results were due to the nature of the blinding in the two studies.

In the RE-LY study, investigators were aware of who was treated with warfarin. Did the knowledge of which treatment subjects were treated alter the how these subjects were

managed? That is, were those treated with dabigatran handled differently from those treated with warfarin? The reviewers performed several analyses looking at the consequence of subjects who had non-endpoint events, which predict added risks e.g. a TIA. No disparity of event rates in comparing the warfarin versus the DE treatments.

When events occurred, the decision to send the event for adjudication was predicated on the information on the case report forms. Since not all hospitalizations were submitted for adjudication, the unblinded investigator who authored the information on the CRF was pivotal in directing such events for adjudication and ultimately how many events were detected.

The primary statistical reviewer's however noted that given the robustness of the data and the need for 46 and 97 events in the DE 110 and DE 150 doses, respectively to overcome the non-inferiority conclusion. In order to reverse the superiority effect of the DE 150 dose an additional 33 events would be needed to abrogate the superiority effect. It is unlikely that the level of unblinding can be responsible for the results obtained in the RE-LY study.

The clinical reviewers did an excellent review of whether indeed DE 150 is truly superior to warfarin. The INR control among those treated with warfarin in this open-label study did not substantially differ from INR control in previous studies but was inferior to optimum obtainable INR control. The primary endpoint, however, was markedly driven by the results in the study sites which had lesser success in INR control. Any mortality difference was also driven largely by subjects enrolled in those sites.

These results indicate that among those well-controlled with warfarin, the benefit of DE treatment seems less convincing. Table 11 compares the HR based on the quartiles of center-level INR control and compared the warfarin results DE's effect in the same centers. The upper quartile for control had outcomes that were indistinguishable for those of DE 110 and DE 150.

| TTR center level INR control | | Worst quartile TTR < 58.5% | Second quartile TTR \geq 58.5% to < 66.8% | Third quartile TTR > 66.8% to < 74.2% | Best quartile TTR \geq 74.2% |
|------------------------------|---------|----------------------------|---|---------------------------------------|--------------------------------|
| DEM 110 BID versus warfarin | HR | 0.95 | 0.79 | 0.97 | 0.92 |
| | 95%CI | 0.64, 1.40 | 0.54, 1.16 | 0.65, 1.44 | 0.59, 1.44 |
| | p-value | 0.8 | 0.23 | 0.87 | 0.7 |
| DEM 150 BID versus warfarin | HR | 0.6 | 0.53 | 0.65 | 0.9 |
| | 95%CI | 0.39, 0.94 | 0.35, 0.81 | 0.42, 1.02 | 0.57, 1.41 |
| | p-value | 0.02 | 0.003 | 0.06 | 0.63 |

Table 11: Hazard ratio for the primary endpoint as a function of study site quartile of INR in TTR

The effect on mortality outcomes based on centers in the upper and lower half of INR-control as shown in Table 12 indicates much of any benefit is attributable to subjects who enrolled in study sites with poor INR control as assessed by the time in therapeutic range (TTR).

| | DE 110 versus warfarin | DE 150 versus warfarin |
|--|-----------------------------|-----------------------------|
| According to SAP | 0.77 (0.80, 1.03) [p=0.13] | 0.88 (0.77, 1.0)[p=0.052] |
| Subjects with center level control (TTR < 67%) | 0.77 (0.65, 0.92) [p=0.005] | 0.78 (0.66, 0.93) [p=0.007] |
| Subjects with center level control (TTR ≥ 67%) | 1.08 (0.89, 1.3)[p=0.43] | 1.01 (0.84, 1.23 [p=0.89] |

Table 36 of medical review

Table 12: Mortality in RE-LY trial based on center level INR control as assessed by TTR**Safety:**

The major safety concern from the use of a thrombin inhibitor is bleeding. Based on the previous experience with another thrombin inhibitor, ximelagatran, there was also considerable interest in the potential liver toxicity of DE.

Bleeding:

Bleeding events were dichotomized into major or minor bleeds. Major bleeds were defined as bleeding associated with a decrease of hemoglobin of 20 grams/liter; the need for transfusion of two units of blood; or symptomatic bleeds into a critical area such as intraocular, intracranial, intra-spinal, retroperitoneal, intra-articular, pericardial or intra-muscular with compartment syndrome. Major bleeds were further categorized as life threatening bleeds if they were: fatal; symptomatic intracranial; or provoked a reduction of hemoglobin of 50 grams/liter with hypotension requiring intravenous inotropic support or surgical intervention.

All major bleeding events were to be adjudicated. Hemorrhagic strokes were not also counted among major bleeds. Minor bleeds were defined as clinically meaningful bleeds not fulfilling the criteria of a major bleed.

The specifics of the major bleeding events are taken from the clinical safety review.

Table 13: Major bleeding events in the RE-LY trial

| | DE 110 | DE 150 | Warfarin |
|-------------------------------|------------|------------|------------|
| N= | 6015 | 6076 | 6022 |
| Subjects with major bleed (%) | 342 (5.7%) | 399 (6.6%) | 421 (7.0%) |
| Number of major bleeds | 406 | 489 | 483 |
| Life-threatening bleeds | 159 | 193 | 233 |

There were substantially fewer events in the DE 110 group compared either to DE 150 or warfarin. These events include a decrease in number of subjects with major bleeds, number of major bleeds and number of life-threatening bleeds. There was no significant difference in comparing warfarin to the DE 150 BID regimen. The risks of bleeding were markedly dependent on the level of INR control. Those subjects with the greater degree of INR control, based on TTR, had the fewest number of serious bleeds among those treated with warfarin compared to DE 110 or DE 150.

Table 14: Hazard rates of major bleeds based on center level INR control (TTR) for the RE-LY study

| TTR center level INR control | | Worst quartile TTR < 58.5% | Second quartile TTR ≥ 58.5% to < 66.8% | Third quartile TTR > 66.8% to < 74.2% | Best quartile TTR ≥ 74.2% |
|------------------------------|---------|----------------------------|--|---------------------------------------|---------------------------|
| DEM 110 BID versus warfarin | HR | 0.64 | 0.74 | 0.90 | 0.93 |
| | 95%CI | 0.46, 0.88 | 0.57, 0.97 | 0.69, 1.17 | 0.68, 1.26 |
| | p-value | 0.005 | 0.03 | 0.43 | 0.62 |
| DEM 150 BID versus warfarin | HR | 0.68 | 0.90 | 1.00 | 1.2 |
| | 95%CI | 0.50, 0.93 | 0.70, 1.16 | 0.77, 1.30 | 0.90, 1.60 |
| | p-value | 0.02 | 0.41 | 1.00 | 0.21 |

Data for medical review Table 49

The location of the adjudicated major bleeds is shown below.

Table 15: Sites of major bleeds RE-LY trial.

| Location of bleed↓ | DE 110 (% of major bleeds) | DE 150 (% of major bleeds) | Warfarin (% of major bleeds) |
|--------------------------|----------------------------|----------------------------|------------------------------|
| Total major bleeds | 397 (100%) | 486 (100%) | 476 (199%) |
| Symptomatic bleeding | 225 (57%) | 285 (59%) | 237 (50%) |
| Gastrointestinal | 155 (39%) | 219 (45%) | 141 (30%) |
| Symptomatic intracranial | 27 (7%) | 33 (7%) | 82 (17%) |
| Intraocular | 16 (4%) | 11 (2%) | 16 (3%) |
| Retroperitoneal | 2 (1%) | 9 (2%) | 12 (2%) |
| Intramuscular | 8 (2%) | 8 (2%) | 19 (4%) |
| Genitourinary | 16 (5%) | 7 (1%) | 7 (1%) |
| ENT | 4 (1%) | 7 (1%) | 7 (1%) |
| Surgical | 8 (2%) | 6 (1%) | 13 (3%) |
| Intra-abdominal | 3 (1%) | 5 (1%) | 2 (<1%) |
| Intra-thoracic | 8 (2%) | 4 (1%) | 7 (1%) |
| Intra-articular | 5 (1%) | 4 (1%) | 7 (1%) |
| Pericardial | 2 (1%) | 3 (1%) | 3 (1%) |
| Other area | 1 (<1%) | 2 (<1%) | 7 (1%) |
| Source unidentified | 1 (<1%) | 1 (<1%) | --- |
| Intra-spinal | --- | --- | 1 (<1%) |

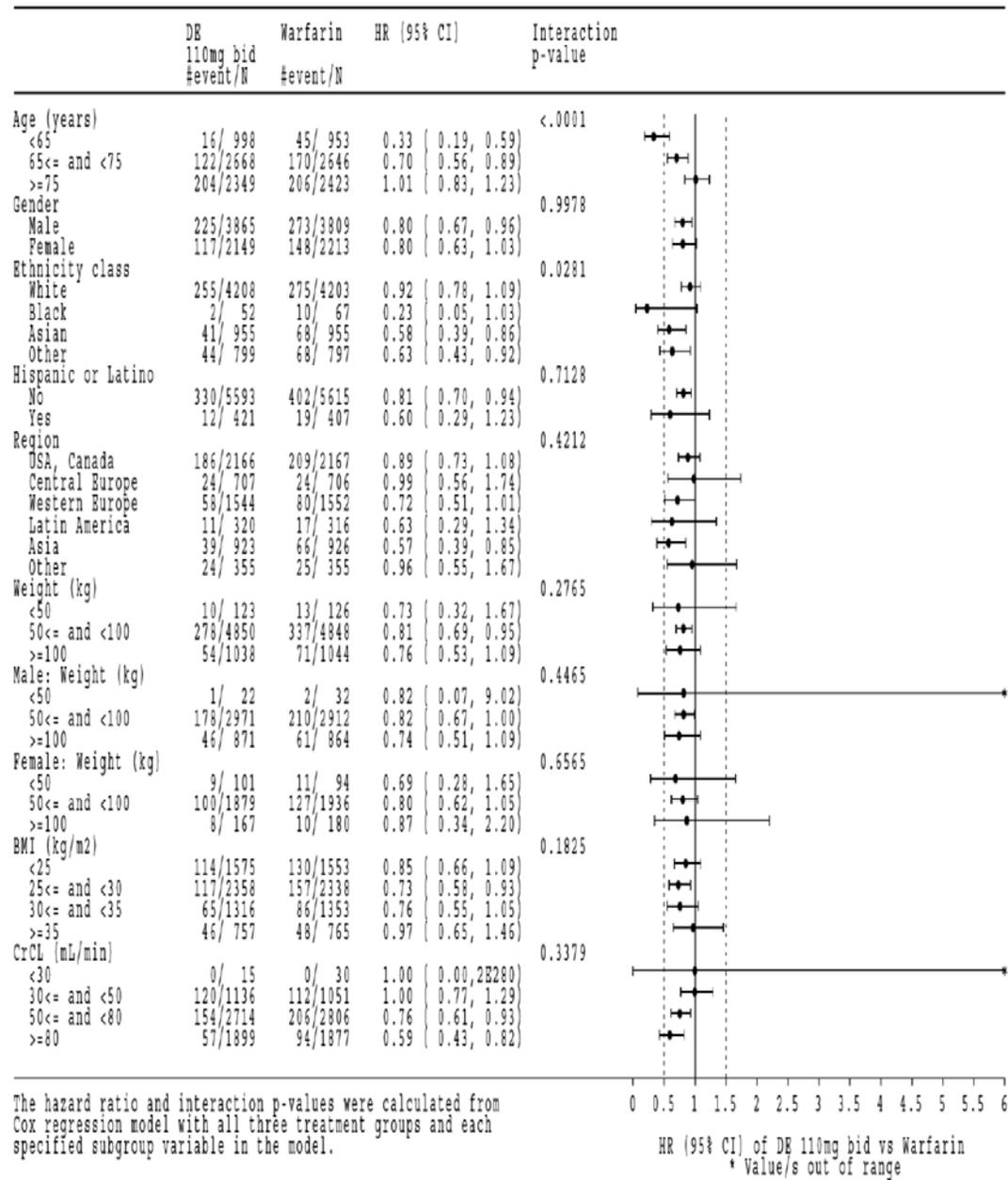
Taken from medical review table 59. Events reclassified by PHRI as to sites of the bleed. There were 15 events which were classified as "other" and were re-categorized by PHRI to a specific organ. That analysis was used in this table.

In addition, these values were the number of intracranial events captured by the "major bleed" CRF and the "investigator assessment of potential outcome events" CRF. The medical reviewers detected other intracranial bleeds as well as other serious bleeds through other CRFs. The numbers here are less than the total numbers of events captured by the clinical reviewers. An additional 0:5:8 events were captured for the DE 110: DE 150 : warfarin groups, respectively, which are not included in the above tabulations

There were many more GI bleeds among those treated with the DE 150 dose. There were many more intracranial bleeds in the warfarin group compared to the two DE doses.

The relationship of the hazard ratios for major bleeds versus baseline demographics for DE 110 (Figure 12) and for DE 150 (Figure 13) compare to warfarin are shown in Figures 12 and 13.

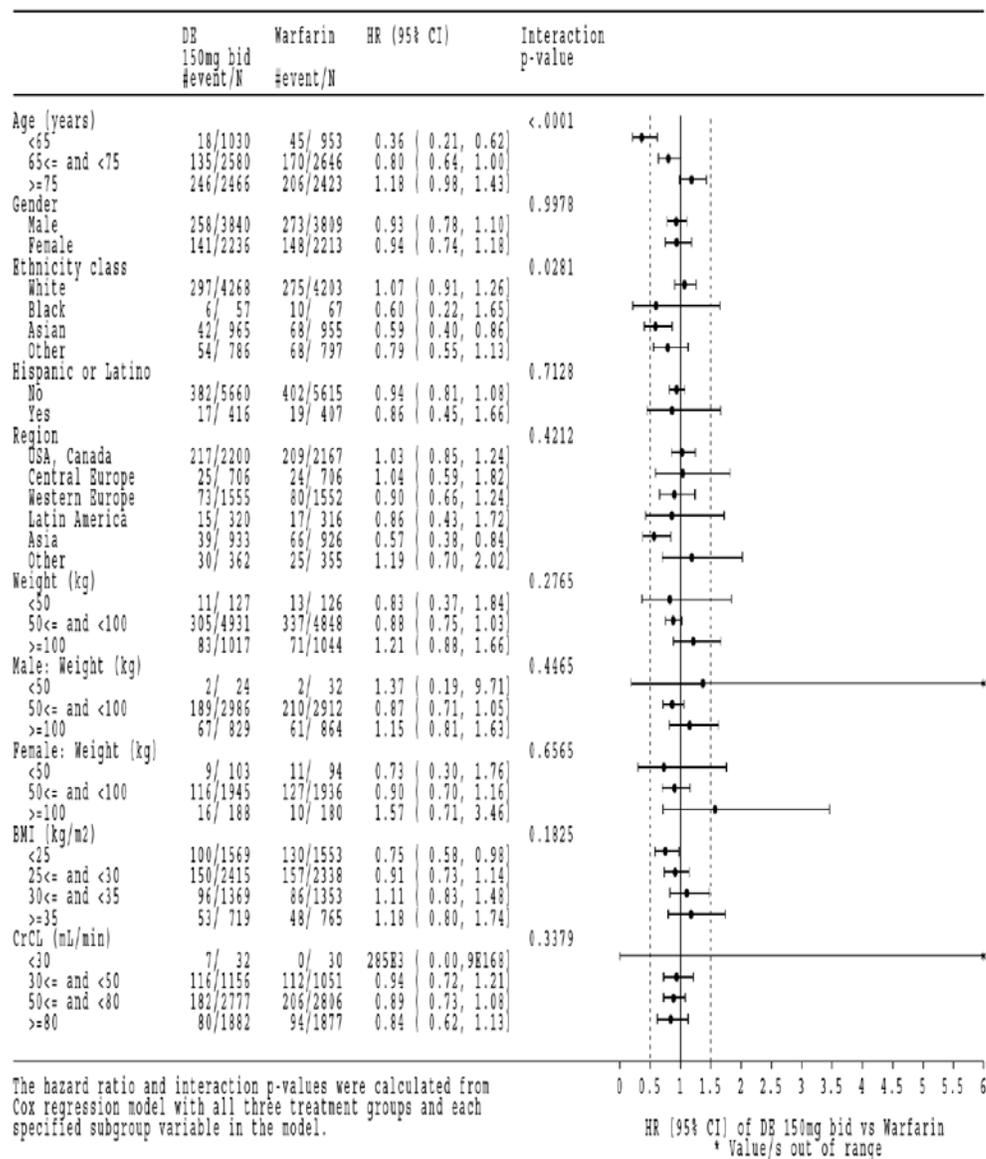
Figure 15. Dabigatran 110 mg v. warfarin subgroup analysis



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

Figure 10: Forest plot based on baseline demographics for the DE 110 versus warfarin, RE-LY trial

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



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

Figure 11: Forest plot based on baseline demographics for the DE 150 versus warfarin, RE-LY trial

For the lower DE dose, there was an increase HR for age and an increase in HR as renal function declines. For those treated with the DE 150 dose, there was also an increase in HR with increasing age and BMI. There was a small increase in HR as the degree of renal dysfunction increased. As the degree of renal dysfunction decreases, exposure to dabigatran increases.

Liver test studies:

The sponsor was mindful of the ximelagatran experience for which a large number of those treated with ximelagatran had meaningful elevations of liver enzymes and bilirubin.

Liver test measurements were frequently measured during the initial enrollment and follow up during the study. Initially subjects were to have centrally measured liver test measurements once monthly but could in addition have such measurements performed locally. Amendment #3 decreased the frequency of liver test monitoring after 6,000 subjects had completed 6 months of therapy to every three months.

There were 55 subjects of interest who had elevated ALT and/or AST > 3 x ULN and bilirubin 2 x ULN not necessarily concurrently, 16: 16: 23 to the DE 110: DE 150: warfarin treatments, respectively. All these events (and some additional cases) were reviewed by two expert hepatologists on the FDA staff: Dr. John Senior and Dr. Leonard Seeff. A review of these 55 subject's disease course found one fatal event in the DE 150 mg dose group which was considered by the hepatologists as unlikely causally related to Dabigatran. There was one other event (in the DE 110 mg dose group) where other potential causes of liver enzyme test elevations were more likely than not attributable to the DE.

The expert FDA hepatologists did not think that routine monitoring of liver functions is necessary based both on the small numbers of such events as well as the futility in mitigating the consequences of such events once they have started. I agree.

Overall adverse events:

Gastrointestinal adverse events were more common in the DE 110 and DE 150 compared to warfarin treatments. There did not appear to be a meaningful difference in comparing the GI events in the DE 110 to the DE 150 mg BID doses. The GI events appear to encompass mostly upper GI tract discomfort. The largest DE related compared to warfarin was dyspepsia. GI adverse events are listed in Table 16. It should be noted that the duration of exposure was approximately 4% less for the DE treatments than for warfarin, and adverse events only up to six days post discontinuation of therapy were assigned to the randomized drugs. The comparison relative to warfarin, therefore, slightly underestimates the GI adverse events relative to warfarin.

Table 16: GI-related adverse events RE-LY trial

| | DE 110 | DE 150 | Warfarin |
|------------------------------------|-------------|-------------|-------------|
| N | 5983 (100%) | 6059 (100%) | 5998 (100%) |
| Overall Gastrointestinal disorders | 2073 (35%) | 2088 (35%) | 1442 (24%) |
| Diarrhea | 355 (6%) | 367 (6%) | 327 (5%) |
| Dyspepsia | 367 (6%) | 345 (6%) | 83 (1%) |
| Nausea | 245 (4%) | 259 (4%) | 208 (3%) |
| Constipation | 187 (3%) | 177 (3%) | 167 (3%) |
| Abdominal pain upper | 178 (3%) | 170 (3%) | 80 (1%) |
| Gastritis | 147 (3%) | 127 (2%) | 87 (1%) |
| Abdominal pain | 130 (2%) | 137 (2%) | 141 (2%) |
| Vomiting | 117 (2%) | 124 (2%) | 117 (2%) |
| Abdominal discomfort | 64 (1%) | 112 (2%) | 64 (1%) |
| Gastro-esophageal reflux disease | 65 (1%) | 99 (2%) | 46 (1%) |
| Rectal hemorrhage | 75 (1%) | 86 (1%) | 46 (1%) |
| Gastrointestinal hemorrhage | 61 (1%) | 78 (1%) | 56 (1%) |
| Hemorrhoids | 75 (1%) | 81 (1%) | 53 (1%) |
| Dysphagia | 61 (1%) | 74 (1%) | 24 (<1%) |
| Colonic polyp | 61 (1%) | 50 (1%) | 51 (1%) |
| Flatulence | 53 (1%) | 61 (1%) | 25 (<1%) |

Source: sponsor's table 12.2.3.2:1

Myocardial infarctions:

There was an imbalance in the number of myocardial infarctions (excluding silent MIs). The difference amounts to approximately 0.2 events/year or approximately 1/3 of the benefit of the decrease in stroke events.

Table 17: Myocardial infarctions during the RE-LY trial

| | DE 110 | DE 150 | Warfarin |
|--------------------------------------|------------------------|-----------|-----------|
| N | 6015 | 6076 | 6022 |
| Total number of MIs as first outcome | 87 ¹ (1.4%) | 89 (1.5%) | 66 (1.1%) |
| MI on drug | 56 (0.9%) | 59 (1.0%) | 46 (0.8%) |
| MI within 30 days off drug | 15 (0.2%) | 13 (0.2%) | 12 (0.2%) |
| MI > 30 days off drug | 15 (0.2%) | 17 (0.3%) | 8 (0.1%) |

Data extracted from slides presented at the advisory committee by Dr. Beasley. ¹ One randomized but not treated subject had an MI.

PK-PD modeling:

The FDA pharmaco-metric reviewers modeled the relationship of the yearly probability of the occurrence of ischemic stroke (note this analysis was not for all strokes and SEEs) versus either the single trough concentration collected at steady state from each individual or for the subset of subjects who had more than one measurement of trough concentrations (approximately 20% of those randomized), the average value for this trough measurement. The relationship between the trough value and the risk of ischemic strokes is shown in Figure 14. There is substantial overlap between the concentrations as measured in the 150 mg BID regimen and those measured in the 110 mg BID regimen. There is a decrease in the yearly probability of an ischemic stroke as the concentration increases. There is an upward inflection of risk as the concentrations of DE falls below the dabigatran concentration of approximately 70 ng/ml. The large difference between the two doses in prevention of events appears to be largely the population of the DE 110 dose group that falls below this value.

There is also a relationship between the risk of life threatening bleeds (not major bleeds) and concentration. This risk also increases as the concentration of DE increases. The shape of this curve is more linear.

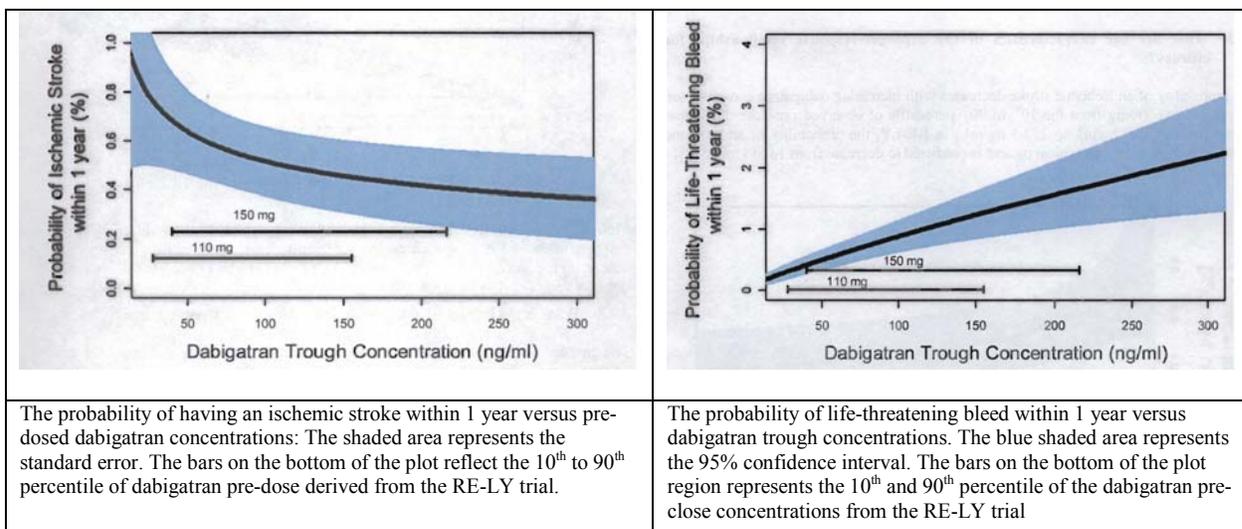


Figure 12: Modeled data for the probability of sustaining a ischemic stroke (left) and risk of sustaining a life-threatening bleed during the RE-LY trial based on pre-dose concentration measurements

Risk and benefit:

In considering the risk to benefit balance that results from increasing the dose and consequently the concentration of dabigatran, the two effects i.e. preventing strokes and provoking bleeds go in opposite directions. As noted above, the shapes of the relationship between concentration and either decreasing the hazard of ischemic stroke or sustaining a life threatening bleed differs.

The medical reviewers performed several analyses that looked for the time to first event for several composite endpoints. These analyses make the assumption that a bleed even a life-threatening bleed and a stroke event can be assumed to have equal consequence.

The value of preventing strokes when compared to the value of preventing life-threatening bleeds, however, is likely not equivalent. Most life threatening bleeds do not result in death. If the bleeding event is not mortal, the subject will likely recover with only modest residua. On the other hand, the majority of strokes resulted in severe disability or death. Both the sense of the advisory committee deliberations as well as the sense within the Division consider preventing a irreversible and debilitating or mortal stroke (about 70% of the stroke events) more worthwhile than preventing a major or even a life threatening bleed.

The value placed on the two consequences of treatments can be partially mitigated by controlling the dabigatran concentrations. As shown in Figure 14, there is a rather sharp upward inflection as the concentration of dabigatran decreases to below a value of approximately 70 ng/ml. At higher concentrations of dabigatran the risk of bleeding to decreasing the risk of stroke becomes more reasonable. I believe that making sure the concentration of dabigatran or the measured dabigatran effect on clotting may allow for better dosing even with the DE 110 mg BID dose.

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/s/

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10/19/2010