

CENTER FOR DRUG EVALUATION AND RESEARCH

**APPLICATION NUMBER:
22-512**

OTHER REVIEW(S)



DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS

Regulatory Project Manager Overview

NDA: 022512
Drug: PRADAXA (dabigatran etexilate mesylate) 75 and 150 mg Capsules
Class: Direct thrombin inhibitor
Sponsor: Boehringer Ingelheim
Indication: PRADAXA is indicated to reduce the risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation
Date of submission: 15 December 2010
Refusal to File: 12 February 2010
Date of re-submission: 19 April 2010
PDUFA date: 19 October 2010
Approval date: 19 October 2010

❖ REVIEW TEAM

- Office of New Drugs, Office of Drug Evaluation I, Division of Cardiovascular & Renal Products
 - Cross Discipline Team Leader (CDTL)
 - Abraham Karkowsky, M.D., Ph.D.
 - Medical Reviewers
 - Nhi Beasley, PharmD (Safety)
 - Aliza Thompson, M.D. (Efficacy)
 - Pharmacology & Toxicology
 - Pat Harlow, Ph.D.
 - Regulatory Health Project Manager
 - Alison Blaus
- Office of New Drug Quality Assessment (ONDQA), Branch I
 - Prafull Shiromani, Ph.D. (Drug Product)
 - Charles Jewell, Ph.D. (Drug Substance)
 - Tapash Ghosh, Ph.D. (Biopharmaceutics)
- Office of Clinical Pharmacology
 - Elena Mishina, Ph.D.
 - Peter Hinderling, M.D. (Drug-Drug Interactions)
 - Sudharshan Hariharan (Bioavailability/Bioequivalence)
 - Kevin Krudys, Ph.D. (Pharmacometrics)
- Office of Biostatistics, Division of Biometrics I
 - Steve Bai, Ph.D.
- Office of Surveillance and Epidemiology
 - John Senior, M.D. (Liver Review)
 - Judy Park and Cathy Miller (DMEPA)
 - Sharon Mills (Medication Guide)
 - Cynthia LaCivita (Risk Evaluation and Mitigation Strategy - REMS)
 - Shawna Hutchins (Risk Evaluation and Mitigation Strategy - REMS)

- Office of Medical Policy, Division of Drug Marketing, Advertising and Communications (DDMAC)
 - Emily Baker – Full Product Labeling
 - Zarna Patel – Patient Labeling
- Office of Compliance, Division of Scientific Investigations (DSI)
 - Sharon Gershon, PharmD (Clinical Studies)
 - Arindam Dasgupta (Bioequivalence Studies)

❖ **BACKGROUND**

PRADAXA is a synthetic, non-peptide, competitive, oral direct thrombin inhibitor, which 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.

The sponsor conducted one pivotal Phase 3 trial, RE-LY, to support their atrial fibrillation indication. This study is entitled, “Randomized Evaluation of Long term anticoagulant therapy (RE-LY) comparing the efficacy and safety of two blinded doses of dabigatran etexilate with open label warfarin for the prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation: prospective, multi-centre, parallel-group, non-inferiority trial (RE-LY).” The two doses studied in RE-LY were 110 mg and 150 mg, twice daily (BID). The results from RE-LY were presented to the Agency and published shortly thereafter in the New England Journal of Medicine, Volume 361 (12); 17Sep09. Upon review of the published RE-LY data, a “rolling review” was granted for this NDA. In the initial submission, the sponsor sought the following indications:

- **Prevention of Stroke and Systemic Embolism**
Dabigatran etexilate is indicated for the prevention of stroke and systemic embolism in patients with atrial fibrillation.
- **Reduction of Vascular Mortality**
Dabigatran etexilate is indicated for the reduction of vascular mortality in patients with atrial fibrillation

On 27 July 2010, the sponsor withdrew the “Reduction of Vascular Mortality” claim citing the following, “In an effort to harmonize the indication statement for PRADAXA globally, we are requesting reduction of vascular mortality in atrial fibrillation patients be removed from the proposed US indication statement in NDA 22-512 at this time.” No further rationale was provided.

A preliminary review of the 15 December 2009 NDA submission revealed a number of errors in the blood transfusion and INR datasets. These errors included transcription errors, transposition errors, and auditing errors. Although we recognized that there will be some errors in the datasets from large trials, the errors found by relatively unsophisticated means in clinically important datasets during preliminary review called into question the overall quality of those datasets and our confidence in them. Upon further consideration, the Division decided to “Refuse to File” the application on 12 February 2010, solely based on the abovementioned data issues. The Division and the sponsor met on 18 February 2010 to discuss the Refuse to File Letter and laid out an acceptable plan for resolving the Agency’s concerns (proposed “Road Map” submitted to the Agency on 16 February 2010).

After addressing the Agency’s concerns and fulfilling their “Road Map”, the sponsor resubmitted the NDA on 19 April 2010. The review of this application proceeded relatively smoothly, meeting all 21st century review timelines, with approximately 170 information requests since 17 September 2009.

User Fee

The user fee for this application was paid in full on 14 April 2010, prior to the re-submission of the application (ID 3010228).

Pediatric Review Committee (PeRC)

The PeRC meeting to discuss this application was held on 1 September 2010. The PeRC and the Division agreed with the sponsor that, "Atrial fibrillation is a relatively rare form of arrhythmia in the pediatric population. When it is seen in an infant or child, it is often associated with a structural heart abnormality, particularly after surgical repair or palliation of congenital heart disease. Other episodes may be associated with metabolic derangements." A full pediatric waiver was granted for this application.

Advisory Committee

The dabigatran etexilate ADCOM was held on 20 September 2010 (please see quick minutes in the action package). The committee was asked a number of discussion questions ranging from the design of the pivotal trial RE-LY, its conduct, and the doses tested. There was only one voting question, "Should dabigatran be approved for the reduction of stroke and non-CNS systemic embolism in patients with non-valvular atrial fibrillation?" This question yielded nine "yes" responses and zero "no" or "abstain" votes.

Trade name

PRADAXA was deemed conditionally acceptable for use on September 21, 2007 and May 10, 2010 and fully acceptable on 18 October 2010, but with suggested changes to the carton and container labels. Those changes are reflected in the labels that appear as an appendix to the Approval Letter. The review Division did not have any concerns with the proposed name.

❖ REGULATORY TIMELINE

- IND filed: 7 July 2003
- End of Phase 2 Meeting: 24 March 2005 (minutes dated 12 April 2005)
- Request for a Special Protocol Assessment for RE-LY dated 26 May 2005
- Special Protocol Assessment Letter from the Agency dated 11 July 2005
- Statistical Analysis Plan (SAP) Meeting with the sponsor on 18 August 2010 (minutes dated 12 September 2008)
- RE-LY data presented to the Agency on 17 August 2009 (minutes 17 September 2010)
- First piece of the NDA submission (nonclinical module) received 17 September 2009
- Last piece of the NDA (the outstanding sections from Module 5) received 15 December 2009
- Refuse to File letter dated 12 February 2010
- Executive Carcinogenicity Assessment Committee (CAC) Meeting: 16 February 2010
- Refuse to File Meeting with the sponsor: 18 February 2010 (minutes dated 15 March 2010)
- NDA re-submitted: 19 April 2010
- Filing Meeting: 17 May 2010
- Priority Designation Letter: 3 June 2010
- 74-day Issues Letter: 2 July 2010
- Mid-cycle Meeting: 19 July 2010
- Advisory Committee: 20 September 2010
- PDUFA Date: 19 October 2010
- Approval Date: 19 October 2010

❖ **REVIEWS**

Below are the conclusions reached by the PRADAXA team members, organized by role or discipline.

Office Memorandum (dated 19 October 2010)

Dr. Unger is recommending approval of the 150 mg BID dose, with a recommendation of 75 mg BID for patients with a creatinine clearance (CrCl) of 15-30 mL/min.

Divisional Memorandum (dated 14 October 2010)

Dr. Stockbridge recommends approval of PRADAXA and noted in his review that like the medical review team and Advisory Committee members, the vast majority of patients should be dispensed the 150 mg dose.

Cross-Discipline Team Leader (CDTL) Review (dated 12 October 2010)

Dr. Karkowsky wrote in his review that PRADAXA should be approved to decrease the risk of strokes and possibly also 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). He believed that the 150 mg BID dosing regimen was clearly effective and should be approved, based on the decreased risk of strokes relative to warfarin. The 110 mg BID dose, however, was thought to be 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. In summary, Dr. Karkowsky said that he recognized that along with the greater efficacy of dabigatran 150 BID; there was also a greater risk of bleeding than the dabigatran 110 mg BID dose. The consequence of that bleeding, however, is usually transient and only infrequently results in mortality or permanent disability. Therefore, 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.

Medical Review (two reviews; one dated 25 August and the other 2 September 2010)

Drs Beasley and Thompson agreed that dabigatran etexilate should be approved for the prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation. Although two doses, 110 mg and 150 mg were proposed by the sponsor, the medical review team concluded that only the 150 mg dose of dabigatran should be approved. Upon their joint review, they also determined that a superiority claim over warfarin should not be granted.

The medical review team's rationale for not approving the 110 mg dose, was related to the merit of adjusting the dabigatran dose based on perceived bleeding risk. While the team agreed that one could attempt to explore the issue by performing subgroup analyses of "net-benefit" in various RE-LY subpopulations, any findings generated by such analyses may be more reflective of chance than true dose-dependent drug effects. Therefore in conclusion, the team agreed that only the approval of the 150 mg dose was appropriate.

Biostatistics Review (dated 20 July 2010)

Dr. Bai concluded that the 150 mg dose of dabigatran was superior to warfarin for the primary (stroke/SEE) efficacy endpoints. Furthermore, he noted that the secondary (stroke/SEE/death and stroke/SEE/PE/MI/vascular death) efficacy endpoints also met the above claims numerically. However, in the statistical review, it was noted that the sponsor did not specify the statistical testing rules and margins for these endpoints in their Statistical Analysis Plan (SAP). Therefore, Dr. Bai determined that the secondary endpoint findings can only be viewed as exploratory.

Upon review of the application, Dr. Bai believed that there were no discrepancies found in any of the sensitivity analyses. Although, dabigatran 150 mg did not show superiority for the US subjects statistically, it was still noted as non-inferior to warfarin and the point estimate (hazard ratio) was also

less than 1.00. Lastly, all the subgroup analyses performed in Section 4 were consistent with the primary efficacy results, concluding that the RE-LY study findings are very robust. To further underscore that conclusion, based on the reviewer's analysis on the impact of different end of trial dates, the dabigatran doses (110 and 150 mg) achieved the non-inferiority long before the end of trial date and dabigatran 150 mg achieved superiority to warfarin more than one year before the end of trial date (see Figure 3.3 of the biometrics review)

Clinical Pharmacology Review (dated 17 August 2010; amended with OD signature on 8 September 2010)
The Office of Clinical Pharmacology reviewed the clinical pharmacology and biopharmaceutics (CPB) information submitted to NDA 022512. The CPB information provided in this was acceptable, from a clinical pharmacology perspective, following agreement with sponsor regarding specific labeling language and post-marketing requirements. In their review, Clinical Pharmacology had 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.

The clinical pharmacology reviewers at the time of their reviews were recommending one post marketing requirement (PMR) and one commitment. Please see the finalized PMRs in the Conclusion section of this review.

- Post Marketing Requirement - The sponsor should manufacture a lower strength of 75 mg and demonstrate bioequivalence following the administration of 2x75 mg versus 150 mg for BIBR 1048MS. This strength will allow for the dose adjustment in severe renal impaired patients.
- Phase IV Commitments (PMC)- Since amiodarone and dronedarone will be among the most commonly used antiarrhythmic 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.

Pharmacometrics Review (dated 24 August 2010)

Dr. Krudys opined on the dosing recommendations, 110 mg and 150 mg twice daily, reached through the data from RE-LY. He also noted that, based on modeling, the maximum benefit of dabigatran could potentially be reached at doses higher than 150 mg twice daily.

Pharmacology & Toxicology Review (dated 13 September 2010)

Dr. Harlow determined that NDA 22-512 was approvable from a nonclinical perspective for the proposed indication. She concluded that most of the toxicities identified in the non-clinical studies were either attributable to the pharmacodynamic effect of dabigatran (BIBR 953 ZW), the active form of the pro-drug, dabigatran etexilate mesylate (BIBR 1048 MS) and that satisfactory safety margins had been demonstrated. However, Dr. Harlow determined that the full prescribing information be clearly written to warn women of child-bearing potential of BIBR 1048 MS's embryo/fetal and peri-natal toxicity to offspring.

The Division met with the Executive Carcinogenicity Assessment Committee (CAC) on 16 February 2010 and their recommendations were as follows (minutes dated 17 February 2010):

Rat:

- The Committee concluded that the rat bioassay was adequate and noted that the sponsor used the doses recommended by the prior Exec CAC protocol agreement.
- The Committee found that the rat carcinogenicity study was negative for any drug related statistically significant neoplasms.

Mouse:

- The Committee concluded that the mouse bioassay was adequate and noted that the sponsor used the doses recommended by the prior Exec CAC protocol agreement.
- The Committee found that the mouse carcinogenicity study was negative for any drug related statistically significant neoplasms.

Dr. Harlow's labeling recommendations have been agreed to by the sponsor and appear as below:

“8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Teratogenic Effects, Pregnancy Category C

There are no adequate and well-controlled studies in pregnant women.

Dabigatran has been shown to decrease the number of implantations when male and female rats were treated at a dosage of 70 mg/kg (about 2.6 to 3.0 times the human exposure at maximum recommended human dose [MRHD] of 300 mg/day based on area under the curve [AUC] comparisons) prior to mating and up to implantation (gestation Day 6). Treatment of pregnant rats after implantation with dabigatran at the same dose increased the number of dead offspring and caused excess vaginal/uterine bleeding close to parturition. Although dabigatran increased the incidence of delayed or irregular ossification of fetal skull bones and vertebrae in the rat, it did not induce major malformations in rats or rabbits.

8.2 Labor and Delivery

Safety and effectiveness of PRADAXA during labor and delivery have not been studied in clinical trials. Consider the risks of bleeding and of stroke in using PRADAXA in this setting [see Warnings and Precautions (5.1)].

Death of offspring and mother rats during labor in association with uterine bleeding occurred during treatment of pregnant rats from implantation (gestation Day 7) to weaning (lactation Day 21) with dabigatran at a dose of 70 mg/kg (about 2.6 times the human exposure at MRHD of 300 mg/day based on AUC comparisons).

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Dabigatran was not carcinogenic when administered by oral gavage to mice and rats for up to 2 years. The highest doses tested (200 mg/kg/day) in mice and rats were approximately 3.6 and 6 times, respectively, the human exposure at MRHD of 300 mg/day based on AUC comparisons.

Dabigatran was not mutagenic in in vitro tests, including bacterial reversion tests, mouse lymphoma assay and chromosomal aberration assay in human lymphocytes, and the in vivo micronucleus assay in rats.

In the rat fertility study with oral gavage doses of 15, 70, and 200 mg/kg, males were treated for 29 days prior to mating, during mating up to scheduled termination, and females were treated 15 days prior to mating through gestation Day 6. No adverse effects on male or female fertility were observed at 200 mg/kg or 9 to 12 times the human exposure at MRHD of 300 mg/day based on AUC comparisons. However, the number of implantations decreased in females receiving 70 mg/kg, or 3 times the human exposure at MRHD based on AUC comparisons.”

Office of New Drug Quality Assessment (ONDQA), Branch I, Review [five reviews dated 19 January (Initial Quality Assessment), 8 June, 29 June, 15 July, and 15 September 2010]

The PRADAXA NDA, both the 75-mg and 150-mg doses, were recommended for approval from a Chemistry, Manufacturing and Control (CMC) perspective. The sponsor provided adequate responses to the CMC information request letters dated 29 June 2010 and 1 September 2010. Additionally, the ONDQA Biopharm and Environmental Assessment reviews were satisfactorily completed with no significant findings or issues. This assessment review was submitted to DARRTS.

It is important to note that the sponsor agreed to a drug product stability commitment to study at least three production scale batches of the 75 mg and 150 mg capsules in the proposed packaging configurations to confirm shelf-life.

❖ **CONSULTS**

Office of Surveillance and Epidemiology Review - Liver (two reviews dated 1 September 2010)

Dr. Senior noted that the data suggest that dabigatran exetilate is somewhat less dangerous than ximelagatran was found to be, but it should not be assumed completely safe from causing idiosyncratic liver toxicity in some people if very large numbers of them are treated with it long-term. Because the population with chronic atrial fibrillation tends to be elderly and to have high prevalence of cardiac disorders and other problems likely to cause liver dysfunction, it would be advisable for patients to have pre-treatment evaluation of liver disease and for the treating physicians and patients both to be alert for early signs of liver dysfunction, with prompt investigation of the probable cause if findings or symptoms occur. Dr. Senior also noted that routine monitoring of serum indicators of liver injury during treatment has been found to be inefficient, ineffective, very burdensome, and is not recommended for PRADAXA.

Office of Surveillance and Epidemiology Review – REMS and Medication Guide (dated 14 October, 15 October and two on 18 October 2010)

The Risk Evaluation and Mitigation Strategy (REMS), Prescribing Information, and Medication Guide were reviewed by Cynthia LaCivita, Sharon Mills, Cathy Miller and Shawna Hutchins. Their review comments were taken into consideration when drafting the final labeling and REMS.

Division of Scientific Investigations (DSI) Review (dated 13 October 2010 and 18 October 2010)

In Dr. Gershon’s review for this NDA, she documented the inspection of 3 domestic and 4 foreign clinical sites, and inspection of the sponsor (Boehringer Ingelheim) and the CRO (b) (4). In general, the clinical sites were chosen for inspection due to relatively high enrollment and greater efficacy favoring the dabigatran arm. The sponsor and CRO inspections were

conducted to evaluate the sponsor's oversight of the study as well as to evaluate the specific issues that may have led to the data quality issues noted in the initial NDA submission.

With respect to the 3 PDUFA domestic site inspections, minor regulatory violations were noted at 2 sites (b) (4) and no regulatory violations were noted at the other site (b) (4). For these sites, the data appear reliable in support of the respective indication.

With respect to the 4 PDUFA foreign site inspections, the regulatory violations noted at 3 sites (b) (4), are considered isolated in nature and unlikely to significantly impact data reliability. A preliminary review of findings from the inspection of the 4th foreign site, (b) (4) site, raised some concerns as to data reliability from this site. Preliminary information provided by the field investigator noted several issues concerning lack of source documentation to support data entered onto the CRF. The preliminary information provided is not sufficient to allow for an assessment as to the pervasiveness of the specific findings noted. As such, at this time, data reliability cannot be confirmed from (b) (4) site.

With respect to inspections of the sponsor and CRO, although regulatory violations were noted, the resubmitted data appear reliable. In general, inspectional findings from the sponsor inspection noted that the sponsor did not implement comprehensive quality assurance systems to ensure the quality of the data prior to initial submission of the application. The most notable finding from the inspection at (b) (4) was lack of written procedures and manuals for key aspects of the study such as monitoring, data management, and adjudication. Additionally, the contract which delegated many study functions to (b) (4) was not signed until almost 2 years into the study. Likewise, the key issue noted during the sponsor inspection was the lack of a signed contract at the beginning of the study (2005), delegating duties and responsibilities to (b) (4). Although the issues noted at the sponsor and CRO inspection may have led to the data quality concerns identified in the original NDA submission, the resubmitted revised data appears reliable in support of the application.

Under the IND, 9 For-Cause inspections of the RE-LY study were conducted between 2007-2010, to include 1) 8 inspections that were conducted due to site closure by the sponsor for GCP non-compliance issues and 2) 1 inspection that was conducted as a result of a complaint. Of these 9 For-Cause inspections, DSI recommends that the data from (b) (4) not be used in support of the application. With respect to the remaining 7 For-Cause clinical investigator inspections, although violations may have been noted at these sites, the violations are not likely to significantly impact data reliability.

In conclusion, Dr. Gershon noted that although quality assurance issues were evident at both the sponsor and (b) (4) inspections, the overall reliability and credibility of the data seems sufficient to recommend that the data be used in support of the indication for this NDA, with the exception of the data from (b) (4) site and the data from two previously conducted For-Cause inspections ((b) (4)).

An audit of the clinical portion of the bioequivalence studies 1160.70 and 1160.66 was also completed and documented in (b) (4) review dated 18 October 2010. Following the above audits, the Division of Scientific Investigations recommended that the data from the clinical portion of these studies was acceptable for Agency review.

Division of Drug Marketing, Advertising and Communications (DDMAC) (dated 14 October 2010) DDMAC reviewed the proposed trade name, PRADAXA, on 13 December 2006, 25 November 2009, and 15 July 2010, and had no concerns regarding the proposed name from a promotional perspective.

Emily Baker finalized her review of the labeling on 14 October 2010 and provided a number of comments. Those comments can be found in her 14 October 2010 review. Zarna Patel, DDMAC patient labeling reviewer, incorporated her comments in DDMAC final labeling review as well as Sharon Mills' review of the Medication Guide.

CONCLUSION

An Approval Letter (cleared by SWAT on 18 October 2010) was issued for this application and signed by the Deputy Office Director, Ellis Unger, M.D., on 19 October 2010. The letter documented the approval of the 150 mg BID dose in patients with creatinine clearance (CrCl) of > 30mL/min and 75 mg BID for those patients with non-valvular atrial fibrillation who have a CrCl of 15-30 mL/min. The 110 mg BID dose was not approved for the following reason cited in the letter:

“We are not approving the 110-mg dose, because you have not identified a population in whom there is compelling evidence that the net benefit of the 110-mg dose exceeds that of the 150-mg dose. Moreover, we are concerned that physicians and patients will use the 110-mg dose instead of the 150-mg dose, when the clinical data suggest that the 150-mg dose is superior.”

The Approval Letter was appended with the agreed upon labeling and the finalized REMS and Medication Guide. The letter also detailed the below post marketing requirements (PMRs) that were already agreed upon by the sponsor in their email communication dated 15 October 2010:

- 1697-1 An *in vitro* study profiling of dabigatran as a substrate or inhibitor of a panel of drug SLC transporters (OATPs, OATs, OCTs) that are proposed as being relevant by the recently published ITC white paper (Giacomini M, Huang S-M, Tweedie D, et al. Membrane transporters in drug development. Nature Review Drug Discovery, 2010, 9: 215-236.)

Final Protocol Submission:	December 2010
Study Completion:	November 2011
Final Report Submission:	February 2012

- 1697-2 An *in vitro* study of the effects of amiodarone and dronedarone on active transport of dabigatran. .

Final Protocol Submission:	December 2011
Study Completion:	September 2012
Final Report Submission:	December 2012

Please also reference the 20 October 2010 Memorandum to File noting the concepts proposed by the review team and the sponsor's proposed studies designed to answer these questions.

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/s/

ALISON L BLAUS
10/20/2010



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

DATE: October 20, 2010

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

Rajanikanth Madabushi, Ph.D., Team Leader, Division of Clinical
Pharmacology I, OCP.

TO Ellis Unger, M.D., Deputy Director, ODE-1.

SUBJECT: Approval of a 75 mg BID dosing regimen for subjects with severe renal
dysfunction (CrCl of 15 – 30 mL/min).

Dosing in subjects with Renal Failure¹:

The RE-LY study is the basis for the approval recommendation for dabigatran etexilate to decrease the risk of stroke and systemic embolic events in subjects with non-valvular atrial fibrillation. In the RE-LY study subjects with severe renal impairment (i.e. an estimated creatinine clearance (CrCl) of 15 - 30 mL/min) were routinely excluded from enrolling in the study. During the course of the RE-LY study, subjects whose clearance dropped below 30 mL/min had their medication temporarily halted until the creatinine clearance improved to above 30 mL/min. If a second episode of a decrease in CrCl to < 30 mL/min occurs, the subject is permanently discontinued.

For the RE-LY study, the decision to not include or to discontinue subjects with markedly decreased renal function was probably a rationale decision. Dabigatran and its metabolites are renally excreted. Allowing patients with marginal renal function to enroll or continue in the study would risk the problem of generating excessive concentrations in these patients and risking additional bleeding. In the RE-LY study, the two dabigatran groups were treated in a blinded manner and controlling for exposure among those with severe renal failure in the treatment dabigatran treatment groups would add an additional level of complexity to the study. Furthermore, fine gradations of doses were not available, so titration of these subjects, while still maintaining these subjects in the appropriate blinded treatment group, would create difficulties. The decision not to enroll or to discontinue patients with severe renal failure in the RE-LY study, however, creates uncertainty about the magnitude of benefit or risk ratio for this population.

¹ The modeled and analytic information that is contained in this memo was almost entirely generated by the Clinical Pharmacology Team.

With respect to the effect of renal dysfunction on dabigatran concentrations, the concentrations of dabigatran (plus glucuronides) when measured at the interdosing interval increases in a continuous manner as the degree of renal function decrease. The clinical pharmacology reviewers produced the following plot. On the x-axis is the creatinine clearance in ml/min on the y-axis is plotted concentrations \pm SD for the 150 mg BID dose group, with the population divided into cohorts of approximately 100 subjects. The value is plotted in the midpoint of the CrCl for each group.

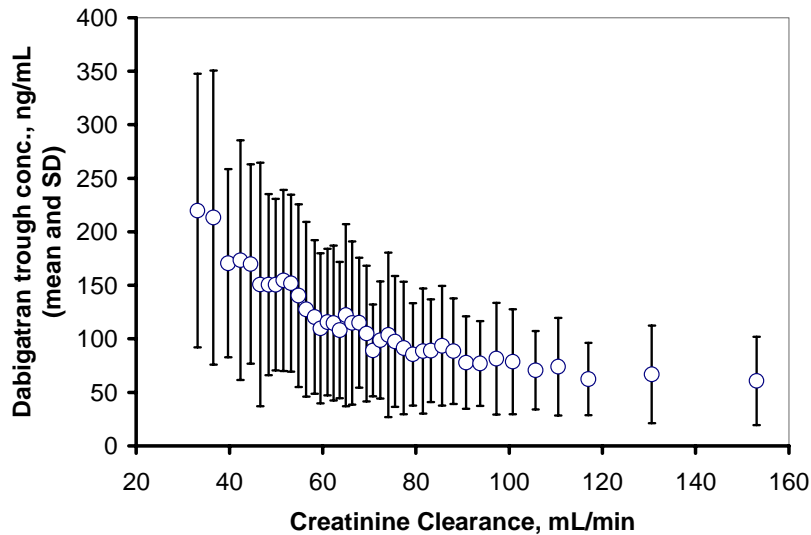


Figure 1 Concentration of dabigatran and metabolites at trough in the 150 mg BID-treated group divided into groups of approximately N=100 based on their enrollment renal function

Despite the increase in the standard deviation of dabigatran plasma concentration as the degree of renal dysfunction increases, the variability in these concentrations, as assessed by the coefficient of variation, seems to be relatively constant. The variability of dabigatran concentrations is shown in Figure 2. If a dose of dabigatran is chosen for severe renal failure patients, the resulting concentrations would not lead to large numbers of subjects whose concentrations fall either too low and would be at risk for being undertreated and therefore, at substantial increased risk for sustaining a stroke or those whose concentrations are excessive and are at a particularly high risk of bleeding.

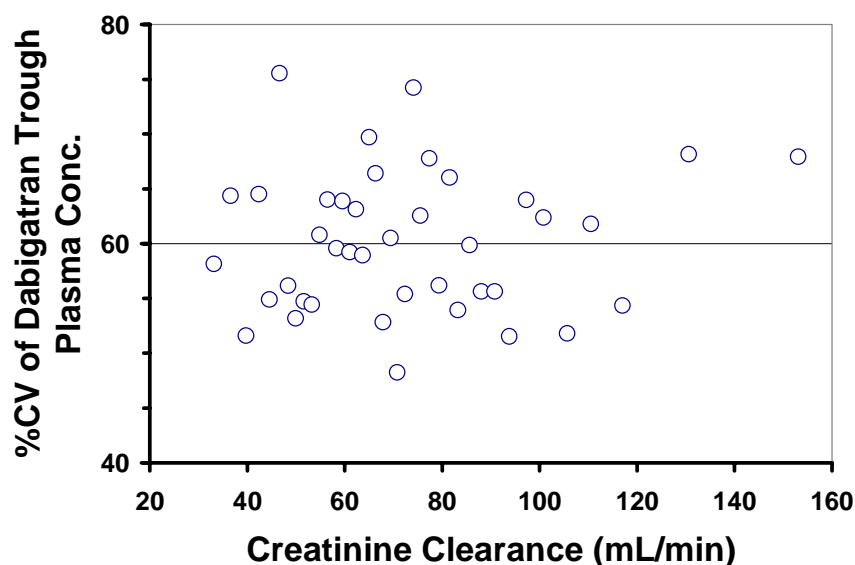


Figure 2: Coefficient of variation of those in the RE-LY study treated with 150 mg dabigatran BID in sequential groups of approximately N=100 based on baseline creatinine clearance.

The clinical pharmacology reviewers performed simulation of various dosing regimens and proposed 75 mg QD for subjects with severe renal impairment (see DARRTS date 9/8/2010). This regimen was expected to provide exposures bounded by the lowest concentrations expected with 150 mg BID in subjects with normal renal function and the highest exposure on an average expected with 150 mg BID dosing in subjects with moderate renal impairment.

Upon further deliberations, the goal of the simulation exercise was revised to model a dabigatran regimen in severe renal dysfunction patients whose concentrations are reasonably similar to that expected in subjects with moderate renal impairment receiving 150 mg BID regimen. This target was based on the fact that the 150 mg BID regimen for those with moderate renal function impairment produced substantial benefit in the RE-LY study.

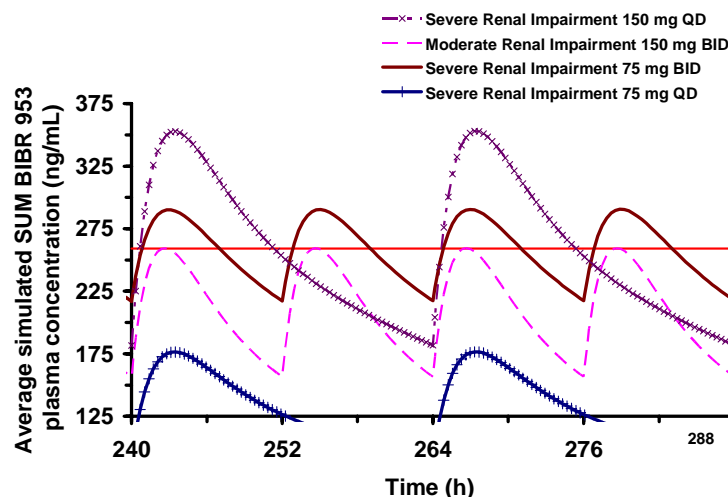


Figure 3: Modeled data for subjects who enrolled in the RE-LY study and simulated data for subjects with severe renal dysfunction based on single dose PK data. The horizontal lines define the concentrations at peak for those enrolled who had moderate renal failure.

There are three dosing regimes shown here to address dose adjustment in subjects with severe renal dysfunction.

The 150 mg QD in severe renal dysfunction patients generate 35% higher peak concentrations compared to 150 mg BID dose regimen in patients with moderate renal dysfunction.

The 75 mg QD in the severe renal dysfunction subjects generates that are on an average lower compared to 150 mg BID in subjects with moderate renal dysfunction.

The 75 mg BID regimen in subjects with severe renal dysfunction is expected to provide 12% higher exposure with low peak-to-trough ratio (1.3) compared to 150 mg BID in subjects with moderate renal dysfunction (peak-to-trough = 1.7). This clinical and clinical pharmacology reviewers did not consider the small increase in peak exposures on the 75 mg BID regimen to be clinically significant. Furthermore, this dosing instructions for the renal population, aside from the different dose strength, is the same as for the general population. No additional instructions need to be provided. The concordance of dosing intervals would minimize any prescription errors that may occur if a once daily regimen would be recommended in this renal sub-population.

There was a single study which enrolled a small number of subjects with compromised renal function. Clotting parameters in addition to dabigatran concentrations were assessed in this study. These results shown below that clotting as assessed by the ecarin clotting time (ECT) ratio² is independent of the degree of renal dysfunction. The

² The ratio is measured value/baseline value. An abnormal baseline value on dabigatran would imply a greater risk of bleeding which is proportionately amplified while on dabigatran. It is unclear how well the ECT predicts bleeding risk in patients with severe renal dysfunction. In these patients clotting factors are normal but there is some degree of platelet dysfunction. In uremic patients there is an abnormality in the

ratio is the relationship between baseline measurements of clotting and those while treated with single doses of dabigatran etexilate. The alteration suggests that the effect of dabigatran concentrations on the ECT ratio would be similar to that of moderate renal dysfunction patients.

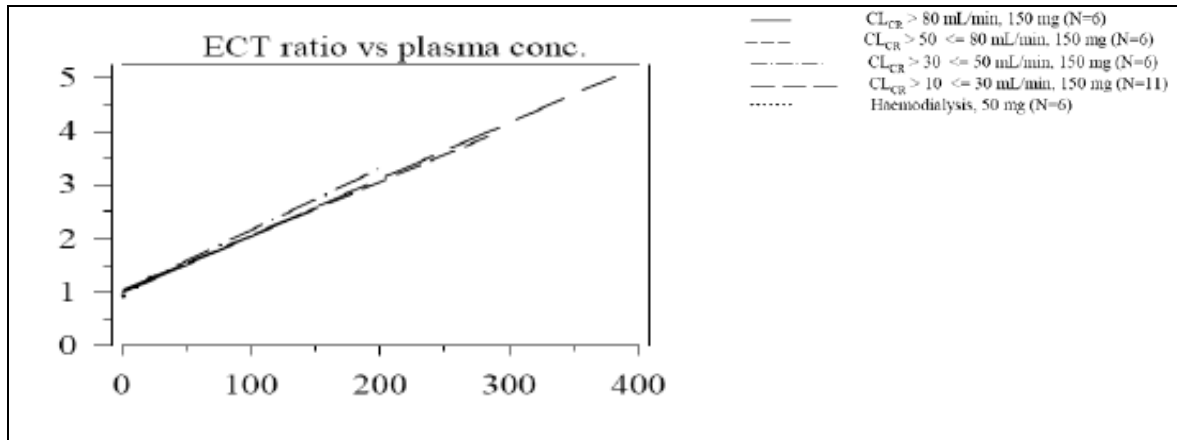


Figure 4 Relationship of ECT ratio versus dabigatran concentrations at different levels of renal function, single dose study

The Division concluded that the best tact is to assure that the population with severe renal dysfunction, not on dialysis, would have access to dabigatran. A dosing regimen of 75 mg BID for this population provides reasonable matching of exposures to that expected with subjects with moderate renal dysfunction. A dose of 75 mg BID was included within the label and will shortly be available for marketing. Since the variability was no greater than the population that was already studied, no monitoring of clotting effect was currently recommended.

The current issues are that the 75 mg dose strength will have the same color code as the 150 mg dose strength but it is encapsulated in a much small capsule size (size 2 for the 75 mg capsule versus size 0 for the 150 mg capsule). The 75 mg dose also has the strength written on the capsule, to further minimize mix up in dose strengths.

The 75 mg strength is compositionally proportional to 150 mg capsules. Hence no further studies with regard to establishing bioequivalence are required to approve this additional dose strength. This recommendation is contrary to that previously recommended by the Clinical Pharmacology Review (DARRTS dated 9/8/2010).

Approving the second dose strength of dabigatran etexilate would now allow for the Trade name PRADAXA®, since dose strength would be required to define which dose is prescribed.

interaction between platelets and the vascular endothelium [Brenner BM (2008). Brenner and Rector's The Kidney, 8th Edition, pp. 1737-8 (Brenner BB and Levine SA Eds.). Philadelphia, PA]. The clinical trial experience had patients treated with anti-platelet drugs and had acceptable risk to benefit ratios. It is likely that there will be increased bleeding risk but the risk would be the same whether the drug used is dabigatran or warfarin.

Since there is no empirical data on this population with regard to bleeding risk, particular attention post-marketing should be paid to bleeding and other safety events in those treated with the 75 mg BID regimen in patients with severe-renal impairment.

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/s/

ABRAHAM M KARKOWSKY
10/19/2010

RAJANIKANTH MADABUSHI
10/19/2010

MEMORANDUM

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

DATE: October 18, 2010

TO: Norman Stockbridge, M.D.
Director
Division of Cardiovascular and Renal Products
(HFD-110)

FROM: Arindam Dasgupta, Ph.D.
Division of Scientific Investigations (HFD-48)

THROUGH: Martin K. Yau, Ph.D. *Martin K. Yau 10/18/10*
Acting Team Leader - Bioequivalence Branch
Division of Scientific Investigations (HFD-48)

SUBJECT: Review of EIRs covering NDA 22512, PRADAXA® (dabigatran etexilate) 110 mg and 150 mg capsules, sponsored by Boehringer Ingelheim Pharmaceuticals, Inc.

At the request of the Division of Cardiovascular and Renal Products (DCRP), the Division of Scientific Investigations (DSI) conducted an audit of the clinical portion of the following bioequivalence studies:

Study Number: 1160.70 (Boehringer Ingelheim Trial Number)

Study Title: "Bioequivalence of two different generations of drug product of 150 mg dabigatran etexilate following oral administration in healthy male and female volunteers (double-blind, randomized, single dose, replicate design in a two treatments, four periods crossover phase I study"

Study Number: 1160.66 (Boehringer Ingelheim Trial Number)

Study Title: "Bioequivalence of two different polymorphs of 150 mg dabigatran etexilate following oral administration in healthy male and female volunteers (double-blind, randomized, single dose, replicate design in a two treatments, four periods crossover phase I study"

Page 2 - NDA 22512, PRADAXA® (dabigatran etexilate) 110 mg and 150 mg capsules, sponsored by Boehringer Ingelheim Pharmaceuticals, Inc.

The audit of the clinical portions of the study 1160.70 and study 1160.66 were conducted at (b) (4)

(September 20-24, 2010) and at (b) (4)

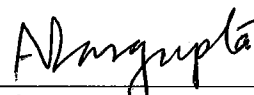
(September 27-30, 2010, 2010), respectively. Following the inspections at (b) (4) and (b) (4)

, no FDA-483 was issued. Please note that at this time, the EIRs for the clinical site inspections have not yet been received by DSI. However due to the PDUFA due date, this review was written based on discussion with the ORA investigator; there are no items that significantly affected the outcomes of studies 1160.70 and 1160.66.

Conclusions:

Following the above inspections, the Division of Scientific Investigations recommends that the data from the clinical portion of studies 1160.70 and 1160.66 can be accepted for agency review.

After you have reviewed this transmittal memo, please append it to the original NDA submission.



Arindam Dasgupta, Ph.D.

Page 3 - NDA 22512, PRADAXA® (dabigatran etexilate) 110 mg and
150 mg capsules, sponsored by Boehringer Ingelheim
Pharmaceuticals, Inc.

Final Classification:

NAI- [REDACTED] (b) (4)

NAI- [REDACTED] (b) (4)

cc:DARRTS

DSI/GLPBB/Ball/Haidar/Yau/Dasgupta/Rivera-Lopez/CF

OND/ODEI/DCRP/Stockbridge/Alison Blaus

OTS/OCP/DCPI/Mehta/Madabushi/Sudarshan Hariharan

HFR-SE2585/Bill Tacket

Draft: AD 10/18/10

Edit: MKY 10/18/10

DSI: 6087

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FACTS: [REDACTED] (b) (4)

Email:

CDER DSI PM TRACK

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/s/

ARINDAM DASGUPTA
10/18/2010

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology**

PATIENT LABELING REVIEW

Date: October 15, 2010

To: Norman Stockbridge, MD, PhD, Director
Division of Cardiovascular and Renal Products (DCRP)

Through: LaShawn Griffiths, RN, MSHS-PH, BSN
Acting Team Leader, Patient Labeling Reviewer
Division of Risk Management (DRISK)

Barbara Fuller, RN, MSN, CWOCN
Patient Labeling Reviewer
Division of Risk Management

From: Sharon R. Mills, BSN, RN, CCRP
Senior Patient Labeling Reviewer, Acting Team Leader
Division of Risk Management

Subject: DRISK Review of Patient Labeling (Medication Guide)

Drug Name (established name): PRADAXA (dabigatran etexilate)

Dosage Form and Route: Capsule

Application Type/Number: NDA 22-512

Applicant: Boehringer-Ingelheim Pharmaceuticals, Inc.

OSE RCM #: 2009-2421

1 INTRODUCTION

This review is written in response to a request by the Division of Cardiovascular and Renal Products (DCRP) for the Division of Risk Management (DRISK) to review the Applicant's proposed Medication Guide (MG). The Applicant resubmitted their original New Drug Application (NDA) for PRADAXA (dabigatran etexilate) after receiving a Refusal to File letter from FDA on February 12, 2010. The proposed indication for PRADAXA (dabigatran etexilate) is for reducing the risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation.

The proposed REMS is being reviewed by DRISK and will be provided to DCRP under separate cover.

2 MATERIAL REVIEWED

- Draft PRADAXA (dabigatran etexilate) Medication Guide (MG) received on May 27, 2010 and further revised by the Applicant on August 17, 2010
- Draft prescribing information (PI) received May 27, 2009, revised by the Review Division throughout the current review cycle and received by DRISK on October 8, 2010
- Approved Effient (prasugrel) PI (NDA 22-307) comparator labeling, dated April 16, 2010 and original approved MG dated July 10, 2009

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level. In our review of the MG the target reading level is at or below an 8th grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We have reformatted the MG, document using the Verdana font, size 11.

In our review of the MG we have:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the prescribing information (PI)
- removed unnecessary or redundant information
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

- ensured that the MG is consistent with the approved comparator labeling where applicable.

4 CONCLUSIONS

The MG is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DRISK on the correspondence.
- Our annotated versions of the MG are appended to this memo. Consult DRISK regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG Please let us know if you have any questions.
- With respect to the comparator labeling, we note that the changes to the Effient MG that were approved in conjunction with S-001 on April 16, 2010 for NDA 22-307 are not reflected in the labeling posted at either Drugs @ FDA or NLM Daily Med. Please ensure that the correct labeling is posted.

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/s/

SHARON R MILLS
10/15/2010

LASHAWN M GRIFFITHS
10/15/2010

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date: October 14, 2010

Application Type/Number: NDA 022512

To: Norman Stockbridge, MD, Director
Division of Cardiovascular and Renal Products

Thru: Zachary Oleszczuk, PharmD, Team Leader
Denise Toyer, PharmD, Deputy Director
Division of Medication Error Prevention and Analysis (DMEPA)

From: Cathy A. Miller, MPH, BSN, Safety Evaluator
Division of Medication Error Prevention and Analysis (DMEPA)

Subject: Label and Labeling Review

Drug Name(s): (b) (4) (Dabigatran Etexilate) Capsules
150 mg

Applicant/Applicant: Boehringer Ingelheim

OSE RCM #: 2009-2234

1 INTRODUCTION

This review responds to a request from the Division of Cardiovascular and Renal Products for DMEPA review of the blister and container labels, carton and insert labeling for the proposed (b) (4) (Dabigatran Etexilte) capsules to identify areas that could lead to medication errors.

1.1 REGULATORY HISTORY

DMEPA found the proprietary name, Pradaxa, acceptable in the IND phase (OSE Review #2006-938 dated September 21, 2007).

In OSE #2010-957 review of the proposed name, Pradaxa, NDA 022512 dated May 10, 2010, DMEPA again found the proposed name, Pradaxa, acceptable. In OSE #2010-957 final review of the proposed proprietary name, Pradaxa, DMEPA also found the name acceptable. However, prior to the final signoff of this review, the Division of Cardiovascular and Renal Products (DCRP) notified DMEPA in an email communication dated September 22, 2010, that they would only be approving the 150 mg strength for this product. This change in product characteristics created a potential for name confusion with the existing product, Prenexa, due to orthographic and phonetic similarities, along with other overlapping product characteristics including single strength availability, oral capsule dosage form and oral route of administration.

In a teleconference dated October 4, 2010 between representatives of the Division of Cardiovascular and Renal Products (DCRP), DMEPA and the Applicant, DMEPA informed the Applicant of the potential for confusion between the proposed name Pradaxa and the currently marketed drug Prenexa and our decision that because of the potential confusion between the two names, DMEPA finds the name unacceptable. DMEPA also provided directives for the Applicant to submit an alternate proposed proprietary name for evaluation by DMEPA.

On October 5, 2010, the Applicant submitted a request for the review of proposed proprietary name, (b) (4) along with proposed contain labels and carton labeling that incorporated the proposed name,

2 METHODS AND MATERIALS

Using Failure Mode and Effects Analysis¹ and the principals of Human Factors, the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the labels and labeling submitted on October 5, 2010, to identify vulnerabilities that could lead to medication errors (see Appendices A through D).

3 CONCLUSION AND RECOMMENDATIONS

Our evaluation of the proposed blister and container labels, carton and insert labeling noted areas of needed improvement in order to minimize the potential for medication errors. We provide recommendations for the insert labeling in Section 3.1 for discussion during the review team's labeling meetings. We request the recommendations for the container labels and carton labeling in Section 3.2 be communicated to the Applicant prior to approval.

Please copy the Division of Medication Error Prevention and Analysis on any communication to the Applicant with regard to this review. If you have further questions or need clarifications on this review, please contact the OSE Regulatory Project Manager, Nina Ton at 301-796-1648.

¹ Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

3.1 COMMENTS TO THE DIVISION

A. Insert Labeling

1. Under *Dosage and Administration* sections in Highlights and Full Prescribing Information, we recommend revising the statement (b) (4) to “Swallow capsule whole. Do not break, chew or empty the contents of the capsules.” to clarify the statement.
2. We recommend revising all instances of the symbol (b) (4) in sections 2.4 *Missed Dose* and 2.5 *Surgery and Intervention* to read “less than” The symbols (b) (4) are dangerous abbreviations that appear on the ISMP List of Error-Prone Abbreviations, Symbols, and Dose Designations¹ because these symbols are often mistaken and used as opposite of intended.

On June 14, 2006, the FDA and ISMP launched a campaign to reduce medication errors related to error prone medical abbreviations and dose designations. As part of that campaign the FDA agreed not to approve labels and labeling that included the use of error prone abbreviations. This abbreviation should be removed throughout all labels and labeling.

B. Medication Guide

1. Under “*How should I take* (b) (4)” section, we recommend revising the statement (b) (4) to “Swallow capsule whole. Do not break, chew or empty the contents of the capsules.” to clarify the statement.
2. Include the storage statement “Once opened, the product must be used within 30 days.” Under the *How do I Store* (b) (4) section.

3.2 COMMENTS TO THE APPLICANT

A. General Comments

Since the product will be available in unit-of-use bottles and must be dispensed to patients in their entirety, ensure that the bottles have child resistant closure.

B. Container Label and Carton Labeling

1. Include the statement “Swallow capsule whole. Do not break, chew or empty the contents of the capsules” on the principal display panel.
2. Increase the prominence of the statement “Once opened, the product must be used within 30 days” as the statement can be overlooked in the current presentation due to lack of sufficient white space on the label. Consider moving this statement up on the side panel, bolding, highlighting, or boxing this statement. Additionally, consider reducing the size of the information on this panel that is not critical (b) (4) to allow more room and increase readability of information that is critical to the proper storage and administration of this product.

4 REFERENCES

Previous OSE Reviews

OSE Review #2010-957 Pradaxa Final Proprietary Name Review (draft pending signoff). Parks, Judy.

OSE Review #2010-957 Pradaxa Proprietary Name Review dated May 10, 2010. Park, Judy

OSE Review #2006-938 Pradaxa Proprietary Name Review dated September 21, 2007. Arnwine, Kristina.

6 PAGES WITHHELD IN FULL IMMEDIATELY AFTER THIS PAGE AS (B)
(4) DRAFT LABELING.

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/s/

CATHY A MILLER
10/14/2010

ZACHARY A OLESZCZUK
10/14/2010

DENISE P TOYER
10/14/2010

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications

****PRE-DECISIONAL AGENCY MEMO****

Date: October 14, 2010

To: Alison Blaus – Regulatory Project Manager
Division of Cardiovascular and Renal Products (DCRP)

From: Emily Baker – Regulatory Review Officer
Zarna Patel – Regulatory Review Officer
Division of Drug Marketing, Advertising, and Communications (DDMAC)

Through: Sheila Ryan – Group Leader
Division of Drug Marketing, Advertising, and Communications (DDMAC)

Subject: **DDMAC draft labeling comments**
NDA 022512 PRADAXA® (dabigatran etexilate) Capsule

DDMAC has reviewed the proposed product labeling (PI) and Medication Guide for PRADAXA (dabigatran etexilate) capsules (Pradaxa), submitted for consult on December 16, 2009.

The following comments are provided in response to the updated proposed PI sent via email on October 8, 2010 by Alison Blaus. If you have any questions about DDMAC's comments, please do not hesitate to contact us.

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/s/

EMILY K BAKER
10/14/2010

ZARNA PATEL
10/14/2010

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES

PUBLIC HEALTH SERVICE

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

CLINICAL INSPECTION SUMMARY

DATE: October 13, 2010

TO: Alison Blaus, Regulatory Project Manager
Aliza Thompson, Clinical Reviewer (Efficacy)
Nhi Beasley, Clinical Reviewer (Safety)
Avi Karkowsky, Team Leader
Division of Cardiovascular and Renal Products/ODE 1

FROM: Sharon K. Gershon, Pharm.D.
Good Clinical Practice Branch 2
Division of Scientific Investigations

THROUGH: Tejashri Purohit-Sheth, MD.
Branch Chief
Good Clinical Practice Branch 2
Division of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections.

NDA: 22-512

APPLICANT: Boehringer-Ingelheim Pharmaceuticals, Inc.

DRUG: Pradaxa (proposed) (dabigatran etexilate mesylate)
110 and 150 mg BID

NME: Yes (in US)

THERAPEUTIC CLASSIFICATION: Priority Review

INDICATIONS: Prevention of stroke and systemic embolism in patients with atrial fibrillation (AF)

SUBMISSION DATE: December 15, 2009 (Initial)
April 19, 2010 (Resubmission)

CONSULTATION REQUEST DATE: January 25, 2010 (original)

DIVISION ACTION GOAL DATE: October 10, 2010

ADVISORY COMMITTEE DATE: September 20, 2010

CLINICAL INSPECTION SUMMARY GOAL DATE: September 23, 2010

PDUFA DATE: October 19, 2010

I. BACKGROUND:

The applicant, Boehringer Ingelheim, submitted this New Drug Application for the use of dabigatran etexilate mesylate in the prevention of stroke and non-CNS systemic embolism in patients with non-valvular atrial fibrillation (AF). Dabigatran etexilate mesylate (Pradaxa®) is an orally available, reversible, direct thrombin inhibitor with a proposed indication for the prevention of stroke and systemic embolism in patients with atrial fibrillation (AF). In support of this indication, the sponsor conducted the RE-LY trial, a large (~18,000 subjects), multicenter, randomized, non-inferiority study of unblinded warfarin administration and blinded administration of two doses of dabigatran (110 mg and 150 mg). RE-LY's primary endpoint was a composite of adjudicated stroke and systemic embolism. Secondary outcome measures included all-cause mortality, incidence of stroke (including hemorrhagic), systemic embolism, pulmonary embolism, acute myocardial infarction and vascular death (including death from bleeding). Additional safety endpoints included major and minor bleeding events, intracerebral hemorrhage, elevations in liver transaminases, bilirubin and hepatic dysfunction.

RE-LY was a large phase III study that enrolled ~ 18,000 subjects at ~ 950 international sites. Subjects with ECG-confirmed atrial fibrillation were randomized to one of three arms: (1) adjusted dose warfarin, (2) dabigatran 110 mg twice daily, or (3) dabigatran 150 mg twice daily. The warfarin arm was open label, but adverse events were adjudicated by reviewers blinded to treatment.

Dabigatran was approved by the EMA (formerly EMEA) in 2008 for the primary prevention of venous thromboembolic events in adults after elective total hip or knee replacement surgery, and is widely used in 28 European countries. Dabigatran is not currently approved for use in the United States.

ORIGINAL SUBMISSION REFUSE TO FILE:

On December 15, 2009, the NDA for dabigatran was filed for a rolling review submission. Following preliminary review of the application, the review division noted a number of transcription and transposition errors in blood transfusion and INR datasets. For example, the data set incorrectly reported that three subjects were transfused with 92 U, 82 U and 62 U, respectively, of a blood product in one day, whereas the CRF reported that these subjects had in fact received 2 U each. Additionally, implausible INR values for subjects were noted when data listings were evaluated. For example, for Subject 1361033, the values for dose and INR appeared to have been transposed for one page, with an INR value > 8 and a dose of ~ 2 mg/week – both highly implausible values. The readily identifiable errors in these datasets led to concerns regarding the overall quality of the datasets, and the Agency issued a refuse to file (RTF) letter to BI on February 12, 2010.

After issuing the RTF letter, FDA met with the sponsor in a face-to-face meeting on February 18, 2010 to discuss these issues with data quality identified during early review of data. The sponsor agreed to perform quality checks on certain key datasets, and shortly thereafter devised a Quality Control (QC) Roadmap plan, which was used to re-assess datasets primarily affecting efficacy and safety results from RE-LY. The applicant described the details of the plan, which included 32 cross checks on CRF pages that might have relevance to the outcome events. In addition, the plan looked for data inconsistencies, verified the accuracy of implausible values (such as INR and warfarin dosages), used sampling checks (re-submitting CRF pages) to evaluate the accuracy of the Optical Character Resolution (OCR) process, and reviewed all SAE narratives (N=4051) for possible unreported outcome events. Serial ECGs for 326 identified subjects were sent to blinded adjudicators for evaluation of a possible silent MI. The entire package underwent a sensitivity analysis and final validation, and the conclusions based on revised datasets were unchanged from those previously reported with respect to safety and efficacy.

A diagram of the applicant's Quality Control Roadmap plan follows.

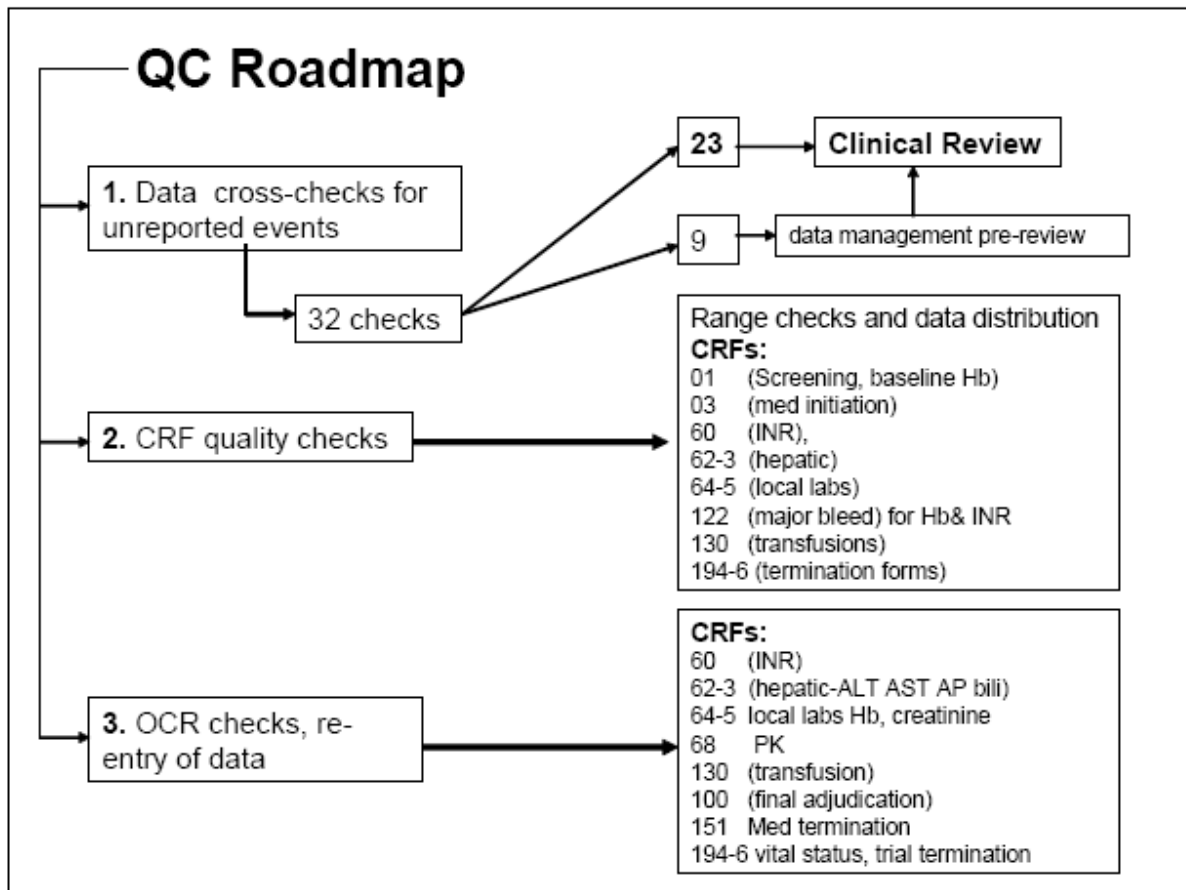


Figure 2.1: Overview of Post-trial QC process of RE-LY

The sponsor re-filed the NDA on April 19, 2010, and met with FDA on April 27, 2010 to discuss the QC Roadmap plan.

In response to the Agency's concerns regarding data quality, BI addressed the specific issues raised by the Agency. With respect to the errors in the INR and blood transfusion datasets, BI noted that these errors in the datasets may have resulted from the use of the optical character resolution (OCR) system (b) (4) whereby the scanned data from the case report forms was inputted incorrectly to the final data set. BI acknowledged that not all data that was submitted via OCR was assessed by the data clerks responsible for verifying the accuracy of the OCR data. Data checks were conducted for key data or datapoints that exceeded pre-specified ranges. (b) (4)

However, these values did not trigger the verification of the data. Per BI, this amounted to a potential error rate of .11%, which the sponsor considered within the pre-specified error rate limits of 0.11.

Additionally, with respect to the blood transfusion errors noted in the datasets, BI stated that the errors in the transfusion data that were documented resulted from the use of a supplementary CRF Page 130, which had been introduced to support an interest of one of the lead investigators, but was not used for the analysis of the main data. The sponsor stated that the units of blood transfused, as recorded on CRF Page 122, were correctly written as 2 units for the 3 subjects referenced earlier, and correctly imputed into the final dataset as 2 units. CRF Page 130 was not used to populate any datasets and was not used for any analyses.

The sponsor did perform the additional quality checks on key datasets that were relevant to the overall quality of the data as outlined in their Quality Control Road Map, and resubmitted revised datasets. The resubmitted datasets, based on review by Drs. Beasley and Thompson, "appear[ed] to match the data contained in the CRFs" and were considered of "sufficient quality to allow substantive review."

A meeting was held between DCRP's Drs. Beasley, Thompson, Ms. Alison Blaus and DSI's Drs. Sharon Gershon, Jean Mulinde and Tejashri Purohit-Sheth on October 5, 2010 to discuss the quality of the resubmitted data. Based on the discussion, it appears that there are no significant concerns from a review division standpoint as to data quality issues with the revised datasets provided in BI's resubmission.

Following resubmission of the revised datasets, DSI was asked to conduct the same PDUFA inspections as previously selected, prior to the RTF letter. A total of 4 foreign and 3 domestic sites were selected using a combination of DSI's Risk Based Model for clinical site selection, and based on sites of particular concern identified by the review division. The primary drivers for site selection were high enrollment numbers and sites where efficacy favored dabigatran (as primary endpoint numbers reached per site were quite small, even a limited number of incorrect assessments on primary endpoint has the potential to significantly impact efficacy analyses and conclusions on approvability for this application).

In addition to the 7 PDUFA clinical investigator inspections, FDA also conducted a sponsor inspection (Boehringer Ingelheim) and a CRO inspection (Population Health Research Institute (PHRI)) to evaluate the sponsor's oversight over the study as well as to evaluate the specific issues that may have led to the quality issues noted in the initial submission of the application. The sponsor and the PHRI inspections were a joint FDA- EMA inspection.

In addition to the above PDUFA related inspections that were conducted, 8 for-cause inspections were conducted of sites that had been closed "for-cause" by the sponsor (allegations of GCP non-compliance). In addition, one site (Pilcher) was inspected for-cause, as a result of a complaint.

The pivotal study was audited during the inspections:

Protocol 1160.26: "Randomized Evaluation of Long Term Anticoagulant Therapy (**RE-LY**) Comparing the Efficacy and Safety of Two Blinded Doses of Dabigatran Etxilate With Open Label Warfarin for the Prevention of Stroke and Systemic Embolism in Patients With Non-Valvular Atrial Fibrillation: Prospective, Multi-Centre, Parallel-Group, Non-Inferiority Trial."

II. RESULTS (by Site):

Type of Inspection	Clinical Investigator/Entity	Inspection Dates	Final Classification
Clinical Investigator – Domestic	Site #376 Vance Eugene Wilson 695 N Clyde Morris Blvd Daytona Beach, FL 32114	July 26 – August 10, 2010	VAI – data acceptable
	Site #32 Michael Ezekowitz 100 Lancaster Avenue Wynnewood, PA19096	July 2 – 7, 2010	NAI – data acceptable
	Site #351 Melvin J. Tonkon, M.D. (Charle Morcos)	03/24-4/15/2010	VAI – data acceptable
	Site #901 Maria Anastasiou-Nana Therapeutic Clinic	July 26 – 30, 2010	Preliminary VAI by field – EIR pending

Type of Inspection	Clinical Investigator/Entity	Inspection Dates	Final Classification
Clinical Investigator – Foreign	80 Vas. Sofia Avenue & Lourou Athens 11528 GR		
	Site #682 Paolo Costi 911 Montee des PionniersTerrebonne Quebec J6V 2H2 CA	August 23 – 27, 2010	Preliminary VAI – EIR pending
	Site #1345 Dirk J.A. Lok Nico Bolkesteinlaan 75 Deventer SE7416 NL	August 9 – 13, 2010	Preliminary VAI – EIR pending
	Site #882 Philippe Igigabel 1 rue des Erables Tierce 49125 FR	August 2 – 5, 2010	Preliminary NAI – EIR pending
Sponsor (joint FDA-EMA)	Boehringer Ingelheim Danbury, CT	August 23-26, 2010	Preliminary VAI - EIR pending
CRO (joint FDA-EMA)	Population Health Research Institute (PHRI) Hamilton Health Sciences/McMaster University Hamilton, ON	August 15 – 19, 2010	Preliminary VAI – EIR pending

Key to Classifications

NAI = No deviation from regulations.

VAI = Deviation(s) from regulations.

OAI = Significant deviations from regulations. Data unreliable.

Pending = Preliminary classification based on information in 483 or preliminary communication with the field;
EIR has not been received from the field and complete review of EIR is pending.**1. Vance Eugene Wilson**

695 N Clyde Morris Blvd Daytona Beach, FL 32114

Rationale for Site Selection: Dr. Vance Eugene Wilson's site was chosen for inspection because his site showed a more favorable efficacy outcome (primary endpoint), as compared to the study as a whole. The Review Division was concerned that although the number of primary endpoint numbers reached per site was quite small, even a limited number of incorrect assessments on primary endpoint had the potential to significantly impact efficacy analyses and conclusions on approvability for this application.

a. What was inspected: At this site, 61 subjects were consented, 4 subjects were considered screen failures for having exclusionary CrCl blood levels, 1 subject declined to participate, and 56 subjects were randomized. The inspection reported that 4 subjects died during this study (#36, 29, 45 and 54). The inspection audited source data (laboratory reports, progress notes, ECGs, INR test results, hospitalization records, concomitant medications, health history records and medical procedures) and corresponding case report forms for 17 subjects. No major data discrepancies were noted for the records reviewed.

The FDA field investigator reviewed the monitoring reports on file, and noted that there were 15 monitor visits to this site. The monitors reviewed adverse events, drug accountability, LFT monitoring, subject eligibility criteria, protocol violation and staff participation. The FDA field investigator reviewed sponsor and IRB correspondence, and drug accountability records as well.

b. General Observations/Commentary: The inspection report noted that the IRB granted approval to the site on October 28, 2005; the first subject was enrolled in December, 2005; and Dr. Wilson attended the Investigator's Meeting (held by BI) on January 14, 2006. The inspection report noted that 13 subjects did not complete the study for the following reasons: death (36, 29, 45 and 54); elevated CrCl (51, 33); thrombocytopenia (46), abdominal pain (05); decided not to continue (21, 8); transferred to different site (40); labile hypertension (43); joint contracture (11).

It was also reported that the sponsor frequently reminded the site about INR monitoring and management of patients on warfarin. Review of documents revealed that on December 2007, the site's % time INR in range was 58.9%, and by June 20, 2008, the cumulative mean % time in INR range was 64.1%. The protocol required that all patients on warfarin undergo INR monitoring at least every 4 weeks, or more frequently, at the discretion of the investigator. As per the review division, the median time in INR range for all submitted INR data was calculated to be 67.1%. All PT/INR testing was performed on site.

Concerning the monitoring of LFT, the inspection observed that some testing was done outside the protocol-allowed windows, but that the site had reported these protocol deviations to the IRB. The reasons for late testing were primarily related to the subjects' availability to come to the clinic for testing.

The inspection reviewed the follow-up testing done on 2 subjects (003, 051) who exhibited out of range LFT values (Alert Status 1), to ensure they followed the guidelines provided to the site. No issues were noted.

The field inspector noted that drug accountability records were well-maintained, and documented key information concerning kit number, dispensing date, quantity of drug returned, tracking and confirmation emails from the IVRS, and a list of all kit numbers allocated to the subjects. The field inspector noted that temperature logs were routinely checked for proper drug storage.

The field investigator issued a one-observational (4 item) FDA-483 for failure to follow the protocol. Specifically, the inspection revealed:

- a) 2 subjects were dispensed the wrong medication kit (Subject 047 on January 30, 2007 and Subject 051 on April 29, 2008). However, in each instance, the site noted the error, brought the subject back to the clinic, and dispensed the correct kit. It was documented that the IRB was notified in each instance.
- b) Subjects 051 and 033 each, had creatinine levels of ≤ 30 ml/min on 2 consecutive occasions, but were not discontinued from the study. Dr. Wilson reported this as an oversight on his part – he did not report this as a protocol deviation.
- c) Subject 043 was reported at screening as having exposure to Hepatitis C, but was randomized into the study on December 4, 2006, prior to the site receiving the viral testing results. Upon receiving the lab results on January 23, 2007, the site notified the sponsor and obtained a waiver for the subject to continue in the study;
- d) Small bleeds reported by Subjects 012, 022, 023, 025, 037, and 033 were not reported on the corresponding CRF. The field inspector observed a Note to File (dated September 21, 2009), which revealed these unreported small bleeds found during the final monitoring visit. The Note stated that the sponsor indicated that no further action was needed, since at that time, the database was locked.

On October 5, 2010, DSI reviewer Sharon Gershon discussed with Dr. Beasley the significance of these small bleeds in terms of safety evaluation, and Dr. Beasley did not consider them relevant to overall safety analyses for this study, as the evaluation of safety was based on major bleeds.

In addition the inspection found that a possible adverse event of hyperglycemia (11.2 and 22.5 mmol/L at Visit 8 and Visit 9, respectively) experienced by Subject 057, was not reported until the subject began participation in the extension study. At that time, the sponsor instructed the site to report diabetes as a baseline condition.

c. **Assessment of data integrity:** Although regulatory violations were noted, these are considered isolated in nature and unlikely to significantly impact the reliability of the data from this site. However, the review division may wish to consider the impact of the 2 subjects who should have been excluded from the study, due to elevated CrCl levels. In general, the study was conducted adequately, and the data generated by this site may be used in support of the respective indication.

2. Michael Ezekowitz, MD

100 Lancaster Avenue Wynnwood, PA19096

Rationale for Site Selection:

(b) (6)

This site also had no reported primary endpoint events.

a. What Was Inspected: A total of 53 subjects were screened, 49 subjects were randomized, and 46 subjects completed the study at this site. The field investigator reviewed subject records for 26 subjects (51% of enrolled subjects) for evidence of underreporting of adverse events, and occurrence of primary efficacy endpoints. The inspection compared source records with CRFs and with the data listings provided from the sponsor. Other records reviewed included monitor/sponsor correspondence, IRB correspondence, test article accountability records and financial disclosure. The inspection reviewed the signed and dated informed consent documents for all 53 subjects.

b. General Observations/Commentary: In general, the study appeared to have been conducted adequately at this site. There was no evidence of under-reporting of adverse events at this site, and no occurrence of primary efficacy endpoints (i.e. stroke or systemic emboli) at this site. The inspection report noted that all SAEs and 2 subject deaths (#0032-007 and #0032-017) were reported in a timely manner to the sponsor and the IRB. No major issues were noted at this site, and no Form FDA-483 was issued to Dr. Ezekowitz.

c. Assessment of Data Integrity: No major data discrepancies were noted at this site. The data appear reliable in support of the NDA.

3. Melvin J. Tonkon/Charle Morcos

Apex Research Institute, Santa Ana, CA

Rationale for Site Selection: This site was selected as part of the PDUFA related inspections as the Risk Based Site Selection model identified this CI as a relatively high risk site based on prior inspection classification of OAI.

a. What was inspected: The RE-LY study was initiated by Melvin J. Tonkon, M.D., who passed away on (b) (6) Nabil Charle Morcos, M.D., Ph.D., received IRB approval to assume responsibility as the principal investigator for this study on August 24, 2006. This was an initial inspection for Dr. Nabil Morcos.

A 100% thorough review was conducted on the subject records for all 6 subjects screened and randomized into the study, including informed consent documents, source records, case report forms comparing the primary efficacy endpoints data and safety endpoints with data listings from the sponsor. All training records, drug accountability logs, and correspondence from the IRB, Sponsor and monitor were reviewed. Review of records revealed that there were no TIAs, strokes, non-CNS systemic embolism events or myocardial infarctions. The site reported one death (Subject 0351001), who was randomized to the dabigatran arm, and who took the last dose on 7/15/2006, and died in (b) (6). This was appropriately documented on the NDA data listings submitted to FDA. The inspection revealed that all bleeding events were reported to the sponsor.

1 page withheld in full immediately after this page as (b)(4)
CCI/TS.

4. Maria Anastasiou-Nana

Therapeutic Clinic, 80 Vas. Sofia Avenue & Lourou Athens 11528 GR

Note: This site inspection has been completed, but the report is not yet available from the field. The basis for this summary is through emails and discussions with the field auditor. An inspection summary addendum will be generated if conclusions change upon receipt and review of the EIR by DSI.

Rationale for Site Selection: Dr. Maria Anastasiou-Nana was a high enrolling foreign clinical investigator site for the RE-LY study. She also enrolled all screened subjects, and had many discontinuations.

In a letter to the Agency dated June 29, 2010, the sponsor indicated that in preparing for the FDA inspection at Dr. Nana's site, the following issues were identified as previously not reported: the site enrolled 145 subjects with 3 outcome events of stroke/SEE (1 dabigatran 110 mg, 0 dabigatran 150 mg, and 2 warfarin), and 5 major bleeding events (1 dabigatran 110 mg, 2 dabigatran 150 mg and 2 warfarin).

DSI requested additional information from the sponsor, with respect to the above findings. In a letter dated June 30, 2010, the sponsor provided the following:

1. the date of the qualifying ECG of Subject 009 was retrospectively changed to make the subject eligible for the study. Specifically, the baseline ECG made during the baseline visit on July 21, 2006, did not show AF; therefore a previous ECG showing AF within the last 6 months was needed to fulfill the inclusion criteria. The site used an ECG showing AF, taken December 15, 2006, blackened out the date (which was still readable) and recorded a date of February 15, 2006, to make this subject eligible to participate in the study.

2. Sub-Investigator (b) (6) authorized colleagues to use his name and signature for study-related activities. By doing this it was not possible to identify the individuals who actually performed an examination or approved a document.

3. Source documents were found to be incomplete or retrospectively completed. CRF entries/changes were not supported by adequate source documentation. For example, for Subject 026, the source data worksheet was not completed until Visit 6, whereas the CRF was completed at Visit 13. For visits 7-13, no source documentation was available for the data documented in the CRF. The sponsor noted similar findings for multiple other subjects.

Additional findings relayed by the sponsor included: several entries/changes in CRFs could not be supported by adequate source documentation (e.g. visit dates, study drug dispensation, date of CRF signature and lab data); some source document worksheets were completed retrospectively; and for some ECG printouts, the printed date of recording was completely blackened and the date of the study visit was added manually.

a. What was inspected: The field investigator reviewed 14 subject records out of 145 enrolled subjects (~ 10%), to include laboratory reports, source documents and CRFs to ensure consistent records, specifically for eligibility criteria, endpoint data and adverse events. Regulatory binders including study approval, screening and enrollment logs, training, financial disclosures, and protocol queries were also reviewed.

b. General observations/commentary: The field inspector revealed that there was adequate hospital documentation/source documentation available to evaluate the data and the adequacy of the data at this site. The field inspector stated that many records reviewed appeared complete, except for those findings listed on the FDA-483. The most pervasive finding was a lack of source documentation for some information and data that was entered directly onto the CRF. At the conclusion of the inspection, a multi-part 3 observational FDA-483 was issued for: 1) failure to maintain accurate and complete records; 2) failure to report all adverse events; and 3) failure to follow the investigational plan. Specific issues identified were the following:

1. there was not adequate source documentation to support information contained in the CRF. Specifically,

a) Source document worksheets did not include specific information asked of patients regarding medical history such as history of fainting, falling or fractures; involvement in motor vehicle accidents as the driver; if patient had a fall within the last year; if the patient ever had a bone fracture, etc. In addition, required Stroke Evaluation and Bleeding Evaluation questions were not included in source documents. Reportedly, the information was documented directly onto the Case Report Forms. As of this report, no information is available to determine how pervasive this finding was.

b) Source document worksheets did not always include information such as Outcome Events, Adverse Events, and Compliance. For example, for Subject 062, there was nothing recorded under Comments for the 6 month visit; for Subject 002, there was nothing recorded under Comments for the 1- month, 3- month, and 6- month visit; for Subject 001, there was nothing recorded under Comments for the 1-month, 3- month, 6- month and 9- month visits. The following examples were provided:

i.) There was no source documentation for Subject 001 for the randomization time of 11:00 AM recorded in the Case Report Form.

ii) Waist and hip measurements were not routinely recorded in the source documentation worksheet for all records reviewed.

iii.) For Subject 002, there was an INR value dated July 7, 2006 documented on the CRF, but there was no supporting laboratory report for this value.

iv..) For Subject 143, there was no source documentation or laboratory reports for INR values recorded on the CRF on March 7, 2008 and March 21, 2008.

2. There was inaccurate information on the Case Report Form. For instance for Subject 001, the medical history indicates the patient previously smoked, whereas the CRF indicates the subject never used tobacco.
3. Dates were not always correct as printed on ECG tracings - incorrect dates were blackened out and new dates were handwritten on the forms.
4. Not all adverse events were reported in the Case Report Forms. For instance, Subject 010 experienced and reported low grade fever and fatigue. This subject experienced elevated liver function tests.
5. Subject 145 was screened prior to obtaining written informed consent.
6. Not all sub investigators who were involved in the study and completed Case Report Forms were appropriately identified, and also lacked documentation of training. For example, Dr. Pantzios lacked appropriate credentials.

c. Assessment of data integrity: Based on preliminary information provided by the field investigator, it is difficult to confirm validity of the data from this site at this point in time. On assessment of preliminary findings from the inspection, it appears that some or all data may not be reliable from this site. As the field inspector is unavailable to answer questions concerning the pervasiveness of the issues identified during the inspection, final recommendations on data reliability cannot be made at this time. Once the EIR is received, DSI will conduct a complete review to determine the reliability of the data from Site #901. In the interim, DSI is unable to confirm validity of the data and recommends that the review division consider excluding the data from this site in their primary evaluation of efficacy and safety.

5. Paolo Costi

911 Montee des PionniersTerrebonne
Quebec J6V 2H2 CA

Note: This inspection has been completed, but the report is not yet available from the field. The basis for this summary is by emails and discussions with the field auditor. An inspection summary addendum will be generated if conclusions change upon receipt and review of the EIR by DSI.

Rational for Site Selection: Dr. Paoli Costi's site was selected for inspection as the site had a greater efficacy outcome (primary endpoint) compared to the study as a whole. Additionally, as this was a foreign site and as the majority of sites for this study were foreign, the review division wanted to ensure that enough representative foreign data was sufficiently audited.

What was inspected: The site screened 41 subjects and enrolled 39 subjects. The following five subject study records were audited during the inspection:

Subject No.	Randomization
006	Warfarin
018	Warfarin
027	150 mg Dabigatran
035	110 mg Dabigatran
036	150 mg Dabigatran

For these five subjects the audit review included a review of source documents (hospital records, study visit records, and local laboratory results); randomization records, test article accountability records and a review of the following data tables: subject eligibility; subject randomization and termination; study medication discontinuations; AE/SAE data; protocol violations; concomitant medications; laboratory values; INR values; stroke reports; hospitalization reports; major bleed reports and minor bleed reports. The FDA inspection confirmed a signed ICD for all 41 screened subjects.

b. General Observations/Commentary:

The field investigator issued a 4 observational, FDA-483 to Dr. Costi for the following violations: (1) failure to follow the protocol; (2) failure to maintain adequate documentation, including case histories and drug accountability reconciliation records; (3) failure to report all adverse events; and (4) failure to have the Ethics Committee/Board perform continuing review annually – sometimes it was done retroactively. Specifically, the findings were as follows:

1) review of source records for adverse events revealed that the principal investigator or sub-investigator, did not always review the assessment of adverse events. One unreported adverse event of diabetes was noted for Subject 006.

2) Review of the INR local laboratory results revealed that not all local INR lab results were reported for Subject 006 (randomized to the warfarin arm). For example the following local INR values were reported on the laboratory report, but not reported to the CRF:

Local Laboratory Date	INR Value
1/23/07	(b) (4)
1/23/07	
1/24/07	
8/16/07	
5/13/08	
5/14/08	
5/15/08	
5/16/08	
5/17/08	
5/18/08	
5/19/08	
5/20/08	

Reviewer Comments: The INR values for 1/23/07 and 1/24/07 are highly implausible values. The inspection did not report that this finding was pervasive with all subjects and appeared limited to only this subject.

3) The field inspector noted that 4 of 5 subjects met eligibility requirements, and that the site used a different method (than what was described by the protocol) for calculating creatinine clearance. The inspection reported that with respect to Subject 006, if the creatinine clearance had been calculated per the protocol instructions the subject would not have met eligibility requirements. The inspection reviewed the creatinine clearance values for all 41 subjects screened, and Subject 006 was the only subject whose eligibility status would have changed, based on the calculation performed.

4) With respect to Subject 006, the field inspector noted a few other minor data discrepancies between source records and the sponsor's data listings. For example, Adverse Event Report 5 had a start-date reported as January 7, 2008, whereas the source records documented the start-date as January 21, 2008. Data listings reported Alkaline Phosphatase with a value of 17, whereas the source records documented a value of 19. The INR value for October 28, 2008 was reported as 2.6 by the sponsor, whereas source records documented it as 2.7; and the date of the INR value of January 14, 2009, should have been reported as January 15, 2009.

5) The field investigator reviewed sponsor and Independent Ethics Committee correspondence, and noted that the site failed to ensure that the study was reviewed at least annually by the local ethics review board. For example, initial approval was granted on May 9, 2006. In a letter dated September 19, 2007 the local ethics review board granted a retroactive approval for the time period of May 9, 2007 until May 9, 2008. In a letter dated June 10, 2008 the local ethics review board granted a retroactive approval for the time period of May 9, 2008 to May 9, 2009. In a June 4, 2009 letter the local ethics review board re-approved the study until May 9, 2010.

6) The FDA field inspector noted that the site failed to return test article to the designated party at the conclusion of the study. The Final Drug accountability and Reconciliation was not performed by the site. For example, the Site Inventory (In/Out) Logs for all test articles (Warfarin 1mg, 3mg, 5mg, and Dabigatran Etexilate) indicates that test article remains at the site. The Inventory (in/out) logs were not reviewed and signed by the investigator or designee responsible for the inventory of medication as required.

7) The FDA inspection noted the site was confused as to when to use CRF Page 140 "Interruption of Anticoagulation Report" and CRF Page 151 "Study Medication Discontinuation/Restart." The sponsor's data table listed information recorded on CRF Page 151, but not CRF Page 140. The inspection reported that 2 events found documented on CRF Page 151 should have been listed on CRF Page 140.

The site stated that they received conflicting information from the monitor on how to report this information. The inspection noted that a company (b) (4), was the initial monitor at the site, and they went out of business in August 2007. The site was left without monitoring between May 2, 2007 and December 11, 2007 (~ approximately 7 months).

c. Assessment of Data Integrity: Although regulatory violations were noted at this site, they are unlikely to importantly impact data reliability. DSI recommends that the above findings pertinent to Subject 006 be taken into consideration in evaluation of safety and efficacy of the product, in support of the NDA.

6. Dirk J.A. Lok

Nico Bolkesteinlaan 75

Deventer SE7416 NL

Note: This inspection has been completed, but the report is not yet available from the field. The basis for this summary is by emails and discussions with the field auditor. An inspection summary addendum will be generated if conclusions change upon receipt and review of the EIR by DSI.

Rationale for Site Selection: The Site Selection tool revealed that Dr. Dirk J.A. Lok was both a high enroller for this study, with a disproportionate number of deaths in the warfarin arm. In addition, this was a foreign site.

a. What Was Inspected: This site enrolled 104 subjects. The inspection corroborated source records with case report forms, and data listings for efficacy and safety endpoints; reviewed inclusion and exclusion criteria; and reviewed test article accountability records in terms of validating that the records were present. The field inspector reviewed the monitoring logs, to ensure the frequency of monitoring at this site.

b. General Observations/Commentary: The site used electronic records, and were reported as fairly complete. The study coordinator was not looking at the complete case file, so missed reporting a few adverse events. The inspection issued a 2-observational FDA-483, noting the following regulatory violations: (1) failure to follow the protocol; and (2) failure to prepare accurate case histories with respect to observations and data pertinent to the investigation. Specifically, the inspection observed that not all adverse events were reported. For example:

Source records documented that Subject 1345 010 experienced eczema during a visit with the cardiologist on [REDACTED] (b) (6), Subject 1345 050 reported flu on February 18, 2007, and Subject 1345 075 reported a nose bleed on November 21, 2007. These 3 events were not reported on the Case Report Form.

The field investigator noted that there was no assurance that all subjects were asked all questions for the Stroke Evaluation and Bleeding Evaluation form (CRF 25) as she found no worksheet or source documents pertaining to these questions or answers. As the protocol required these questions be asked at each visit, the site should have documented the responses in the source records, before transferring the information to the CRF. Instead the site entered the information directly onto the CRF, so there could be no source data verification. According to the field inspector, this observation applied to all subject records. The CRF 25 was designed to collect information from a regularly scheduled, 9-month follow-up visit (1, 3, 6, 9, and 12 months, then every 4 months for duration of trial). The form was used to assess for changes in

neurological and bleeding status since the subject's last visit, up to and including this visit. If the subject reported a stroke or a major or minor bleeding event since the last scheduled visit, a Stroke Report CRF 110 or outcome event CRF 122 or 124 CRF was required to be completed. Therefore, it appears that any, or all outcome events, including stroke and/or bleeding event, would have been captured on the appropriate separate CRF.

The inspection observed the following with respect to failure to maintain accurate case histories:

1) For Subject 1345 021, questions were answered by the wife during a call made to a subject's home on October 30, 2007 for Visit 9 (16 month visit). The protocol required the questions to be asked to the patient exactly as they are written on the Case Report Form.

2) Not all concomitant medications taken during the study were reported on the Case Report Forms. For example, for Subject 1345038, a clinic note on August 20, 2007, documented digoxin QD was stopped, with instructions to restart digoxin as QOD (every other day) on August 23, 2007. The CRF at the following visit did not document a change in the digoxin medication. For Subject 1345 050, research notes document that Cordarone, Atrovent and Spiriva were prescribed on December 10, 2007. These medications were not documented on the Case Report Form.

c. Assessment of Data Integrity: The main issue identified during the inspection, was that there was no source documentation to support information noted on the Stroke and Bleeding CRFs; the site, instead, entered the information directly into the electronic CRF. This CRF was designed to capture information at the 9-month, regularly scheduled visit, and did not contain final outcome stroke and/or bleed events, as this information was captured by additional CRFs. As this observation was related to only CRF 25, and not noted for any of the other CRFs that captured the primary efficacy and safety data, this finding doesn't appear to significantly impact the reliability of the primary efficacy and safety data. The data appears acceptable in support of the NDA.

7. Philippe Igigabel

1 rue des Erables
Tierce 49125 FR

Note: This inspection has been completed, but the report is not available from the field. The basis for this summary is by emails and discussions with the field auditors. An inspection summary addendum will be generated if conclusions change upon receipt and review of the EIR by DSI.

Rationale for Site Selection: The Site Selection tool showed that Dr. Philippe Igigabel's site showed greater efficacy with respect to the primary endpoint, than the study as a whole. This was a foreign site and enrolled all screened subjects.

a. What was Inspected: Site #882 enrolled 30 subjects at 10 smaller satellite sites, listed as 882 A - L. Each sub-site randomized between 1 to 5 subjects, and had its own physician investigator. As per the sponsor, French law required that medical records remain under full

control of the responsible physician, and review of records could only be done at the actual trial site. Therefore, the inspection audited records at Sub sites 882 A, 882 B, and 882 C, as these sites were all located at a same address.

Site No.	PI Name	Number of Subjects
882 A	Philippe Igigabel	5 subjects randomized
882 B	(b) (6)	5 subjects randomized
882 C	(b) (6)	3 subjects randomized

b. General Observations: The inspection reviewed the source records for all subjects at the 3 sub-sites, and corroborated the source records with the CRFs and the data listings. In general, the study appeared to have been conducted adequately. However, there was one isolated violation noted at Sub site 882C. Specifically, there were very minimal source documents for one isolated subject at this sub site. Otherwise, the other data were verifiable, and no significant data discrepancies or regulatory violations were noted. No FDA-483 was issued.

c. Assessment of Data Integrity: Only an isolated regulatory violation was observed at Dr. (b) (6) sub site with respect to one subject, and this finding is unlikely to significantly impact data reliability from this site in general. DSI recommends the data from this site as reliable in support of the indication.

8. Population Health Research Institute (PHRI)

Hamilton Health Sciences/McMaster University
Hamilton, ON

Note: This inspection has been completed, but the report is not available from the field. The basis for this summary is by emails and discussions with the field auditors. An inspection summary addendum will be generated if conclusions change upon receipt and review of the EIR by DSI.

Rationale for Site Selection: This CRO site was chosen for inspection because the site was responsible for data management, and given the initial concerns raised regarding data quality, inspection of this site was deemed necessary for evaluation of the data quality issues.

a. What Was Inspected:

The (b) (4) inspection reviewed the following processes, procedures, and study related activities:

- The history regarding the transfer of sponsor obligations from BI to (b) (4)
- Review of (b) (4) study responsibilities
- Review of the (b) (4) data management system

- A review of the firm's investigation into discrepancies noted regarding INR values
- The IVRS randomization process and procedures
- Adjudication process and procedures
- Training of study adjudicators
- Review of the Data Management Plan
- Review of the Data Safety Monitoring Board
- Review of Data Quality Review Meetings
- Review of study specific SAE reporting and reconciliation procedures
- Review of the use of CRF 194 "Vital Status Report" and the reporting of Death Report CRF's completed by PHRI
- Review of liver function test reporting
- Limited data audit of (b) (4) CRF vs. INR Wafarin data for Site 682 for Subjects 001, 006, 025 and 034.; F/U on Transfusion CRF errors (CRF vs. (b) (4) for Subjects 00855-030; 01337-032; and 01654-034; F/U on INR data error (CRF vs (b) (4) for subject 01361-033; and F/U protocol deviations site 251.

b. General Observations/Commentary:

The RE-LY study was initiated November 28, 2005, the first subject was enrolled December 20, 2005 and the last subject was closed out April 1, 2009 (~ 3.5 years). A Letter of Intent between sponsor Boehringer Ingelheim (BI - Canada) Ltd and Hamilton Health Sciences Corporation (HHSC) through its Population Health Research Institute (PHRI), was signed by BI on April 27th, 2006 and by PHRI on May 1-2, 2006. This Letter covered the organizational structure and conduct of the RE-LY study, and specifically stated, "this is not intended to create legal obligations between the parties. Rather the parties intend to continue negotiations with a view to concluding a definitive agreement relating to the conduct of the Study."

The Letter of Intent distributed the various tasks and responsibilities between the sponsor and the CRO (PHRI), but as explained, was not a legally binding contract between the two parties. Rather, a subsequent contract – entitled "RE-LY Clinical Trials Management and Agency Agreement" was signed by the 2 parties (July 16, 2007 and July 26, 2007) and became effective on July 10, 2007. This contract set out the terms and conditions upon which both parties agreed to "organize and carry on the trial services so as to implement the protocol RE-LY."

Although regulatory violations were noted during the inspection of PHRI, no Form FDA 483 was issued. The reason was because the official contract whereby the sponsor transferred responsibilities to PHRI did not become effective until July 2007. PHRI stated the reason for the delay was due to negotiations on the terms of the agreement. Below are the issues that were discussed with PHRI at the close of the inspection:

1) There were no procedures, plans, or manuals, either written and/or in place prior to performing critical study-related functions, prior to enrollment (December, 2005). Examples of documents not in place were:

a) No data management plan in place until October 2006.

- b) No Data Safety Monitoring Board charter in place until May 2006.
- c) No Data Quality Review Meeting (DQRM) Charter in place prior to DQRM meetings; there was no indication who was responsible for identifying agenda items, for obtaining information, or how meeting minutes would be written and distributed.
- d) Study specific SAE reporting procedures were not finalized until October 2006.
- e) Adjudication manuals were not reviewed and approved before study initiation. There was no version control of the adjudication manual, and no documentation to indicate if significant revisions regarding the adjudication process were communicated to the adjudicators. Quality control was not performed, as per manual instructions. For example, adjudicators were not trained using consistency cases, as described. There were ~37 “unrefuted” deaths and ~12 “unrefuted” outcomes which were adjudicated by only one individual, even though the Manual stated there would be 2 adjudicators per each event. It is also noted that the final scope of work did not detail that the adjudication responsibility would be transferred to PHRI, even though PHRI performed the adjudication.
- f) There was no written procedure describing the SAE reconciliation process. The SAE Reconciliation Manual provided during the inspection was dated April 27, 2010. Two SAE/AE databases were maintained throughout the trial. PHRI maintained the main SAE database, which collected SAE information from the trial centers, and communicated that information to the Data Safety Monitoring Board, and to the sponsor. The sponsor maintained the Drug and Safety database, and reported SAE events to FDA.

The sponsor made information from their database available to PHRI for reconciliation. The inspection reported that as of the final reconciliation on June 15, 2009, there were approximately 110 SAEs in the PHRI database that were not in the BI database. When asked about this discrepancy, PHRI gave explanations such as: discrepant event name, discrepancies with respect to gender, date of birth, and onset dates, making correct matches difficult. PHRI stated that repeated queries were made between PHRI and the sponsor, and these discrepancies appeared to be resolved.

2) Vital status report (CRF 194) was created near study completion and captured text which indicated possible AEs, SAE, or outcome events (other than death); however, these potential outcome events were not extracted into the database. For example, for Subject 1726008, the Vital Status CRF indicated that the subject had an ischemic stroke in the summer of 2008. This event was not captured as an outcome event.

Reviewer Comments: The vital status report was intended to collect death outcomes for subjects who either dropped out or withdrew consent, and was collected by PHRI later in the study. As the QC Roadmap plan reviewed all SAE narratives, it is hoped that any additional outcome events were noted during that review.

3) With respect to the discrepant blood transfusion values, (Subjects 00855 030, 01337 032, and 01654 033), PHRI was not able to state if the errors were due to OCR read or data operator error. The data operator clerks were to tab thru each field on the CRF created by the OCR, to ensure all data was captured correctly. PHRI explained that the errors probably occurred because of the high number of numeric fields, which correlated with a higher propensity for errors to occur. They also stated that the software program did not include reasonable range checks for implausible values. The inspection collected copies of the CRFs for 2 of the 3 subjects with discrepant values.

Reviewer's comments: Per discussions with Drs. Beasley and Thompson, and based on information provided by BI, it appears that data operator clerks did not do 100% checks of OCR data. Data was only checked if they were outside of the range checks for implausible values. At this juncture, it is not completely clear as to why the OCR data errors were not picked up initially; however, the sponsor's re-submitted data appear to have corrected the initially noted errors.

Following the inspection, a Form FDA-483 was not issued to PHRI, especially as many of the responsibilities were not officially transferred to PHRI in writing. The preliminary information provided doesn't allow for the determination of which findings occurred after the final contract was signed in July 2007. However, it is anticipated that the CRO will be held accountable for any deficiencies noted following contract finalization.

c. Assessment of Data Integrity: Although a Form FDA-483 was not issued to this CRO, issues were noted during the inspection, which may have led to some of the data errors noted in the original submission. However, based on the sponsor's re-evaluation and re-submission of the revised datasets, no significant issues with respect to the resubmitted datasets are apparent, and the resubmitted data are considered reliable in support of the resubmission.

9. Boehringer Ingelheim

Danbury, CT

Note: This inspection has been completed, but the report is not yet available from the field. An inspection summary addendum will be generated if conclusions change after receipt and review of the EIR by DSI.

a. What Was Inspected: The inspection included review of written agreements for the transfer of obligations to CROs, clinical investigator selection/training, monitor training/qualifications, monitoring procedures and visit reports, adjudication, data management, quality assurance audits, correspondence with clinical sites and CROs, test article packaging/labeling/accountability, data safety monitoring, adverse event reporting, the adjudication process, and the process for SAE reconciliation. The inspection also included review of the quality control roadmap process with respect to data inconsistencies and the OCR process.

The FDA field inspectors also reviewed monitoring reports for 6 clinical sites that were inspected: Paolo Costi, D.J.A. Lok, Philippe Igigabel, Vance Eugene Wilson, Michael Ezekowitz, and Patrick Simpson.

b. General Observations: At the conclusion of the inspection, a 3 observational FDA-483 was issued to the sponsor for the following violations:

1) transfer of obligations to a contract research organization was not described in writing. The dates of the RE-LY Trial were from ~ November 2005 through March 15, 2009, and the first subject was enrolled at Site 1332 on November 30, 2005. According to the Letter of Intent, PHRI had study responsibilities that included set up of randomization systems for all sites, review of data queries and editing, coding of adverse events, validation of database and data reporting programs, storage of CRFs and study documentation, and many other supporting functions that included overall data management for the study.

2) failure to ensure proper monitoring of the study and ensure the study is conducted in accordance with the protocol and/or investigational plan. Specifically:

(a) According to SOP 001-MCS-40-109 effective October 1, 2004 entitled “Development of Trial Monitoring Manual” Section 4.1 “the final Trial Monitoring Manual needs to be completed and approved prior to initiation of the clinical trial.” Boehringer Ingelheim failed to have a RE-LY Trial Monitoring Manual prior to the start of the Trial. Site 1332 in the Netherlands was the first site initiated for the RE-LY Trial. A trial initiation visit was performed at this site on November 28, 2005 by a CRA and CML (clinical monitor lead).

The following unapproved versions of the RE-LY Trial Monitoring Manual were available for initial training of CRAs and CMSs (clinical monitors): Draft Core Version 3/November 2005; Core Version 1/January 6, 2006; Core Version 1.0/March 20, 2006. On March 28, 2007, the first approved RE-LY Trial Monitoring Manual Core Version 2.0/March 9, 2007 was made available. This document contains additional specifics for Source Document Verification and Clarification of Case Report Forms Questions/Pages not included in previous versions.

(b) (4)



(c) Adjudication Committee: According to the RE-LY Protocol Final Version dated September 12, 2005, Section 6.1 Study Organization “Independent Event Adjudication

Committee(s) will be established for the blinded adjudication of primary and secondary outcome events and major bleeding, bleeds requiring discontinuation, hospitalization or physician intervention. An Adjudication Committee Charter, under which the principles of the PROBE design can be carried out, will govern their activities.” Based on RE-LY Central Adjudication Committee January 2007 Meeting Minutes, training of Adjudicators was to consist of “review of the Adjudication Manual and Guiding Principles and then completing a series of adjudication test cases.”

There is no documentation that an approved Adjudication Committee Charter was established prior to the first adjudicated cases reviewed in December 2006. An approved Draft Version 3/April 24, 2007 of the RE-LY Adjudication Manual and Version 3/September 14, 2007 Appendix X Adjudication Guiding Principles was used for training.

3) Failure to assure that foreign clinical research was conducted in accordance with the ethical principles stated in the “Declaration of Helsinki” and the laws and regulations of the country in which the research was conducted. Specifically, around February 2009, clinical sites in the Netherlands began to collect vital status information from subjects who had withdrawn consent to continue participation in the study. Reportedly, a total of 31 subjects from 13 clinical sites in the Netherlands who had participated in the RELY clinical trial withdrew consent during the course of the clinical trial, for whom vital status follow-up information was obtained. There is no documentation to show that approval (from Ethics Committee) was given to request this information from subjects who had withdrawn consent.

c. Assessment of Data Integrity: The inspection of the sponsor confirmed the finding that no signed contract was in place between the sponsor and PHRI until July 2007, mid-way through the study. Most study-related responsibilities pertaining to data management, including adjudication of outcome events, were delegated to PHRI. The sponsor provided generic versions of many study related documents during the inspection, which were not specific to the RE-LY study. Many study related documents were not finalized until after the study began. The review of monitoring files for six sites confirmed that monitoring was adequate.

The field inspectors discussed the OCR (b) (4) issue during the inspection, and the sponsor provided evidence that they had conducted several audits of PHRI, throughout the study period. However, as the validation of the OCR and (b) (4) process was performed at PHRI, though an independent contractor, it appeared that the sponsor had little direct oversight of the OCR process itself, as this responsibility was held primarily at PHRI. The sponsor made available a copy of their data management plan, but it was difficult to say if the sponsor had any oversight of the validation or OCR process, other than maintaining a copy of the data management (DM) plan.

The issues identified above, appear to have played a role in the data quality issues that were raised initially in the original submission. However, based on the sponsor’s re-evaluation and re-submission of the revised datasets, no significant issues with respect to the resubmitted datasets are apparent, and the resubmitted data are considered reliable in support of the resubmission.

FOR CAUSE INSPECTIONS/SPONSOR SITE CLOSURES:

In addition to the PDUFA related inspections, DSI had conducted 9 additional For-Cause related CI inspections at various time points between 2007 and 2010 with respect to the RE-LY study. Of these, 8 CI sites were inspected based on sponsor notification of site closure due to Good Clinical Practice noncompliance and 1 as a result of a complaint. Of the 9 sites that were inspected as For-Cause, significant issues were noted at 2 of the 9 inspected sites: (b) (4)

Based on the inspection results from the 9 sites, DSI recommends that the data not be used from (b) (4) sites in support of the application. A tabular summary of the previously conducted For-Cause related inspections follows.

RESULTS: For-Cause Inspections

	Principal Investigator	Site No.	Subjects enrolled	Dates of Inspection	Final Classification
Sponsor Site Closures	Terry Arnold	108	31	07/07-22/09	VAI
	Raymond Carlson	128	6	07/29-31/08	VAI
	Michael DiGiovanna	146	4	09/30/ – 10/07/09	NAI
	Lillian Harstine	354	7	11/10/08 – 01/21/09	VAI
	Ellis Lader	251	52		VAI
	(b) (4)	265	(b) (4)		
		354			
	Patrick Simpson	006	24	03/17 – 04/30/10	VAI
For-Cause (Complaint)	George Pilcher	Site 232	44	12/10-18/07	VAI

IV. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

For this NDA, 3 domestic and 4 foreign clinical site inspections were conducted, in addition to a sponsor and CRO inspection. In general, the clinical sites were chosen for inspection due to relatively high enrollment and greater efficacy favoring the dabigatran arm. The sponsor (Boehringer Ingelheim) and CRO inspections (Population Health Research Institute (PHRI)) were conducted to evaluate the sponsor's oversight of the study as well as to evaluate the specific issues that may have led to the data quality issues noted in the initial NDA submission.

With respect to the 3 PDUFA domestic site inspections, minor regulatory violations were noted at 2 sites (Wilson and Tonkon), and no regulatory violations were noted at the other site

(Ezekowitz). For these sites, the data appear reliable in support of the respective indication.

With respect to the 4 PDUFA foreign site inspections, the regulatory violations noted at 3 sites (Costi, Lok and Igigabel), are considered isolated in nature and unlikely to significantly impact data reliability. A preliminary review of findings from the inspection of the 4th foreign site, Dr. Maria Anastasiou- Nana's site, has raised some concerns as to data reliability from this site. Preliminary information provided by the field investigator noted several issues concerning lack of source documentation to support data entered onto the CRF. The preliminary information provided is not sufficient to allow for an assessment as to the pervasiveness of the specific findings noted. As such, at this time, data reliability cannot be confirmed from Dr. Nana's site.

With respect to inspections of the sponsor and CRO, although regulatory violations were noted, the resubmitted data appear reliable. In general, inspectional findings from the sponsor inspection noted that the sponsor did not implement comprehensive quality assurance systems to ensure the quality of the data prior to initial submission of the application. The most notable finding from the inspection at PHRI was lack of written procedures and manuals for key aspects of the study such as monitoring, data management, and adjudication. Additionally, the contract which delegated many study functions to PHRI was not signed until almost 2 years into the study. Likewise, the key issue noted during the sponsor inspection was the lack of a signed contract at the beginning of the study (2005), delegating duties and responsibilities to PHRI. Although the issues noted at the sponsor and CRO inspection may have led to the data quality concerns identified in the original NDA submission, the resubmitted revised data appears reliable in support of the application.

Additionally, 9 For-Cause inspections of the RE-LY study were conducted between 2007-2010, to include 1) 8 inspections that were conducted due to site closure by the sponsor for GCP non-compliance issues and 2) 1 inspection that was conducted as a result of a complaint. Of these 9 For-Cause inspections, DSI recommends that the data from (b) (4) not be used in support of the application. With respect to the remaining 7 For-Cause clinical investigator inspections, although violations may have been noted at these sites, the violations are not likely to significantly impact data reliability.

In conclusion, although quality assurance issues were evident at both the sponsor and PHRI inspections, the overall reliability and credibility of the data seems sufficient to recommend that the data be used in support of the indication for this NDA, with the exception of the data from Dr. Nana's site and the data from two previously conducted For-Cause inspections (b) (4).

NOTE: The EIR (Establishment Inspection Reports) from inspections at the 4 foreign clinical sites (Sites 901, 682, 1345, 882), the sponsor's (Boehringer Ingelheim) site, and the CRO's (PHRI) site have not yet been received or reviewed by DSI. Observations noted above are based on the Form FDA 483 and/or communications with the field investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the EIR.

{See appended electronic signature page}

Sharon K. Gershon, PharmD
Good Clinical Practice Branch II
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CONCURRENCE:

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/s/

SHARON K GERSHON
10/13/2010

TEJASHRI S PUROHIT-SHETH
10/13/2010

Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF SURVEILLANCE AND EPIDEMIOLOGY

DATE: 31 August 2010

FROM: John R. Senior, M.D., Associate Director for Science, Office of Surveillance and Epidemiology (OSE)

TO: Norman Stockbridge, M.D., Director, Division of Cardio-Renal Products (DCRP), Office of New Drugs (OND)
Bach Nhi Beasley, M.D., Medical Reviewer (Safety), DCRP

VIA: Gerald Dal Pan, M.D., Director, OSE

SUBJECT: Supplementary report on hepatic effects of dabigatran etexilate (PRADAXA®, Boehringer Ingelheim), NDA 22-512, resubmitted 19 April 2010 for priority review: post-marketing cases; follow-up to consultation of 30 July 2010

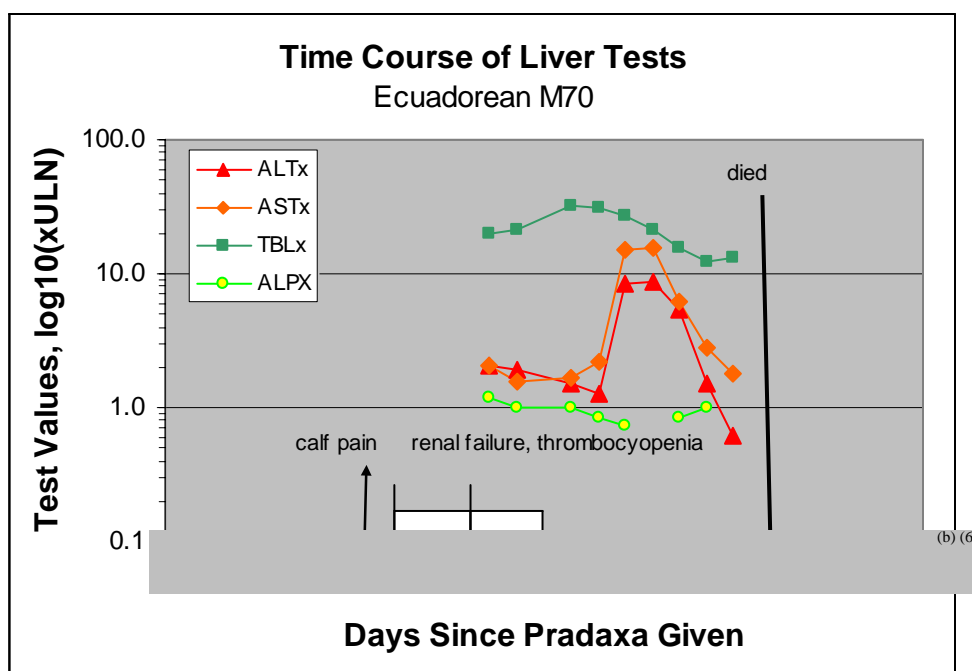
Documents reviewed:

- 1) CIOMS reports and hospital records for 3 cases
 - 2) Additional medical literature articles on dabigatran and melagatran
-

The supplemental request dated 27 August from the review division asked us to consider a few cases reported from countries where dabigatran has been approved as an anticoagulant for preventing thromboemboli following knee-replacement surgery. These cases reviews supplement the more structured review of the RE-LY controlled trial data on 18,113 patients randomized to warfarin or to dabigatran 100 mg or 150 mg b.i.d. submitted 30 July in response to the request of 26 April 2010 (OSE # 2010-894). The cases for review were selected from the Hepatic Safety Response submitted by the sponsor on 15 July as amendment #0115 to NDA 22-512.

Case 2009-RA-00265RA: A 70-year-old Ecuadorean man with a history of hypertension for 8 years was treated briefly with Pradaxa 110 mg b.i.d., from 21 to 23 July 2009 for painful right calf thrombophlebitis diagnosed by ultrasound at a private clinic in the small town of Ibarra, Ecuador. Because he developed mild abdominal pain and diarrhea on 22 July, the physician stopped the dabigatran on (b) (6) and started the patient on Coumadin (warfarin) 5 mg daily. The abdominal pain and diarrhea disappeared on (b) (6), but he had malaise and was deeply icteric, and was admitted at the clinic for treatment with intravenous fluids, where he was found to have prothrombin time of 28.8 second (normal 11-14), INR 2.57 and warfarin was stopped because of "Coumadin intoxication." He had leukocytosis of 15,800 (90% neutrophils), and platelets of 15,000, oral hematoma, epigastric and right upper abdominal tenderness, and renal insufficiency (serum creatinine 5.9 mg/dL; urea 252 mg/dL). He was transferred to the intensive care unit of the hospital in Ibarra on (b) (6), where renal insufficiency was confirmed by serum creatinine 10.9 mg/dL, urea 359 mg/dL but only slight elevations of serum alanine and aspartate aminotransferase were found. He was thought to have acute liver failure, hepatorenal syndrome,

thrombocytopenia, and possible sepsis from an unknown source. He did not respond to treatment, developed hypotension with further rise in ALT and AST, acidosis and multiorgan failure, and died on (b) (6). The records are difficult to sort out, despite the translation provided by the Clinical Safety Officer for Boehringer Ingelheim, Dr. Luis Ernesto Roza M. The copies of the original records in Spanish have numerous illegible entries. The case was reported to the sponsor on 14 October 2009, not on 11 June 2010 and submitted 24 June as claimed in the CIOMS report.

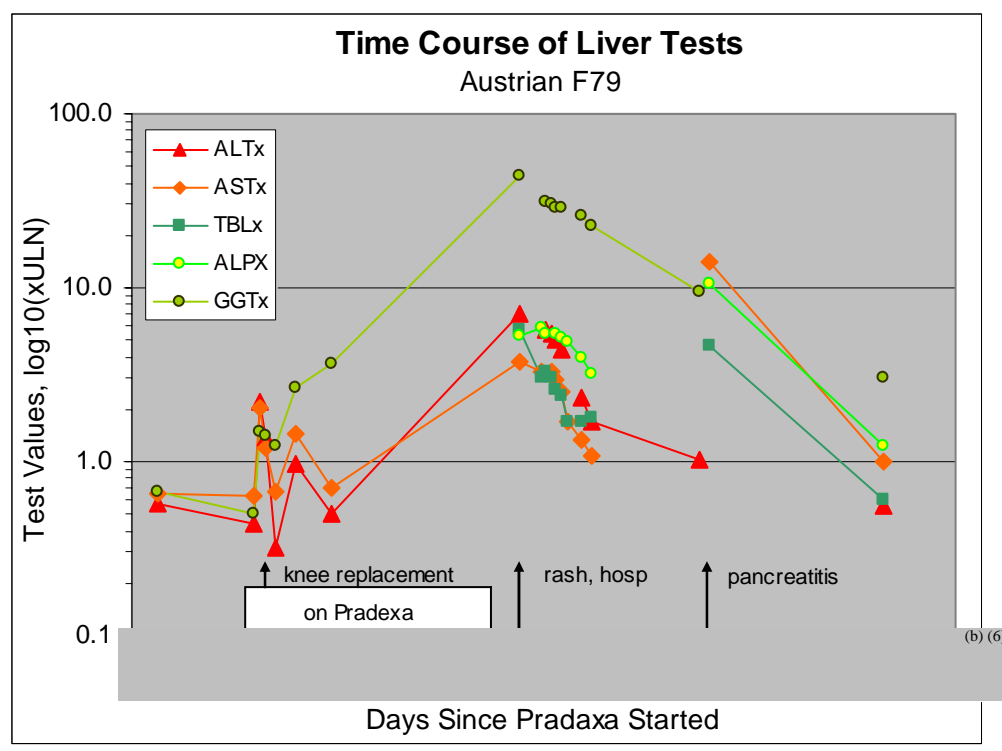


Comment: It does not appear that the treating physicians had found the true cause of this man's disastrous illness and fatal outcome. Hepatocellular injury as a probable cause of liver failure is questionable, although he was deeply jaundiced at the outset, but with little evidence of acute liver injury initially, only worsening after hypotension and acidosis had occurred. Sepsis of biliary tract origin with disseminated intravascular coagulation syndrome was suspected but not proved. It seems unlikely that a few doses (perhaps 4 to 6 of dabigatran 110 mg during the two-day period 21-23 July would have caused this degree of jaundice and thrombocytopenia, nor is it likely that two doses of 5 mg of Coumadin on July 23 and 24 could be held to have caused "Coumadin intoxication." The role of acetaminophen is unclear. He was said to have been taking 1 g every 6 hours, but it was not known really how much he took. If he had sepsis, it was neither found nor effectively treated. The most likely cause for this fatal sequence of events is uncertain, and is not revealed by the source documents obtained, but is unlikely to have been caused by either dabigatran or warfarin. No autopsy was performed.

Case 2010-AP00222AP: This patient is an obese, diabetic Austrian woman 79 years of age who was evaluated in Vienna in January 2010 for her second knee replacement for osteoarthritic knee pain and disability. She had a history of mild-to-moderate congestive failure, right bundle branch block, hypertension, cholecystectomy, hyperuricemia, and reduced pulmonary function, and had

been on a long list of 33 medications in addition to dabigatran even before 5 more for anesthesia on (b) (6), the day of her surgical procedure for the left knee replacement. She was started on dabigatran 75 mg b.i.d. on 23 and 24 January, none on 25 January, 75 mg once on the day of surgery, then b.i.d. until it was stopped 9 March, about 6 days after it had been planned.

On (b) (6) she reported a whole-body skin rash, with itching and jaundice, and was admitted to hospital in Vienna the next day for evaluation. Elevated serum enzyme activities were found, and serum bilirubin was 6.9 mg/dL, confirming the obvious jaundice of her skin, and a peak level of alanine aminotransferase (ALT) of 7 times the upper limit of the normal reference range (xULN) was found. However, there had been slight elevations of ALT immediately after the surgical procedure that fell back into the normal range, as had aspartate aminotransferase (AST) activities. The first sustained and progressive elevation was that of gamma-glutamyltransferase (GGT) that went to almost 44 xULN on 18 March, accompanied by serum alkaline phosphatase (ALP) levels of 5 to 6 xULN, and she was treated with 24 other drugs over the ensuing five-six weeks, only to sustain an attack of acute abdominal pain associated with a sharp rise in serum lipase attributed to acute pancreatitis, all of which finally subsided about (b) (6) months after her surgery.



Comment: This reaction was predominantly cholestatic and of moderate severity, with an ALTx/ALPx ratio of only 1.3 on 18 March, and even lower afterward, evidence for a mainly cholestatic liver injury that appeared to be very possibly caused by dabigatran, even considering all of the other medications she was taking. No other cause was found that was probable or very likely, and we are left to conclude it was possibly caused by dabigatran. Her principal symptom was pruritus, and the main physical findings were rash and jaundice, but there was no evidence of liver failure or serious hepatocellular dysfunction.

Case 2010-CN-00363CN: A Canadian man of unstated age was reported to have been treated with dabigatran 150 mg b.i.d. for prophylaxis of thromboembolism from atrial fibrillation (not approved for that use). After 12 weeks he was reported to have “liver disorder and liver function test abnormalities that satisfied Hy’s Law criteria,” but no detailed information was provided. Liver biopsy was said to be not diagnostic. No data were reported for laboratory test results, and the patient is said to have recovered. The local physician concluded that the effects noted were related to dabigatran and not to other possible causes. Further information was said to be requested but has not been obtained or reported.

Case 2009-UK-00975UK: A 65-year-old man in the United Kingdom died of gastrointestinal bleeding, with coagulopathy and “liver function test abnormal” following (b) (6) days of dabigatran treatment for atrial fibrillation (?off-label). No data on laboratory values were reported, but the reported concluded the death was not related to abnormal liver function tests.

Comment: These two cases are mentioned but cannot be discussed because of obviously lacking information. We are left to accept the treating physicians’ word and opinion as to the cause of the abnormalities reported, with no opportunity to assess the causality based on data. This is a most unsatisfactory state of affairs, especially in view of the concerns about ximelagatran-induced hepatic injuries that led to the non-approval of that drug in 2004 and the similarity of dabigatran to it. It may be unlikely that dabigatran has caused these cases of interest concerning possible hepatotoxicity, but we need to have information gathered and reported promptly and fully in order to reach an independent conclusion as to causality. Experience has shown that drug-induced liver injury is usually quite rare, and that hepatic test and functional abnormalities are more likely to be caused by other processes of disease, infection, other drugs or chemicals, and it is important to find out the probable cause, some of which may be treatable. If another cause is found, and treated if amenable (such removing gallstones, treating heart failure, etc.) then it may be reasonable to resume treatment with dabigatran without undue risk of harm. It is in the interest of the sponsor, not to mention of the patient and treating physician, to investigate cases of potentially serious liver injury, find the probable cause, treat it to resolution, and report the cases fully and promptly.

Determination of the probable, very likely, or definite cause of liver dysfunction to have been caused by a drug is highly dependent upon the clinical information available to rule in or rule out other causes. No pathognomonic tests or findings exist to prove a diagnosis of drug-induced liver injury, which may mimic any known liver disease both clinically and histologically. The diagnosis can only be made by exclusion, and the easiest course is to find some other cause, which is actually more likely. The finding of elevated ALT and TBL levels is not a diagnosis, nor even enough to satisfy the criteria for Hy’s Law, but requires that other possible causes be ruled out (see guidance of July 2009). Although the guidance was written to apply to pre-marketing clinical studies, many of the concepts expressed are pertinent also to investigating cases that occur after approval. Sponsors are urged to encourage both their investigators and treating physicians to investigate possible causes of liver dysfunction (serum enzyme elevations are NOT measures of liver dysfunction, and only indicate injuries), to find the probable cause and treat it if it is amenable, and thus exonerate the drug as the likely cause.

These considerations are pertinent to the post-marketing situation, if dabigatran is approved for preventing strokes and thromboembolic events in patients with chronic atrial

fibrillation, who are also likely to have underlying heart diseases and other clinical problems that may cause liver dysfunction.

Recommendations:

- 1) The findings from these cases do not suggest that dabigatran is likely to cause serious liver injury, but neither do they rule it out. Only experience in the clinical use of a new drug can shed light on the difficult questions of how severe the liver injury may be and how likely it is to have been caused by it, an evaluation that is highly dependent on the amount and quality of the information reported.
- 2) It is not sufficient to rely on the various opinions of treating physicians regarding likely causality, which vary widely depending on their training and knowledge. It is necessary to obtain clinical information to support those views, report it fully and promptly, to allow independent assessment of the data.
- 3) The sponsor is strongly urged to discuss this matter thoroughly with the review division and OSE, if dabigatran is approved for long-term prevention of thromboembolism in patients with atrial fibrillation or other indications. The issue of better investigation and reporting of cases of possible dabigatran-induced liver injury and dysfunction may be addressed in labeling discussions.

John R. Senior, M.D.

cc: OSE 2010-894suppl
N. Stockbridge, DCRP
S. Grant, DCRP
BN Beasley, DCRP
L Seeff, OSE

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

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/s/

JOHN R SENIOR

09/08/2010

also linked to consultation request of 4/26

Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF SURVEILLANCE AND EPIDEMIOLOGY

DATE: 30 July 2010

FROM: John R. Senior, M.D., Associate Director for Science, Office of Surveillance and Epidemiology (OSE)

TO: Norman Stockbridge, M.D., Director, Division of Cardio-Renal Products (DCRP), Office of New Drugs (OND)
Bach Nhi Beasley, M.D., Medical Reviewer (Safety), DCRP

VIA: Gerald Dal Pan, M.D., Director, OSE

SUBJECT: Hepatic effects of dabigatran etexilate (PRADAXA®, Boehringer Ingelheim), NDA 22-512, resubmitted 19 April 2010 for priority review

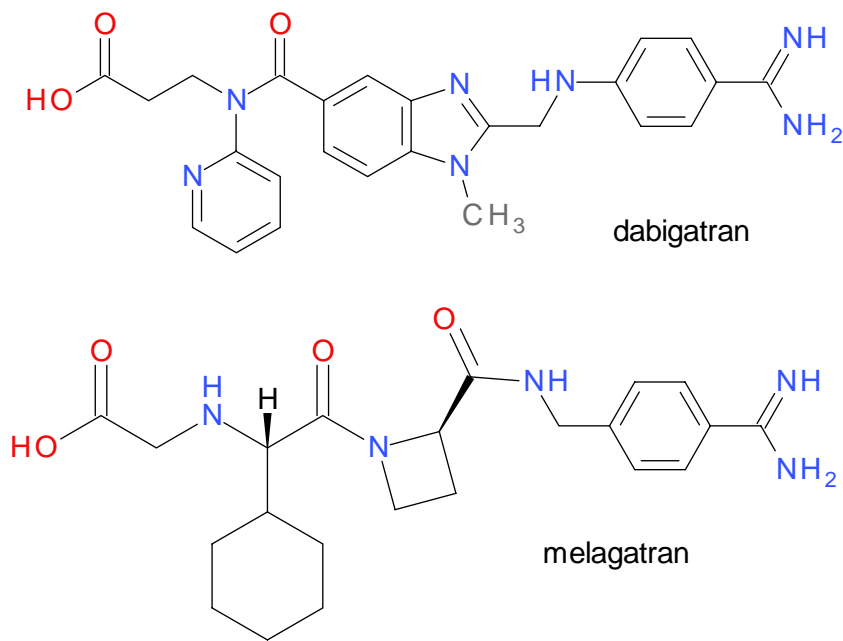
Documents reviewed:

- 1) Consultation request dated 26 April 2010, with desired completion date 30 July, assigned OSE #2010-894.
 - 2) Selected medical literature articles on dabigatran and melagatran
 - 3) Submitted data on 18,110 patients with chronic atrial fibrillation in 44 countries randomized to oral dabigatran 110 or 150 mg b.i.d. or warfarin in RE-LY study.
-

The request from the review division asked us to consider carefully the data gathered during the very large worldwide clinical trials carried out among patients with chronic atrial fibrillation who were at risk for thromboembolic strokes and other complications of their disease, comparing oral dosing with open-label dabigatran etexilate 110 mg or 150 mg b.i.d. or warfarin for two years in a study called RE-LY (randomized evaluation of long-term anticoagulation therapy) to assess prevention of stroke or systemic embolism. Because of previous hepatotoxicity attributed to a similar compound, ximelagatran, the consultation request asked for focus especially on liver effects of the dabigatran.

Dabigatran was developed as a non-peptide direct thrombin inhibitor, BIBR 953 (Hauel et al., 2002), a very polar compound that had the most favorable activity profile as an anticoagulant in vivo. To make the compound more readily absorbed after oral administration, a derivative with much greater lipophilicity, BIBR 1048, was made by conjugating it with an etexilate moiety, really a double pro-drug. By 1999 the latter compound was in phase II trials, and by April 2002 proof-of-principle had been demonstrated for prevention of thromboembolism and stroke due to atrial fibrillation (Mungall, 2002). Almost concurrently, another oral direct thrombin inhibitor had been developed by AstraZeneca, melagatran, with two protecting groups conjugated to it as ximelagatran H 376/55 (Gustafsson et al., 2001) to improve its gastrointestinal absorption, which were then removed in the circulation after absorption. Melagatran and dabigatran are eliminated mainly in the urine (Gustafsson, 2003).

The similarity in structure of the two active “-gatrans” is evident:



The blocking moieties at both ends of these molecules that make them more lipophilic and better absorbed across the intestinal membranes differ, but those are removed in the plasma after the prodrugs are absorbed.

Ximelagatran (EXANTA®, AstraZeneca) was more quickly developed, and its NDA 21-686 was submitted 23 December 2003, requesting approval for use of 24 and 36 mg tablets for preventing venous thromboembolism in patients undergoing knee replacement surgery and for prevention of stroke and other thromboembolic complications associated with atrial fibrillation. After review of the data, especially the longer-term effects in the atrial fibrillation studies, concern was raised about hepatotoxicity. A clearly increased incidence of elevated serum aminotransferase activities was seen in patients receiving ximelagatran compared to those on Coumadin (warfarin), and also a marked increase in those showing both elevated alanine aminotransferase (ALT) activity more than three times the upper limit of the normal range (3xULN) and serum total bilirubin (TBL) of >2xULN, thus raising concern about potential “Hy’s Law” cases (Temple, 2000). In addition there were three very serious cases, one fatal, that were very likely induced by ximelagatran. It was argued by the sponsor that these unexpected liver problems might be handled by monitoring patients for serum aminotransferase elevations after the drug was started, but the CardioRenal Advisory Committee convened in September 2004 voted 12-0 against recommending approval, and a not-approvable letter was sent 8 October 2004. A dissenting opinion was later published by consultants to the sponsor (Lee et al., 2005). The sponsor contested the decision and did not withdraw NDA 21-686 until January 2007 but began extensive investigations to seek a possible explanation for the idiosyncratic susceptibility of some patients to long-term ximelagatran exposure, concluding that a finding of an allele HLA DRB1*0701 was associated with tendency to show hepatocellular injury (Cederbrant, 2009).

Mindful of this experience, Boehringer Ingelheim proceeded a bit more slowly (Ezekowitz, 2004) and amassed the huge total of 18,113 patients with chronic atrial fibrillation enrolled in the RE-LY clinical trial worldwide (Connolly et al., 2009). The protocol for the study advised investigators to pay particular focus to monitoring liver function and symptoms. Monthly testing for injury was used to find elevated serum enzyme activities of alanine or aspartate aminotransferase (ALT or AST) or alkaline phosphatase (ALP) $>2\times\text{ULN}$, calling for weekly test repeats until all values $<2\times\text{ULN}$; if $>3\times\text{ULN}$ or serum total bilirubin concentration $>2\times\text{ULN}$ but patients with Gilbert syndrome $4\times\text{ULN}$; repeat test weekly until all $<2\times\text{ULN}$. If ALT or AST $>5\times\text{ULN}$ or $>3\times\text{ULN}$ with TBL $>2\times\text{ULN}$ (Gilbert's $>4\times\text{ULN}$) study drug was to be stopped and sponsor notified. Further details of what should be done were specified in the protocol for study 1160.26. Of note, patients were to be evaluated for the cause of the abnormal findings to rule out disease, by reviewing history of the concomitant medications, alcohol use, disease history, ultrasound scan of the biliary tract, and by further lab analyses. A separate manual outlined details. Consequently, patients were enrolled in 44 countries, totaling 18,110 for whom serial liver tests were available (6,014 on D110; 6,075 on D150; and 6,021 on warfarin).

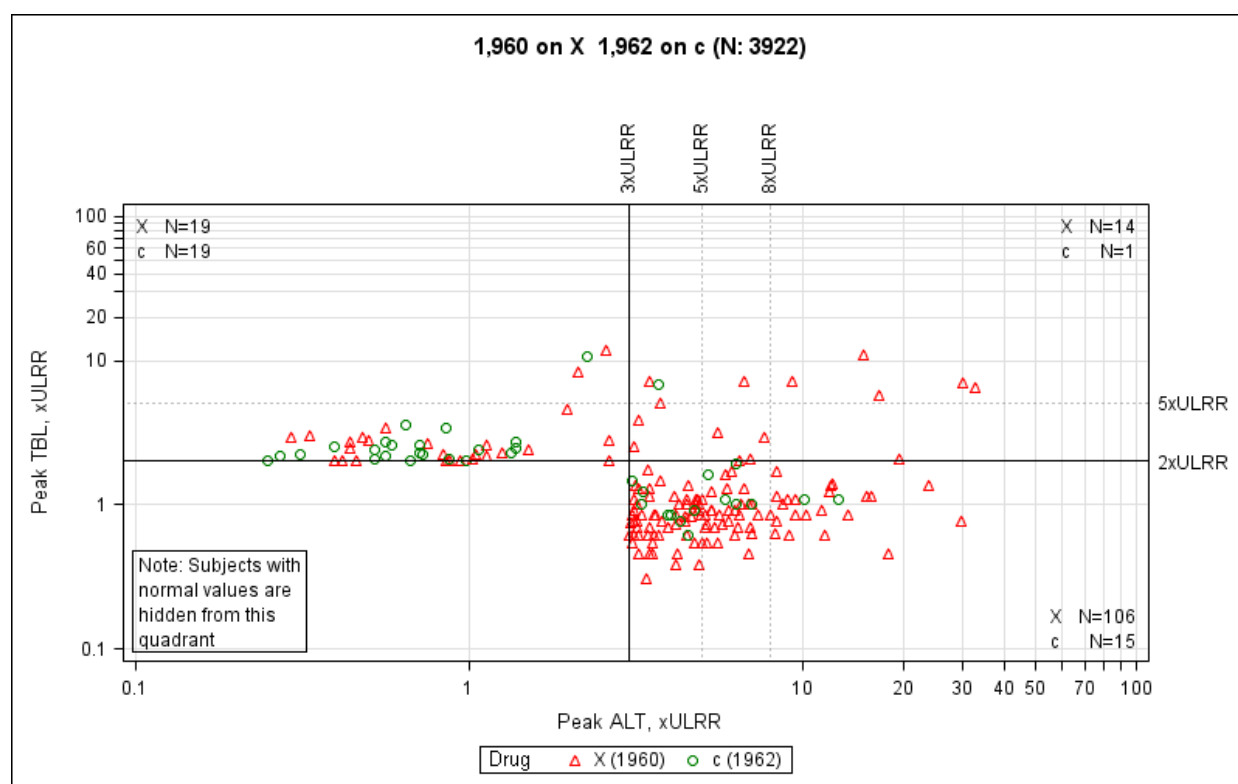
The initial submission of the application for NDA 22-512 was made on 15 December 2009, and the review division (Cardiovascular & Renal Products, DCRP) had granted priority and rolling review for the application, but preliminary inspection of the data in January 2010 disclosed discrepancies, and the application was refused for filing. The sponsor was notified 12 February 2010 of the decision and what would be required to correct it. Resubmission of the NDA 22-512 was made on 19 April 2010.

Because the application for dabigatran exetilate for the same indication of preventing stroke and systemic thromboembolic events in patients with chronic atrial fibrillation was so similar to the not-approved submission for ximelagatran in 2004, and the drugs and mechanisms of action so similar, comparisons of delayed hepatotoxicity from dabigatran were highly important. To start this process, we used a research review system, eDISH, that was developed under the CDER Regulatory Science Review (RSR) enhancement program after the ximelagatran experience, to consider in close detail *individual cases* of special interest for possibly serious hepatotoxicity selected out of the huge number of patients studied in the trials carried out for dabigatran at over 650 sites in 44 countries around the world. For comparison, we looked at the clinical trial called SPORTIF V of ximelagatran versus Coumadin conducted in the United States and Canada as a double-blind study in 3922 patients with chronic atrial fibrillation randomized in equal numbers to one or the other agent in 2000-2002. Using the eDISH analytical system (Guo et al.), we first looked at the results for EXANTA® (AstraZeneca).

(b) (4)

What is displayed is an x-y plot of the peak ALT and peak TBL as log-log values of the multiples of the ULN for each patient, in four quadrants defined by vertical line at ALT $3\times\text{ULN}$ and horizontal line at TBL $2\times\text{ULN}$. It is immediately obvious at a glance that there were 7 times more patients who showed ALT elevations on ximelagatran (X) as on Coumadin (C), and 14 times more who also showed bilirubin elevations as well as ALT elevations (the Hy's Law quadrant, upper right or "NE"). By

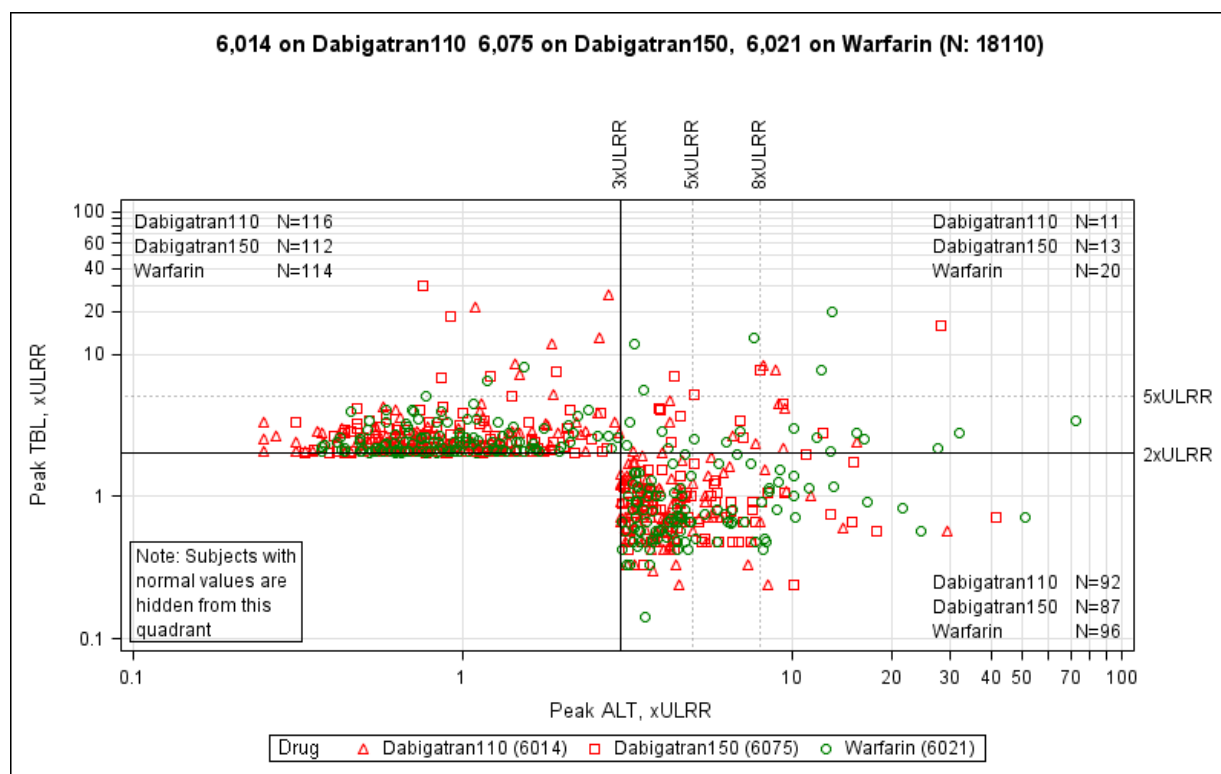
clicking the pointer over any symbol, a time-course graph is generated showing all of the data reported for that individual patient, so the time relationships of the variables can be seen easily. It is evident from looking at a few of these graphs that the bilirubin peak does not always occur on the same date as the ALT peak value, and if caused by hepatocellular injury, may follow it by some variable time. Also available for inspection is the table of data used to generate the graph (click on [Show patient records](#)), and supplemental narrative information is obtained by clicking on the patient's number xxxx. The power of the analytical system is that it uses the computer capabilities for very rapid search through a great mass of data to identify a quite small number of patients of special interest out of the large number in the total study, then showing the results in an x-y plot that permits instant pattern recognition by the viewer. The second step then initiates the process of medical differential diagnosis of the probable cause for the findings, first with a time course graph, and then the third step is reading of narrative information. Using this process and system, it is usually possible to determine the clinical severity of the liver injury, and then to estimate the likelihood that it was caused by the drug (drug-induced liver injury, DILI) to which the patient was exposed, *if the information provided permits that estimate to be made.*



Instant pattern recognition shows 120 patients with ALT >3xULN on ximelagatran, compared to 16 on Coumadin, and in the potential Hy's Law quadrant (NE, upper right) only 1 Coumadin patient (green circle, C) versus 14 on EXANTA (X). Time course and narrative information on the lone patient on C in the NE quadrant reveals that his test abnormalities were caused by cancer of the pancreas and not by warfarin. In contrast, 7 patients on X had at least probable DILI, 1 more possible DILI, out of the 14 total (for details see Appendix B). Keep this image in mind as we go on to consider the dabigatran data.

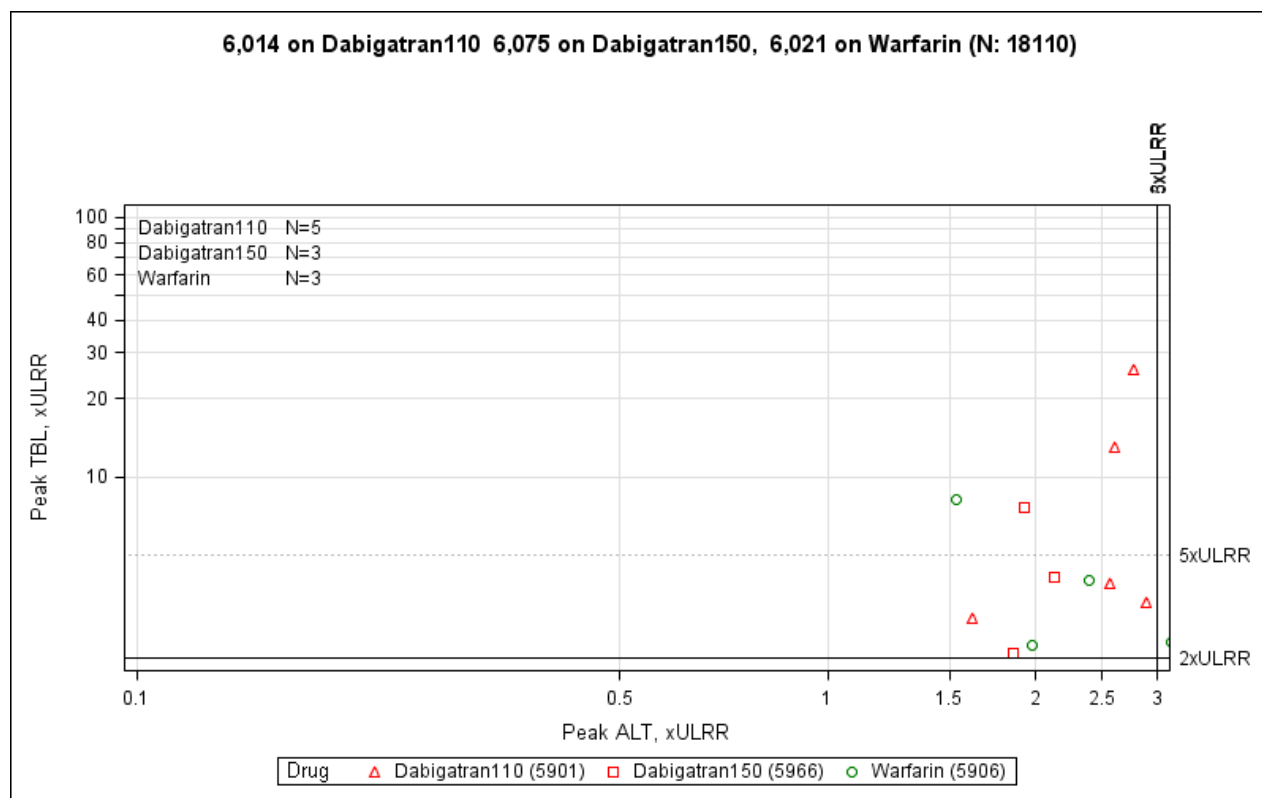
The RE-LY study was many times bigger than the SPORTIF V study, by 4.5-fold, and involved a very large number of patients. Major differences -- in addition to the passage of time to some 6 years later -- included the fact that numerous studies were conducted in Asia, South America, and elsewhere, and that this was an open-label study so patients and investigators knew who was getting which drug. It is difficult to know if the standard of patient care was consistent or uniform, but it does not appear from the poor quality of the narratives submitted for dabigatran that it was comparable to the double-blind trial conducted in the United States and Canada for SPORTIF V. According to the protocol for the RE-LY study 1160.26, investigators were supposed to initiate weekly retesting of liver markers, and to search for possible causes of the test abnormalities, which weren't done consistently at many of the sites.

When we used the eDISH system to look at the RE-LY data, the pattern was quite different:



The preponderance of ALT elevations in patients on the experimental drug (ximelagatran) over those on warfarin seen previously in the eDISH right lower and right upper quadrants where peak ALT elevations are plotted for each patient, is not seen in the similar plot for dabigatran versus warfarin. It is puzzling why there were so many warfarin-associated potential Hy's Law cases in RE-LY, compared to SPORTIF V, by a factor of about 6.5 fold higher incidence (20 of 6021 vs 1 of 1962). Some explanation for this should be found, which would require using all available information for each patient to find a good or plausible probable cause for the findings. In the SPORTIF V study the only potential Hy's Law case turned out to be caused by pancreatic carcinoma, and warfarin is not a drug known to be associated with or causative of hepatotoxicity despite the multitude of patients who have been exposed to it for years or decades. A first step in assessing the RE-LY data is to look more closely at the 20 warfarin cases in the right upper (NE) quadrant. Next, each of the cases on dabigatran needs to be examined similarly, using the same

criteria, even though the review assessment is not blinded. In addition, because the sponsor counted peak AST activity elevation $>3\times\text{ULN}$ as being potential Hy's Law cases if also showing $\text{TBL} >2\times\text{ULN}$, such cases should be included even if the peak ALT may have not been $>3\times\text{ULN}$, which produced 11 more cases in the far right edge of the NW quadrant in which bilirubin elevations were plotted, 3 each in patients on warfarin and D150, and 5 in those on D110.



Finally, the 14 ximelagatran cases in the SPORTIF V upper right quadrant required reassessment by the same process and criteria used for judging causality and severity for the RE-LY study, as was the 1 case in the patient on warfarin.

As mentioned above, the eDISH analytical system and tool for assisting review of selected cases of special interest for potential DILI is very effective in getting a broad picture of results in a very large study. It also provides tools to aid the medical reviewer in the very difficult task of making a differential diagnosis of causality from findings constituting a clinical syndrome, namely that of serum total bilirubin elevations resulting from hepatocellular injury likely to have been caused by a suspected drug, bearing in mind that a firm diagnosis of probable DILI cannot be *made*, but can only *be left* after other causes have been *ruled out*. Thus DILI is a diagnosis of exclusion. How far a reviewer should go in trying to rule out every conceivable cause of serious liver injury has been the source of much debate, but there is some practical limit that is not yet defined even by the world's leading expert hepatologists. The process of ruling out potential causes is entirely dependent on the information available to the assessor, and on the capability of that assessor in applying the information to infer the conclusion of DILI likelihood. This is much simplified by finding a clear-cut alternative cause such as acute viral hepatitis A or B, or less

often hepatitis C or E that are often insidious or even asymptomatic in onset. Other diagnoses that unambiguous are stones in the common bile duct causing extrahepatic biliary obstruction, or acute cholecystitis, and congestive heart failure (Senior, 2010) especially if accompanied by hypotension or arterial hypoxemia. Acute alcoholic hepatitis, autoimmune hepatitis, and liver injury caused by herbal products also should be considered.

In approaching this problem, we built upon the experience of the DILIN (Drug-Induced Liver Injury Network) investigators (Fontana et al., 2010; Rockey et al., 2010), who have collected many hundreds of cases of putative DILI and have tried to establish consistent and standardized methods and processes of adjudication. First, it is necessary to determine the clinical severity of the liver injury, ranging from simple, mild, asymptomatic elevation of serum aminotransferase enzyme activities indicative of acute hepatocellular injury, to devastating liver failure necessitating liver transplant or causing death. It has been our practice to classify severity of liver injury in five grades:

- 1) ALT or AST $>3\times\text{ULN}$, usually transient and reversible by adaptation = mild
- 2) Also TBL $>2\times\text{ULN}$, after or concurrent, indicating early functional loss = Hy's Law case
- 3) Serious, meaning disabling, requiring or prolonging hospitalization
- 4) Acute liver failure, with secondary failure of brain or kidney function due to liver injury
- 5) Fatal, or requiring liver transplantation

The severity of liver injury cannot be reliably graded by the highest observed level of serum enzyme activity, despite the earlier views of expert panels using consensus of opinions, as widely used (*misused?*) by oncologists and others following the system

A scale for categorizing severity was developed at the National Cancer Institute, beginning in 1982 but modified many times since then. It has been very widely used by oncologists and has been increasingly used by other specialists to grade severity of adverse effects, as the Common Toxicity Criteria (CTC), Hepatic (page15). In its current version, serum ALT, AST, and ALP activities are graded as 1) mild, if $>\text{ULN} - 2.5\times\text{ULN}$; 2) moderate, if $>2.5-5\times\text{ULN}$; 3) severe, if $>5-20\times\text{ULN}$; and 4) life-threatening, if $>20\times\text{ULN}$. We have utilized the concept to grade severity but reject the use of highest observed serum enzyme elevations because none of them measure liver function, but only the rate of injury; it is loss of liver *function* that determines clinical severity. Even quite high serum ALT activities of $20-30\times\text{ULN}$ may be entirely asymptomatic and reversible, and might even remain undetected unless blood is drawn for measurement. Further, these enzyme activities change quite rapidly over time; a highest single measurement may miss the true peak, and does not indicate whether the values are falling or rising.

The narrative data usually provides sufficient information to estimate severity, but the next step is more difficult: to estimate the likelihood that the injury was caused by the drug suspected, and not by liver disease, nor by another drug, herbal or chemical toxicant. No pathognomonic test of procedure, even liver biopsy, can be used to make the diagnosis of DILI; it is diagnosed only by excluding other causes, and DILI can mimic the clinical and histologic appearance of any known liver disease. Search for reliable methods to carry out this difficult task in medical differential diagnosis has challenged the best experts in hepatology (Fontana, 2010), and is not settled yet.

The attribution of causality assessment was also pioneered by the National Cancer Institute, and is defined in its manual (pages 3, 11) suggesting that relationship to the investigational agent be

judged as: 5, Definite, if clearly related; 4, Probable, if likely related; 3, Possible, if it may be related; 2, Unlikely, if doubtfully related; and 1, Unrelated, if clearly not related. This concept was later refined and modified by the DILIN group which established ranges of estimated percentage likelihood as 1, Definite, if >95% likely and beyond a reasonable doubt; 2, Highly likely, if 75-95% likely, and clear, convincing, but not definite; 3, Probable, if 50-74%, if supported by a preponderance of evidence; 4, Possible, if 25-49% likely and equivocal; and 5, Unlikely, if <25% likely, and some other cause (Rockey et al., 2010). *(Note that the DILIN uses a scale that is reversed from that proposed by the NCI.)*

In this assessment of the estimated likelihood that dabigatran, warfarin, or ximelagatran may have caused the liver test and clinical abnormalities, we employed a modified scale that has been used for several years at the FDA, combining elements of both the NCI and DILIN approaches:

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

Note that this FDA scale of causality attribution returns to the NCI idea of more likely being rated higher, uses approximately the DILIN percentage categories but is (6 – DILIN = FDA). It allows combination with the 0-5 severity score, so that the SEVxLIK product can be used to estimate the relative clinical importance of a case (Senior, 2010), so a case of acute liver failure probably caused by the drug (product = 12) or a serious case very likely caused by the drug (also =12), up to death or liver transplant definitely caused by the drug (product = 25) would be much more important than just serum enzymes increased.

In addition to estimating the severity (SEV) and causality likelihood (LIK) of DILI, it was early recognized that the adjudication depended very heavily on the amount and quality of information available in the submitted data, and also upon how well that information was used to justify and support the conclusion of causal attribution. Therefore, we graded each case for completeness of information available to make the causal diagnosis (CMP) and the plausibility of the inference based on the information (INF), again using scales from 0 to 5, as follows:

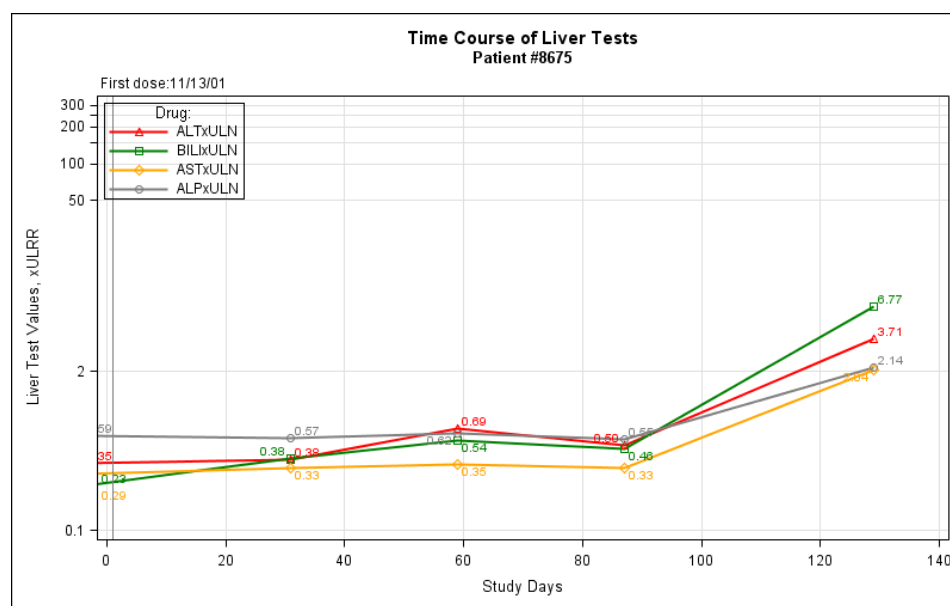
CMP	INF
0: no information provided	0: totally unsupported attribution
1: a couple of items	1: very poor or weak attribution
2: several items	2: somewhat supported attribution
3: most of the key items	3: well supported conclusion
4: all key items	4: very good basis for causal decision
5: enough for definite conclusion of cause	5: incontrovertible causality assessment

We had not employed previous methods to evaluate the quantity and quality of information used to make the differential diagnosis of the likelihood of what caused the abnormal findings, so made only an initial attempt to do this, but have included scores to indicate our assessment of the information available as reported in the submitted NDA data. Finally, we listed what appeared to be the most probable cause for each patient. We looked closely at the 44 cases shown by

eDISH in the upper right (NE) quadrant, 20 of whom were on warfarin, 13 on dabigatran 110 mg b.i.d., and 11 on dabigatran 150 mg b.i.d. Because the sponsor also included patients whose peak AST was $>3\times\text{ULN}$, we examined 11 more cases of which 3 were on warfarin, 5 on dabigatran 110 mg b.i.d., and 3 on dabigatran 150 mg b.i.d. Besides these 55 cases we also returned to the 15 cases from the EXANTA SPORTIF V study that fell into the eDISH right upper quadrant. Full tabulations of the abstracted data from narratives, clinical courses, and scores assessed for each of the 70 patients evaluated are shown in Appendix A for the RE-LY study and Appendix B for the SPORTIF V study, but truncated tabulations are shown below for comment. Absent enough information, the probable diagnosis may be uncertain.

In making these assessments, both Dr Leonard Seeff and I independently reviewed the clinical data for each case, made estimates for CMP, INF, SEV, LIK, and probable cause, and then some days later compared notes. Remarkable concordance was reached, perhaps because we defined criteria in advance, and both have had considerable experience in making these adjudications.

To illustrate how this process worked, let us consider the case of the 78-year-old man in Jamaica NY who had been randomized to Coumadin (warfarin) in the SPORTIF V study comparing effects of Coumadin to EXANTA® (ximelagatran, AstraZeneca):



The history of Patient #8675 included constant atrial fibrillation, congestive heart failure (CHF), coronary artery disease, ischemic cardiomyopathy, hypertension, peripheral neuropathy, hyperlipidemia, and cholecystectomy. The patient was randomized on 13-Nov-2001 and allocated to receive Warfarin. On about (b) (6), approximately four months after randomization and while still receiving the study drug, the patient was hospitalized with previously undiagnosed pancreatic cancer that presented as abnormal liver function tests. The patient also had a recent history of hematuria. All previous liver function tests had been within normal limits. The study drug was permanently discontinued five days prior to admission. On admission, ASAT and ALAT were 1.25 and 1.75 times the upper limit of normal, total bilirubin and alkaline phosphatase were 12.8 mg/dL and 275 U/L, respectively. An abdominal computed tomography (CT) scan was suggestive of pancreatic mass consistent with pancreatic cancer. Endoscopic retrograde cholangiopancreatography revealed occluded common bile duct; stenting was unsuccessful.

Percutaneous biliary stenting was performed. Repeat laboratory results showed total bilirubin 15.8 mg/dL and alkaline phosphatase 209 U/L; ASAT and ALAT returned to normal limits. A CT-guided biopsy of the mass revealed adenocarcinoma. Due to the patient's poor functional status, it was decided not to treat the pancreatic cancer, and was discharged to hospice care. On (b) (6), the patient died from pancreatic cancer. An autopsy was not done. The study investigator assessed the pancreatic cancer and hyperbilirubinemia as unrelated to the study drug. Additional safety surveillance resulted in the following information: Expressed as multiples of ULN, the following values were noted by the central laboratory (b) (6) months after start of study drug (day (b) (6)): ALAT 3.71 x ULN, ASAT 2.04 x ULN, ALP 2.14 x ULN and bilirubin 6.77 x ULN. All previous values had been normal.8675 (#END#)

Comment: As located by eDISH, the patient in question was 1190-8675 in the SPORTIF V study, and clicking on the symbol for that patient brought up the time course of liver tests for him over the period of his observation. That made it clear that nothing happened for about 3 months from when he was randomized to warfarin on 13 November 2001 through the monthly testing on 7 February (87 days), but when retested on 21 Mar 2002 elevations in bilirubin to 6.77xULN, ALT to 3.71xULN were found, and he was hospitalized a (b) (6) days later on (b) (6), where it was discovered that he had pancreatic carcinoma. The work-up was modest for all possible causes for such findings, but permitted a well supported conclusion that the tumor was the definite cause of the findings and not warfarin toxicity. The severity of the liver findings was serious (hospitalized) but no mention was made of liver failure. The warfarin was stopped, and he died from inoperable pancreatic cancer (b) (6) later. Thus, a grading of CMP 2, INF 3, SEV 3, LIK of wILI 0 and cause definitely pancreatic cancer 5, but not warfarin 0.

Using this process for the patients randomized to warfarin in the RE-LY study, we found:

Potential Hy's Cases Randomized to warfarin (20)							
site-subj	Country	sex age	CMP	INF	SEV	LIK wILI	probable cause
0814-015	Czech Repub	F85	1	2	3	1	Very likely heart failure
1057-028	India	M81	1	1	3	2	Probable uncertain
0528-006	Argentina	M69	2	1	3	1	Possible heart failure or uncertain
0687-006	Canada	F79	2	3	4	1	Very likely heart failure
0044-035	United States	F89	2	3	2	1	Very likely gallstones
1704-014	Thailand	M65	3	4	3	0	Definite biliary stones
1678-011	Taiwan	M78	3	4	2	1	Very likely acute hepatitis B
1433-069	Poland	M53	1	1	1	2	Probable uncertain
1704-022	Thailand	M85	2	4	3	1	Very likely strongyloides
0427-001	United States	M75	1	2	3	1	Very likely alcoholic hepatitis
1322-011	Mexico	F78	3	3	3	0	Definite cholangiocarcinoma
1219-003	Japan	M68	2	3	2	0	Definite acute cholecystitis
1292-005	Malaysia	M47	2	2	2	1	Very likely herbal hepatotoxicity
0523-010	Argentina	F78	3	3	3	1	Very likely pancreatic tumor
0693-015	Canada	M67	2	2	2	1	Very likely gallstones
0945-008	Germany	M61	3	3	4	0	Definite heart failure & shock
1531-026	Singapore	M80	1	2	3	1	Possible heart failure or uncertain
0266-011	United States	M72	2	2	2	2	Probable uncertain
0111-030	United States	F86	3	3	2	0	Definite cd stones
0637-019	Denmark	M75	2	3	2	0	Definite cholangiocarcinoma

There did not appear to be any cases of probable, very likely, or definite warfarin-induced liver injury; the three cases rated as “possible” were so done because of missing or poor information available. Note the relatively high incidence of heart failure as the probable cause, not entirely to be unexpected in this elderly population with histories of heart disease. Biliary tract disease was noted in both men and women, not only gallstones but acute cholecystitis and pancreaticobiliary tumors. We had an initial concern that the relatively high incidence of potential Hy’s Law cases in patients on warfarin in the RE-LY study, compared to that previously seen in the SPORTIF V study of ximelagatran might have indicated a subtle bias because of the open nature of the RE-LY study. This was fueled also by the rapid attribution of the elevated serum ALT and TBL to “warfarin-induced liver toxicity” by the investigator at site 0528 in Argentina, with virtually no work-up to consider other alternative causes for the findings in a patient admitted because of tachycardia and treated with digoxin and diuretics.

For the patients randomized to dabigatran 110 or 150 mg b.i.d., we found:

Potential Hy’s Cases Randomized to D110 (11)							
site-subj	country	sex age	CMP	INF	SEV	LIK dILI	probable cause
1683-031	Taiwan	M78	2	3	3	1	Very likely heart failure
0028-020	United States	M66	3	3	3	1	Very likely Augmentin
1393-003	Norway	M79	3	4	3	0	Definite pancreatic cancer
1585-006	South Korea	M67	3	3	3	3	Possible heart failure
1059-002	India	M55	3	2	3	2	Probable heart failure
1438-138	Poland	F82	2	2	3	1	Possible antibiotic, uncertain
1294-057	Malaysia	M55	1	1	1	1	Very likely uncertain
1094-028	Israel	F80	3	3	1	1	Possible heart failure, uncertain
0951-020	Germany	F72	1	1	2	0	Definite uncertain
0115-006	United States	M69	2	2	2	1	Very likely cd stones
1583-029	South Korea	M78	1	1	1	1	Very likely uncertain

Potential Hy’s Cases Randomized to D150 (13)							
site-subj	country	sex age	CMP	INF	SEV	LIK dILI	probable cause
0249-006	United States	F57	2	4	5	0	Definite heart failure & shock
1058-005	India	M70	4	3	3	1	Very likely uncertain
1423-020	Philippines	M65	2	2	2	1	Very likely heart failure
0611-037	Bulgaria	M78	2	2	3	1	Very likely heart failure
1621-011	Sweden	M83	4	4	3	0	Definite pancreatic cancer
0156-046	United States	M33	0	0	3	0	Definite uncertain
0059-018	United States	F80	3	3	3	1	Very likely heart failure
0416-008	United States	M66	3	3	3	0	Definite biliary tract disease
0265-015	United States	M76	3	3	3	1	Very likely heart failure
1676-048	Taiwan	M74	2	2	3	1	Possible herbal or uncertain2
1292-003	Malaysia	M69	2	2	2	1	Very likely herbal
0059-014	United States	F68	3	3	3	1	Very likely cd stones
1193-005	Japan	M73	3	2	2	0	Probable cd stone; possible AAH

cvPotential Hy's Cases Because AST but not ALT >3xULN (11)								
site-subj	Country	s-a	drug	CMP	INF	SEV	LIK	probable cause
0113-002	United States	M71	warf	2	2	4	1	Very likely heart failure
1011-003	Hungary	M74	warf	2	3	3	0	Definite pancreatic carcinoma
1588-004	South Korea	M69	warf	3	2	3	0	Definite alcoholic hepatitis
0193-001	United States	M71	D110	3	4	3	0	Definite heart failure & shock
0550-05	Austria	M66	D110	2	2	1	1	Very likely alcoholic liver disease
0901-008	Greece	M41	D110	1	1	1	0	Definite heart failure
1162-010	Italy	M63	D110	2	3	3	0	Definite heart failure & shock
1412-062	Philippines	M60	D110	2	2	3	1	Very likely heart failure
0955-043	Germany	M78	D150	2	3	2	0	Definite cholangiocarcinoma
1060-009	India	F75	D150	1	2	3	1	Very likely heart failure, sepsis, shock
1673-005	Taiwan	M53	D150	0	1	1	0	Probable uncertain; possible heart failure

It should be noted that of the 55 cases on dabigatran or warfarin in RE-LY study selected for close and detailed inspection and clinical adjudication for probable cause of the findings, there were 23 out of 6021 randomized to warfarin, 16 out of 6014 to dabigatran 110 mg b.i.d., and 16 out of 6075 to dabigatran 150 mg b.i.d. There was no preponderance of potential Hy's Law findings for any of the drugs, and even after careful and laborious causality adjudication, no indication of a notably greater frequency of more serious or more probable cause of liver injury findings from dabigatran. There were 42 men and 13 women so analyzed, among whom heart failure with or without hypotension or shock was the most probable cause for the liver injury, not surprising since this sample population of mostly quite elderly patients with chronic atrial fibrillation and previous heart disease were in and out of heart failure and often died of heart failure. Biliary tract disease also must be excluded, including both stones and tumors. Antibiotic, herbal preparations, and alcoholic hepatitis also need to be considered.

When these findings are compared to similarly adjudicated ximelagatran cases, the difference is quite apparent:

Potential Hy's Law Cases in SPORTIF V study of Ximelagatran and Coumadin							
site-subj	s-a	drug	CMP	INF	SEV	LIK	probable cause
1190-8675	M76	C	2	3	3	0	Definite pancreatic carcinoma
2160-5402	F73	X	3	3	3	3	Probable X; possible heart failure
0620-7259	M80	X	4	4	3	4	Very likely X; unlikely heart failure
0540-7986	F81	X	4	3	2	3	Probable X
0690-6546	M75	X	3	2	2	2	Probable uncertain; possible X
9570-8387	F80	X	2	2	3	3	Probable X
0020-7024	M74	X	2	2	3	2	Probable uncertain; possible X
1000-6995	M62	X	1	2	2	1	Very likely uncertain
9390-6560	M74	X	2	2	1	3	Probable X
0490-6221	M82	X	1	1	2	3	Probable X; possible uncertain
0695-5111	M76	X	2	2	3	1	Possible renal CA; possible uncertain
0200-8434	M85	X	2	2	1	1	Possible biliary sludge or uncertain
2690-8209	M81	X	2	2	1	1	Very likely biliary tract disease
0860-6686	F80	X	1	1	1	0	Probable heart; possible biliary
0080-6438	F68	X	3	1	3	1	Very likely dengue fever

There were 7 of the 14 cases on ximelagatran that were adjudicated probable, 1 very likely, and the other 7 very unlikely (1), unlikely (5), or only possible (1). Case 0620-7259 died as a result of delayed coagulation factor deficiency and exsanguinated from bleeding duodenal ulcer, and there were two other cases that were fatal but not in the SPORTIF V series, one of which appeared caused by hepatitis B.

On balance the data seem to show a considerably lower risk of serious hepatic harm from dabigatran than from ximelagatran, but it should be borne in mind by evaluators, the sponsor, investigators, and treating physicians that this is a rather fragile population in which serious liver injury from cardiac decompensation with or without shock or reduced liver perfusion is quite frequent, and the incidence of biliary tract disease rather high. Even though this was a very large study in terms of the numbers of patients enrolled, many of them were not well followed or investigated according to protocol. Indeed, cases of serious liver injury may occur if hundreds of thousands or millions of patients are treated with long-term dabigatran. Nevertheless, it does not appear worthwhile to advise routine serum enzyme monitoring during prolonged anticoagulation treatment, but it would be advisable to carry out baseline evaluation of liver tests before starting treatment. Once treatment begins, it would be important for both the physician and patient to be on the lookout for indications of liver injury, whether it be symptoms of dark urine, scleral or skin jaundice, anorexia, right upper quadrant abdominal discomfort or pain, and for evidence of heart failure, shock, or hypoxemia that should occasion liver testing and work-up to find the probable cause. We bear in mind that there have been a few cases of possibly serious liver injury or dysfunction reported in patients taking dabigatran after marketing in countries where it has been approved. Analyses of those cases should be added to what we have learned from the RELY study. We plan to submit such analyses as an addendum to this consultation before the end of August.

Recommendations:

- 1) The data suggest that dabigatran exetilate is somewhat less dangerous than ximelagatran was found to be, but it should not be assumed completely safe from causing idiosyncratic liver toxicity in some people if very large numbers of them are treated with it long-term.
- 2) Because the population with chronic atrial fibrillation tends to be elderly and to have high prevalence of cardiac disorders and other problems likely to cause liver dysfunction, it would be advisable for patients to have pre-treatment evaluation of liver disease and for the treating physicians and patients both to be alert for early signs of liver dysfunction, with prompt investigation of the probable cause if findings or symptoms occur..
- 3) Routine monitoring of serum indicators of liver injury during treatment has been found to be inefficient, ineffective, very burdensome, and is not recommended.

John R. Senior, M.D.

cc: OSE 2010-894
N. Stockbridge, DCRP
S. Grant, DCRP
BN Beasley, DCRP
L Seeff, OSE

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Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22512	ORIG-1	BOEHRINGER INGELHEIM PHARMACEUTICA LS 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/

JOHN R SENIOR
09/08/2010

Office of New Drug Quality Assessment

DATE: July 2, 2010
TO: NDA 22-512 Extended Review Team
FROM: Charles F. Jewell, Ph.D. (Drug Substance)
THROUGH: Christine Moore
SUBJECTS: Considerations for Inspection (CFI) of Boehringer Ingelheim for NDA 22-512

NDA 22-512 was submitted by Boehringer Ingelheim for PRADAXA™ (dabigatran etexilate mesylate) 75 mg, 110 mg and 150 mg capsules. The proposed indication is stroke prevention in atrial fibrillation.

This memo includes an overview of the drug substance manufacturing process and findings from the CMC review. This NDA submission contained QbD information for the development for the drug product, but not for development of the drug substance. These findings are for consideration by the Office of Compliance and Office of Regulatory Affairs regarding pre- and post-approval inspections. It should be verified that all the critical attributes mentioned in this memo are adhered to in the production of each batch of drug substance.

Drug Substance

Dabigatran etexilate mesylate is a mesylate salt of a double pro-drug which gets converted to the free acid of dabigatran, by esterases which hydrolyze the ethyl ester to give the acid portion and the hexyloxycarbonyl group to give the amidine portion. The active form is known as BIBR 953 and is a "zwitter ion".

The drug substance is a yellow white or yellow crystalline solid which is composed of mostly the anhydrous polymorphic form known as modification I, but is allowed to contain up to (b) (4) of the anhydrous polymorphic form known as modification II. (b) (4)

Otherwise, both modifications perform equivalently in drug product manufacture, and the drug products from each were shown to be bioequivalent in man with similar dissolution profiles *in vitro*. The drug substance is classified as BCS Class II, indicating poor aqueous solubility but good membrane permeability. It has better aqueous solubility at pH 1-3 but is also more susceptible to aqueous hydrolysis under these acidic conditions, as well as under basic conditions.

The applicant is qualifying two manufacturing processes that are similar in many respects, meaning they both share two starting materials in common, but the third starting material represents two variations in the way the (b) (4) is revealed in the process. The Boehringer Ingelheim site in Ingelheim, Germany is seeking qualification for both of these processes, while a second site by (b) (4) is seeking qualification for the second process that was developed. These processes are referred to by the applicant as the (b) (4) process and the (b) (4) process. When the (b) (4) site is used for manufacture, the drug substance is (b) (4) at (b) (4)

Stability studies have lead to the establishment of a re-test date of (b) (4) months for the drug substance when stored in appropriate containers to limit exposure to moisture. This limits (b) (4) degradation.

The flow diagram for the (b) (4) process is captured in the Appendix (see Figure 1 and Figure 2). This process is performed at the site:

Boehringer Ingelheim Pharma GmbH & Co. KG
Binger Strasse 173, 55216 Ingelheim am Rhein, Germany, FEI 3002806556

The flow diagram for the (b) (4) process is captured in the Appendix (see Figure 3 and Figure 4). This process is performed at the site:

Boehringer Ingelheim Pharma GmbH & Co. KG
Binger Strasse 173, 55216 Ingelheim am Rhein, Germany, FEI 3002806556

and at the site:

(b) (4)

with (b) (4) done at the following site for the (b) (4) process:

(b) (4)

In order to obtain drug substance with required impurity limits, it is critical for all starting materials to meet the established specifications, especially with regard to impurity limits. (See Table 1, Table 2, Table 3 and Table 4 in the Appendix) Note that in Table 4 there are some differences in the specification for the starting material (b) (4) when used in the (b) (4) Process vs. the (b) (4) Process.

The other critical quality parameters for these processes are:

(b) (4)

6 Pages Withheld in Full Immediately Following This Page as (b)(4) CCI/TS.



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

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/s/

CHARLES F JEWELL
07/09/2010

RICHARD T LOSTRITTO
07/15/2010

<div><div>DSI CONSULT</div><div>Request for Biopharmaceutical Inspections</div></div>

DATE: 22 June 2010

TO: Associate Director for Bioequivalence
Division of Scientific Investigations, HFD-48

THROUGH: Norman Stockbridge, Division Director, Division of Cardiovascular and Renal Products,
HFD-110

FROM: Alison Blaus, Regulatory Project Manager, Division of Cardiovascular and Renal
Products, HFD-110

SUBJECT: Request for Biopharmaceutical Inspections
NDA 22-512
PRADAXA (dabigatran etexilate) 110 mg and 150 mg Capsules

Study/Site Identification:

As discussed with you, the following studies/sites pivotal to approval (OR, raise question regarding the quality or integrity of the data submitted and) have been identified for inspection:

Study #	Clinical Site (name, address, phone, fax, contact person, if available)	Analytical Site (name, address, phone, fax, contact person, if available)
1160.70	PAREXEL International GmbH Klinikum Westend, Haus 18 Spandauer Damm 130 Berlin, Germany Contact: Dr. Kathrin Reseski	
1160.66	CRS Clinical Research Services Mannheim GmbH Grenadierstrasse 1 68167 Mannheim, Germany Contact: Dr. med. Sybille Baumann	

International Inspections:

(Please note: International inspections require sign-off by the ORM Division Director or DPE Division Director.)

We have requested an international inspection because:

X There is a lack of domestic data that solely supports approval;

Other (please explain):

Goal Date for Completion:

We request that the inspections be conducted and the Inspection Summary Results be provided by **August 22, 2010**. We intend to issue an action letter on this application by **October 19, 2010**.

Should you require any additional information, please contact:

Sudharshan Hariharan
Clinical Pharmacology Reviewer
WO51 RM1362
10903 New Hampshire Avenue
Silver Spring, MD 20993

Concurrence:

Hariharan, Sudharshan (OCP Reviewer)
Madabushi, Rajnikanth (Team leader, Office of Clinical Pharmacology)
Norman Stockbridge (Division Director)

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

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/s/

ALISON L BLAUS
06/22/2010

SUDHARSHAN HARIHARAN
06/22/2010

RAJANIKANTH MADABUSHI
06/22/2010

NORMAN L STOCKBRIDGE
06/22/2010

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements (except SE8 and SE9)

Application Information		
NDA # 22-512 BLA# N/A	NDA Supplement #:S- N/A BLA STN # N/A	Efficacy Supplement Type SE- N/A
Proprietary Name: PRADAXA Established/Proper Name: dabigatran etexilate Dosage Form: Capsules Strengths: 110 & 150 mg		
Applicant: Boehringer Ingelheim Agent for Applicant (if applicable): N/A		
Date of Application: 19 April 2010 Date of Receipt: 19 April 2010 Date clock started after UN: N/A		
PDUFA Goal Date: 19 October 2010	Action Goal Date (if different): N/A	
Filing Date: 18 June 2010	Date of Filing Meeting: 17 May 2010	
Chemical Classification: (1,2,3 etc.) (original NDAs only) 1		
Proposed indication(s)/Proposed change(s):		
1.1 Prevention of Stroke and Systemic Embolism Dabigatran etexilate is indicated for the prevention of stroke and systemic embolism in patients with atrial fibrillation.		
1.2 Reduction of Vascular Mortality Dabigatran etexilate is indicated for the reduction of vascular mortality in patients with atrial fibrillation.		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:	<div style="display: flex; flex-direction: column;"> <div style="margin-bottom: 10px;"> <input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) </div> <div> <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) </div> </div>	
<i>If 505(b)(2): Draft the “505(b)(2) Assessment” form found at:</i> http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/ucm027499.html <i>and refer to Appendix A for further information.</i>		
Review Classification: <i>If the application includes a complete response to pediatric WR, review classification is Priority.</i> <i>If a tropical disease priority review voucher was submitted, review classification is Priority.</i>	<div style="display: flex; flex-direction: column;"> <div style="margin-bottom: 20px;"> <input type="checkbox"/> Standard <input checked="" type="checkbox"/> Priority </div> <div> <input type="checkbox"/> Tropical Disease Priority Review Voucher submitted </div> </div>	
Resubmission after withdrawal? <input type="checkbox"/>		Resubmission after refuse to file? <input checked="" type="checkbox"/>
Part 3 Combination Product? <input type="checkbox"/> <i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i>	<input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Drug/Device <input type="checkbox"/> Biologic/Device	
<input type="checkbox"/> Fast Track <input checked="" type="checkbox"/> Rolling Review <input type="checkbox"/> Orphan Designation	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)]	

<input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC Other:	<input type="checkbox"/> PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)			
Collaborative Review Division (if OTC product): N/A				
List referenced IND Number(s): 65,813 & 102,821 (ACS)				
Goal Dates/Names/Classification Properties	YES	NO	NA	Comment
PDUFA and Action Goal dates correct in tracking system? <i>If not, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	X			
Are the proprietary, established/proper, and applicant names correct in tracking system? <i>If not, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.</i>	X			
Are all classification properties [e.g., orphan drug, 505(b)(2)] entered into tracking system? <i>If not, ask the document room staff to make the appropriate entries.</i>	X			
Application Integrity Policy	YES	NO	NA	Comment
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at:</i> http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm		X		
If yes, explain in comment column.			X	
If affected by AIP, has OC/DMPQ been notified of the submission? If yes, date notified:			X	
User Fees	YES	NO	NA	Comment
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	X			
<u>User Fee Status</u> <i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send UN letter and contact user fee staff.</i>	Payment for this application: <input checked="" type="checkbox"/> Paid <input type="checkbox"/> Exempt (orphan, government) <input type="checkbox"/> Waived (e.g., small business, public health) <input type="checkbox"/> Not required			

<p><i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.</i></p>	<p>Payment of other user fees:</p> <p><input checked="" type="checkbox"/> Not in arrears <input type="checkbox"/> In arrears</p>
<p>Note: 505(b)(2) applications are no longer exempt from user fees pursuant to the passage of FDAAA. All 505(b) applications, whether 505(b)(1) or 505(b)(2), require user fees unless otherwise waived or exempted (e.g., small business waiver, orphan exemption).</p>	

505(b)(2) (NDAs/NDA Efficacy Supplements only)	YES	NO	NA	Comment																
Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?			X																	
Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (see 21 CFR 314.54(b)(1)).			X																	
Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug (see 21 CFR 314.54(b)(2))?			X																	
<p>Note: If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9).</p> <p>Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan or pediatric exclusivity)? Check the Electronic Orange Book at: http://www.fda.gov/cder/ob/default.htm</p>			X																	
<p>If yes, please list below:</p> <table border="1" style="width: 100%;"> <thead> <tr> <th style="width: 25%;">Application No.</th> <th style="width: 25%;">Drug Name</th> <th style="width: 25%;">Exclusivity Code</th> <th style="width: 25%;">Exclusivity Expiration</th> </tr> </thead> <tbody> <tr><td> </td><td> </td><td> </td><td> </td></tr> <tr><td> </td><td> </td><td> </td><td> </td></tr> <tr><td> </td><td> </td><td> </td><td> </td></tr> </tbody> </table>					Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration												
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration																	
<p><i>If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 108(b)(2). Unexpired, 3-year exclusivity will only block the approval, not the submission of a 505(b)(2) application.</i></p>																				
Exclusivity	YES	NO	NA	Comment																
Does another product have orphan exclusivity for the same indication? Check the Electronic Orange Book at: http://www.fda.gov/cder/ob/default.htm		X																		
<p>If another product has orphan exclusivity, is the product considered to be the same product according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]?</p> <p><i>If yes, consult the Director, Division of Regulatory Policy II,</i></p>			X																	

Office of Regulatory Policy (HFD-007)				
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? (<i>NDAs/NDA efficacy supplements only</i>) If yes, # years requested: 5 <i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>	X			

Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (<i>NDAs only</i>)?		X		
If yes , did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? <i>If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.</i>			X	

Format and Content				
<i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i>	<input type="checkbox"/> All paper (except for COL) <input checked="" type="checkbox"/> All electronic <input type="checkbox"/> Mixed (paper/electronic) <input checked="" type="checkbox"/> CTD <input type="checkbox"/> Non-CTD <input type="checkbox"/> Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission , which parts of the application are submitted in electronic format?				
Overall Format/Content	YES	NO	NA	Comment
If electronic submission , does it follow the eCTD guidance ¹ ? If not , explain (e.g., waiver granted).	X			
Index: Does the submission contain an accurate comprehensive index?	X			
Is the submission complete as required under 21 CFR 314.50 (<i>NDAs/NDA efficacy supplements</i>) or under 21 CFR 601.2 (<i>BLAs/BLA efficacy supplements</i>) including: <input checked="" type="checkbox"/> legible <input checked="" type="checkbox"/> English (or translated into English) <input checked="" type="checkbox"/> pagination <input checked="" type="checkbox"/> navigable hyperlinks (electronic submissions only) If no , explain.	X			
Controlled substance/Product with abuse potential: Is an Abuse Liability Assessment, including a proposal for		X		

scheduling, submitted?				
<i>If yes, date consult sent to the Controlled Substance Staff:</i>				
BLAs only: Companion application received if a shared or divided manufacturing arrangement?			X	
If yes, BLA #				

Forms and Certifications				
<p>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, paper forms and certifications with hand-written signatures must be included.</p> <p>Forms include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</p>				
Application Form	YES	NO	NA	Comment
Is form FDA 356h included with authorized signature?	X			
<i>If foreign applicant, both the applicant and the U.S. agent must sign the form.</i>				
Are all establishments and their registration numbers listed on the form/attached to the form?	X			
Patent Information (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
Is patent information submitted on form FDA 3542a?	X			
Financial Disclosure	YES	NO	NA	Comment
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature?	X			
<i>Forms must be signed by the APPLICANT, not an Agent.</i>				
<i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i>				
Clinical Trials Database	YES	NO	NA	Comment
Is form FDA 3674 included with authorized signature?	X			
Debarment Certification	YES	NO	NA	Comment
Is a correctly worded Debarment Certification included with authorized signature? (<i>Certification is not required for supplements if submitted in the original application</i>)	X			
<i>If foreign applicant, both the applicant and the U.S. Agent must sign the certification.</i>				
<i>Note: Debarment Certification should use wording in FD&C Act section 306(k)(1) i.e., “[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.” Applicant may not use wording such as, “To the best of my knowledge...”</i>				

Field Copy Certification (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
<p>For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included?</p> <p><i>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)</i></p> <p><i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i></p>	X			

Pediatrics	YES	NO	NA	Comment
<p><u>PREA</u></p> <p>Does the application trigger PREA?</p> <p><i>If yes, notify PeRC RPM (PeRC meeting is required)</i></p> <p><i>Note: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i></p>	X			
<p>If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?</p>	X			
<p>If studies or full waiver not included, is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included?</p> <p><i>If no, request in 74-day letter</i></p>			X	
<p>If a request for full waiver/partial waiver/deferral is included, does the application contain the certification(s) required under 21 CFR 314.55(b)(1), (c)(2), (c)(3)/21 CFR 601.27(b)(1), (c)(2), (c)(3)</p> <p><i>If no, request in 74-day letter</i></p>	X			
<p><u>BPCA</u> (NDAs/NDA efficacy supplements only):</p> <p>Is this submission a complete response to a pediatric Written Request?</p> <p><i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)</i></p>		X		

Proprietary Name	YES	NO	NA	Comment
Is a proposed proprietary name submitted? <i>If yes, ensure that it is submitted as a separate document and routed directly to OSE/DMEPA for review.</i>	X			PRADAXA – Submitted 4May10
Prescription Labeling	<input type="checkbox"/> Not applicable			
Check all types of labeling submitted.	<input checked="" type="checkbox"/> Package Insert (PI) <input type="checkbox"/> Patient Package Insert (PPI) <input type="checkbox"/> Instructions for Use (IFU) <input checked="" type="checkbox"/> Medication Guide (MedGuide) <input checked="" type="checkbox"/> Carton labels <input checked="" type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is Electronic Content of Labeling (COL) submitted in SPL format? <i>If no, request in 74-day letter.</i>	X			
Is the PI submitted in PLR format?	X			
If PI not submitted in PLR format , was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted , what is the status of the request? <i>If no waiver or deferral, request PLR format in 74-day letter.</i>			X	
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to DDMAC?	X			15 December 2009
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (send WORD version if available)	X			15 December 2009
REMS consulted to OSE/DRISK?	X			15 December 2009
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA?	X			13 November 2009
OTC Labeling	<input checked="" type="checkbox"/> Not Applicable			
Check all types of labeling submitted.	<input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is electronic content of labeling (COL) submitted? <i>If no, request in 74-day letter.</i>			X	

Are annotated specifications submitted for all stock keeping units (SKUs)?			X	
<i>If no, request in 74-day letter.</i>				
If representative labeling is submitted, are all represented SKUs defined?			X	
<i>If no, request in 74-day letter.</i>				
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?			X	
Consults	YES	NO	NA	Comment
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team)				
<i>If yes, specify consult(s) and date(s) sent:</i> Carcinogenicity Statistics Consult - 17Sep09; OSE - Potential liver signal – 26Apr10 DSI – 25Jan10 BE Studies Inspection – 27Jan10	X			

Meeting Minutes/SPAs	YES	NO	NA	Comment
End-of Phase 2 meeting(s)? Date(s): 24Mar05	X			Minutes dated 12Apr05
<i>If yes, distribute minutes before filing meeting</i>				
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? Date(s): 18May09 & 17Aug09	X			Pre-NDA Minutes dated 2Jun09 ; Phase 3 Top-line Minutes dated 17Sep09
<i>If yes, distribute minutes before filing meeting</i>				
Any Special Protocol Assessments (SPAs)? Date(s): 11Jul05	X			SPA for Phase 3 pivotal trial RE-LY
<i>If yes, distribute letter and/or relevant minutes before filing meeting</i>				

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf>

ATTACHMENT

MEMO OF FILING MEETING

DATE: 17 May 2010

NDA #: 22-512

PROPRIETARY NAME: PRADAXA

ESTABLISHED/PROPER NAME: dabigatran etexilate

DOSAGE FORM/STRENGTH: 110 & 150 mg Capsules

APPLICANT: Boehringer Ingelheim

PROPOSED INDICATION(S)/PROPOSED CHANGE(S):

1.1 Prevention of Stroke and Systemic Embolism

Dabigatran etexilate is indicated for the prevention of stroke and systemic embolism in patients with atrial fibrillation.

1.2 Reduction of Vascular Mortality

Dabigatran etexilate is indicated for the reduction of vascular mortality in patients with atrial fibrillation.

BACKGROUND:

The corresponding IND for the dabigatran NDA, use in stroke prevention, was first filed on 7Jul03. Prior to initiating Phase 3, Boehringer Ingelheim met with the Division of Cardiovascular and Renal Products for an End of Phase 2 meeting on 24Mar05 (minutes dated 12Apr05). The sponsor conducted one pivotal Phase 3 trial, RE-LY, to support the indication noted above. This study is entitled, "Randomized Evaluation of Long term anticoagulant therapy (RE-LY) comparing the efficacy and safety of two blinded doses of dabigatran etexilate with open label warfarin for the prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation: prospective, multi-centre, parallel-group, non-inferiority trial (RE-LY)." This study was submitted as a Special Protocol Assessment and the Division replied with comments on 11Jul05. A summary of the data from RE-LY was first presented to the FDA on 17Aug09 and then published in the New England Journal of Medicine, Volume 361 (12); 17Sep09. After the presentation of the RE-LY data, a rolling review was granted for this NDA. The last piece of the submission arrived on 15 December 2009.

Upon review of the 15 December 2009 NDA submission, the Division decided to "Refuse to File" the application on 12 February 2010, based on data integrity issues in RE-LY. The Division and the sponsor met on 18 February 2010 to discuss the Refuse to File letter and an acceptable plan for resolving the Agency's concerns about the data from RE-LY (proposed "Road Map" submitted on 16 February 2010).

As a footnote, there are two other active INDs for dabigatran. One of the INDs, 102,831, resides in the Division of Cardiovascular and Renal Products for the indication of Acute Coronary Syndrome (ACS). The last IND, 63,267, was filed to the Division of Medical Imaging and

Hematology for the prevention and treatment of venous thromboembolic events (VTE). The data from the pivotal Phase 3 trial under 63,267 (RE-COVER) was recently published in the New England Journal of Medicine, 361 (24); 10Dec09.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Alison Blaus	Y
	CPMS/TL:	Edward Fromm	Y
Cross-Discipline Team Leader (CDTL)	Abraham Karkowsky		Y
Clinical	Reviewer:	Nhi Beasley (Safety) Aliza Thompson (Efficacy)	Y Y
	TL:	N/A	N/A
Social Scientist Review (<i>for OTC products</i>)	Reviewer:	N/A	N/A
	TL:	N/A	N/A
OTC Labeling Review (<i>for OTC products</i>)	Reviewer:	N/A	N/A
	TL:	N/A	N/A
Clinical Microbiology (<i>for antimicrobial products</i>)	Reviewer:	N/A	N/A
	TL:	N/A	N/A
Clinical Pharmacology	Reviewer:	Elena Mishina Peter Hinderling (DDIs) Sudharshan Hariharan	N Y N
	TL:	Raj Madabushi	N
Biostatistics	Reviewer:	Steve Bai	Y
	TL:	Jim Hung	N
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Pat Harlow	Y
	TL:	Al DeFelice	Y
Statistics (carcinogenicity)	Reviewer:	Steven Thomson	N
	TL:	Karl Lin	N
Immunogenicity (assay/assay)	Reviewer:	N/A	N/A

validation) (<i>for BLAs/BLA efficacy supplements</i>)			
	TL:	N/A	N/A
Product Quality (CMC)	Reviewer:	Prafull Shiromani (DP) Charles Jewell (DS) Tapash Ghosh (BE)	Y Y N
	TL:	Kasturi Srinivasachar Patrick Marroum	N N
Quality Microbiology (<i>for sterile products</i>)	Reviewer:	N/A	N/A
	TL:	N/A	N/A
CMC Labeling Review (<i>for BLAs/BLA supplements</i>)	Reviewer:	N/A	N/A
	TL:	N/A	N/A
Facility Review/Inspection	Reviewer:	N/A	N/A
	TL:	N/A	N/A
OSE/DMEPA (proprietary name)	Reviewer:	Judy Park	Y
	TL:	Carlos Mena-Grillasca	N
OSE/DRISK (REMS)	Reviewer:	John Hubbard	N
	TL:	Claudia Karwoski	N
Bioresearch Monitoring (DSI)	Reviewer:	Sharon Gershon	Y
	TL:	Tejashri Purohit-Sheth Jean Mulinde	N Y
OSE – Liver only	Reviewer:	Kate Gelperin	Y
	TL:	John Senior, Ted Guo	N, N
Pharmacometrics	Reviewer:	Kevin Krudys	Y
	TL:	Pravin Jadhav	N
Other attendees	Ellis Unger (ODE I –Deputy Director), Norman Stockbridge (DCRP Director), Steve Grant (DCRP Deputy Director), Tom Marciniak (DCRP – Medical), Ginneh Stowe (PERC), Nina Ton (OSE - RPM)		

FILING MEETING DISCUSSION:

GENERAL • 505(b)(2) filing issues? If yes, list issues:	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
• Per reviewers, are all parts in English or English translation? If no, explain:	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
• Electronic Submission comments List comments: None	<input checked="" type="checkbox"/> Not Applicable
CLINICAL Comments:	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input checked="" type="checkbox"/> Review issues for 74-day letter
• Clinical study site(s) inspections(s) needed? If no, explain: The clinical team and DSI have highlighted 9 sites for inspection (3 domestic, 3 foreign, 3 for cause and the sponsor). The sponsor and the CRO (PHRI) will be inspected jointly by DSI and EMA.	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
• Advisory Committee Meeting needed? Comments: Advisory Committee Meeting scheduled. <i>If no, for an original NME or BLA application, include the reason. For example:</i> <ul style="list-style-type: none">○ <i>this drug/biologic is not the first in its class</i>○ <i>the clinical study design was acceptable</i>○ <i>the application did not raise significant safety or efficacy issues</i>○ <i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i>	<input checked="" type="checkbox"/> YES Date if known: 20 September 2010 <input type="checkbox"/> NO <input type="checkbox"/> To be determined Reason: N/A
• If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO

permit review based on medical necessity or public health significance? Comments:	
CLINICAL MICROBIOLOGY Comments:	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
CLINICAL PHARMACOLOGY Comments:	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input checked="" type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> Clinical pharmacology study site(s) inspections(s) needed? 	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
BIOSTATISTICS Comments:	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input checked="" type="checkbox"/> Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) Comments: Exec CAC meeting occurred 9Feb10.	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
IMMUNOGENICITY (BLAs/BLA efficacy supplements only) Comments:	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
PRODUCT QUALITY (CMC) Comments:	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input checked="" type="checkbox"/> Review issues for 74-day letter
<u>Environmental Assessment</u> <ul style="list-style-type: none"> Categorical exclusion for environmental assessment 	<input type="checkbox"/> Not Applicable <input type="checkbox"/> YES

(EA) requested? If no , was a complete EA submitted? If EA submitted , consulted to EA officer (OPS)? Comments:	<input checked="" type="checkbox"/> NO <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<u>Quality Microbiology (for sterile products)</u> <ul style="list-style-type: none"> Was the Microbiology Team consulted for validation of sterilization? (NDAs/NDA supplements only) Comments:	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<u>Facility Inspection</u> <ul style="list-style-type: none"> Establishment(s) ready for inspection? Establishment Evaluation Request (EER/TBP-EER) submitted to DMPQ? Comments: Facility inspection was scheduled for early February. Inspection has been completed and was found to be acceptable.	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<u>Facility/Microbiology Review (BLAs only)</u> Comments:	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<u>CMC Labeling Review (BLAs/BLA supplements only)</u> Comments:	<input type="checkbox"/> Review issues for 74-day letter

REGULATORY PROJECT MANAGEMENT	
Signatory Authority: Ellis Unger (office) 21st Century Review Milestones (see attached) (optional): Comments:	
REGULATORY CONCLUSIONS/DEFICIENCIES	
<input type="checkbox"/>	The application is unsuitable for filing. Explain why:
<input checked="" type="checkbox"/>	The application, on its face, appears to be suitable for filing. <u>Review Issues:</u> <input type="checkbox"/> No review issues have been identified for the 74-day letter. <input checked="" type="checkbox"/> Review issues have been identified for the 74-day letter. List (optional): <u>Review Classification:</u> <input type="checkbox"/> Standard Review <input checked="" type="checkbox"/> Priority Review
ACTIONS ITEMS	
<input checked="" type="checkbox"/>	Ensure that the review and chemical classification properties, as well as any other pertinent properties (e.g., orphan, OTC) are correctly entered into tracking system.
<input type="checkbox"/>	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
<input type="checkbox"/>	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
<input type="checkbox"/>	BLA/BLA supplements: If filed, send 60-day filing letter
<input checked="" type="checkbox"/>	If priority review: <ul style="list-style-type: none"> • notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices) <ul style="list-style-type: none"> ○ Priority Designation Letter dated 3June10 • notify DMPQ (so facility inspections can be scheduled earlier)
<input checked="" type="checkbox"/>	Send review issues/no review issues by day 74
<input type="checkbox"/>	Other:

Appendix A (NDA and NDA Supplements only)

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original application is likely to be a 505(b)(2) application if:

- (1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
- (2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
- (3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),
- (2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and.
- (3) All other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely

for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),
- (2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or
- (3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your OND ADRA or OND IO.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22512	ORIG-1	BOEHRINGER INGELHEIM PHARMACEUTICA LS 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/

ALISON L BLAUS
06/03/2010

Executive CAC

Date of Meeting: February 16, 2010

Committee: David Jacobson-Kram, Ph.D., ONDIO, Chair
Abby Jacobs, Ph.D., ONDIO, Member
Paul Brown, Ph.D., ONDIO, Member
David Joseph, Ph.D., DGP, Alternate Member
Albert Defelice, Ph.D., DCRP, Team Leader

Presenting Reviewer and Author of Draft Minutes: Patricia Harlow, Ph.D., DCRP

The following information reflects a brief summary of the Committee discussion and its recommendations. The Committee met to consider the results of two-year carcinogenicity bioassays in rats and mice.

IND 65,813/NDA 22-512

Drug Name: BIBR 1048 MS (dabigatran etexilate)

Sponsor: Boehringer Ingelheim Pharmaceuticals, Inc.

Background

BIBR 1048 MS is the methanesulfonate salt of a double pro-drug. The active form, BIBR 953 ZW, is a direct inhibitor of thrombin (Factor IIa). In the Phase 3 trial for prevention of stroke in patients with atrial fibrillation, the maximum dose was 150 mg dabigatran etexilate bid.

Rat Carcinogenicity Study

In a 104-week study using 55 Han Wistar rats/sex in the control, low and mid dose groups and 65 Wistar rats/sex in the high dose group, daily doses of 0, 30, 100 and 200 mg/kg/day of BIBR 1048 MS were administered by oral gavage. The exposure in the high dose males and females was 12.4 and 9.6 fold, respectively, the mean human exposure in subjects receiving 150 mg dabigatran etexilate bid.

Although no treatment related effects were observed on body weight or food consumption, a dose-related increase in mortality was observed in both sexes compared to control groups and was attributed to the pharmacodynamic effect of BIBR 1048 MS. Likewise, hematology findings (decreased hemoglobin concentration and red blood cells along with increased reticulocyte counts and coagulation times), macroscopic findings (abnormal dark contents in multiple tissues) and microscopic findings of hemorrhage were dose-related and consistent with the pharmacodynamic action of BIBR 1048 MS.

Increased incidences of neoplasms were observed in the testes and the ovaries. The incidence of testicular Leydig cell adenomas was within the laboratory historical range, and the attained p values for the pairwise test and trend test do not reach the thresholds to classify these tumors as positive by the criteria used by the Exec-CAC. In addition, there was lack of a clear dose-relationship for the incidence of Leydig cell adenomas and the

absence of either Leydig cell hyperplasia or Leydig cell carcinoma in the high dose males.

Although the incidence of ovarian granulosa cell tumors was within the laboratory historical control range, the sponsor's statistical analysis showed that the trend test was statistically significant, but the pairwise test for the high dose group was not. Neither statistical test attained the threshold significance needed to classify ovarian granulosa cell tumors as a positive finding according to the draft FDA Guidance (2001). Furthermore, incidences of granulosa cell hyperplasia were found in the control group as well as the low dose and high dose groups. In addition, a Sertoli cell adenoma, another stromal tumor, was found only in the control group. The incidence of stromal cell tumors (granulosa plus Sertoli cell) does not attain the critical p values needed to classify the stromal cell tumors as positive. There was no anterior pituitary hyperplasia to suggest the possibility that increased LH and FSH might underlie the Leydig and granulosa cell neoplasia, respectively.

In an adequate carcinogenicity study, BIBR 1048 MS did not induce drug related statistically significant neoplasms in either male or female rats.

Mouse Carcinogenicity Study

Using 54 CD-1 mice/sex in the control, low and mid dose groups and 63 CD-1 mice/sex in the high dose group, daily doses of 0, 30, 100 and 200 mg/kg/day BIBR 1048 MS were administered by oral gavage. Males and females were dosed for up to 104 weeks and 102 weeks, respectively. The exposure in the high dose males and females was 5.9 and 7.7 fold, respectively, the mean human exposure in subjects receiving 150 mg dabigatran etexilate bid.

Although no treatment-related effect was observed on bodyweight gain or food consumption, many of the non-neoplastic macroscopic (abnormal dark contents in multiple tissues) and microscopic findings (hemorrhage) were related to the pharmacodynamic action of BIBR 1048 MS. No statistically significant difference in mortality between control and treated groups was observed for either sex; however, a slightly higher mortality in females at 100 mg/kg/d resulted in termination of all female groups during week 102. One factor identified as contributing to the death of female animals treated with BIBR 1048 MS at 100 or 200 mg/kg/day was the presence of large, hemorrhagic ovarian cysts, which are consistent with the pharmacodynamic effect of BIBR 1048 MS.

Increased incidences were observed of some tumors, including bronchioalveolar adenocarcinoma in mid-dose females, pleomorphic lymphoma in mid-dose males, and the combination of benign fibroma, malignant fibrosarcoma and malignant sarcoma in males. However, the incidences of these tumors were within the laboratory historical range and the attained p values do not reach the thresholds to classify these tumors as positive.

In an adequate carcinogenicity study, BIBR 1048 MS did not induce drug related statistically significant neoplasms in either male or female mice.

Executive CAC Recommendations and Conclusions:

Rat:

- The Committee concluded that the rat bioassay was adequate and noted that the sponsor used the doses recommended by the prior Exec CAC protocol agreement.
- The Committee found that the rat carcinogenicity study was negative for any drug related statistically significant neoplasms.

Mouse:

- The Committee concluded that the mouse bioassay was adequate and noted that the sponsor used the doses recommended by the prior Exec CAC protocol agreement.
- The Committee found that the mouse carcinogenicity study was negative for any drug related statistically significant neoplasms.

David Jacobson-Kram, Ph.D.
Chair, Executive CAC

cc:\

/Division File, DCRP
/A. Defelice, Team leader, DCRP
/P. Harlow, Reviewer, DCRP
/A. Blaus, CSO/PM, DCRP
/A. Seifried, ONDIO

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22512	ORIG-1	BOEHRINGER INGELHEIM PHARMACEUTICA LS 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/

ADELE S SEIFRIED
02/17/2010

DAVID JACOBSON KRAM
02/17/2010

DSI CONSULT: Request for Clinical Inspections

Date: January 25, 2010

To: Constance Lewin, M.D., M.P.H, Branch Chief, GCP1
Tejashri Purohit-Sheth, M.D., Branch Chief, GCP2
Division of Scientific Investigations, HFD-45
Office of Compliance/CDER

Through: Aliza Thompson, M.D., Medical Officer, Division of Cardiovascular and Renal Products
Steve Grant, M.D., Deputy Division Director, Division of Cardiovascular and Renal Products

From: Alison Blaus, Regulatory Health Project Manager, ODE 1/DCaRP, (301)796-1138

Subject: Request for Clinical Site Inspections

I. General Information

Application#: NDA-22-512

Applicant/ Applicant contact information (to include phone/email):

Boehringer-Ingelheim (Attn: Michelle Kliewer)

Phone: (203) 791-6519

michelle.kliewer@boehringer-ingelheim.com

Drug Proprietary Name: PRADAXA (dabigatran etexilate)

NME or Original BLA (Yes/No): Yes

Review Priority (Standard or Priority): Priority

Study Population includes < 17 years of age (Yes/No): No

Is this for Pediatric Exclusivity (Yes/No): No

Proposed New Indication(s):

1.1 - Prevention of Stroke and Systemic Embolism

Dabigatran etexilate is indicated for the prevention of stroke and systemic embolism in patients with atrial fibrillation.

1.2 - Reduction of Vascular Mortality

Dabigatran etexilate is indicated for the reduction of vascular mortality in patients with atrial fibrillation.

DSI Consult

version: 5/08/2008

PDUFA:

Action Goal Date: 15 June 2010

Inspection Summary Goal Date: TBD

II. Protocol/Site Identification

All of the requested sites participated in the following study: Randomized Evaluation of Long term anticoagulant therapy (RE-LY) comparing the efficacy and safety of two blinded doses of dabigatran etexilate with open label warfarin for the prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation (RE-LY trial, protocol ID 1160-0026). Based on the results of this trial, the sponsor is proposing the aforementioned indications (see page 1 of consult).

Site # (Name,Address, Phone number, email, fax#)	Number of Subjects	Reason for site audit
376 Vance Eugene Wilson 695 N Clyde Morris Blvd Daytona Beach, FL 32114 US Phone: 386-258-8722 Email: research@daytonaheart.com Fax: 386-253-0079	56	Greater efficacy (primary endpoint) seen at center than study as a whole; U.S. site
682 Paolo Costi 911 Montee des PionniersTerrebonne Quebec J6V 2H2 CA Phone: 450-654-7525-x11104 Email: chlg.rech.cardio@ssss.gouv.qc.ca Fax: 450-470-2610	39	Greater efficacy (primary endpoint) seen at center than study as a whole; foreign site
901 Maria Anastasiou-Nana Therapeutic Clinic 80 Vas. Sofia Avenue & Lourou Athens 11528 GR Phone: 0030-210-3381447, 0030 6932 57 80 45 Email: jnanas@ath.forthnet.gr Fax: 0030-210-7704443	145	High enroller, enrolled all screened subjects; many discontinuations; foreign site

Site # (Name,Address, Phone number, email, fax#)	Number of Subjects	Reason for site audit
1345 D.J.A. Lok Nico Bolkesteinlaan 75 Deventer SE7416 NL Phone: 31-57-053-65-25, 31-570-536525 Email: lokd@dz.nl Fax: 31-57-050-14-55	104	High enroller; disproportionate number of deaths in warfarin arm; foreign site
32 Michael Ezekowitz 100 Lancaster Avenue Wynnewood, PA19096 US Phone: 610-645-3329 Email: parekha@mlhs.org Fax: 610-645-3471	49	(b) (6); no primary endpoint events; U.S. site
882 Philippe Igigabel 1 rue des Erables Tierce 49125 FR Phone: 33-241-426-201 Email: philippe.igigabel@wanadoo.fr Fax:33-241-424-550	30	Greater efficacy (primary endpoint) seen at center than study as a whole; enrolled all screened subjects; foreign site

III. Site Selection/Rationale

The rationale for selecting individual sites is provided in the table above.

Domestic Inspections:

Reasons for inspections (please check all that apply):

- ☒ Enrollment of large numbers of study subjects
- ☒ High treatment responders (specify): greater efficacy seen at center than study as a whole
- ☐ Significant primary efficacy results pertinent to decision-making
- ☐ There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, significant human subject protection violations or adverse event profiles.
- ☐ Other (specify):

International Inspections:

Reasons for inspections (please check all that apply):

- ☒ There are insufficient domestic data
- ☐ Only foreign data are submitted to support an application
- ☐ Domestic and foreign data show conflicting results pertinent to decision-making
- ☐ There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, or significant human subject protection violations.
- ☒ Other (specify): Approximately 70% of subjects were enrolled from foreign sites. This is an NME.

Five or More Inspection Sites (delete this if it does not apply):

We are requesting that 6 sites be inspected, 4 foreign and 2 in the United States. This is an NME and if approved, there could be rapid and widespread use in a large and vulnerable population. Approximately 2.5 million Americans have atrial fibrillation, many of these patients are elderly and/or have multiple comorbidities. While there is another approved drug for this indication (warfarin), the use of this alternative therapy is limited by dietary and drug interactions and the inconvenience of blood test monitoring and in these ways, the study drug may provide significant advantages over available therapy. The sponsor's pivotal trial is an open label non-inferiority study and by nature of its design may be more susceptible to data manipulation/data integrity issues. Finally, the pivotal trial enrolled over 18,000 subjects with over 951 recruiting sites; accordingly more sites should be sampled to provide a more representative view of the study conduct as a whole.

Because a large number of subjects were enrolled at foreign sites, consideration was given to selecting a representative sample of foreign as well as U.S. sites. Of subjects enrolled in the trial, ~30% (5383) were enrolled from U.S. sites, the Netherlands was the next highest at ~7% (1266), then Canada at 6% (1150); favorable efficacy findings were seen in all of the regions from which these sites were chosen. The reasons for selecting individual sites are given above.

Note: International inspection requests or requests for five or more inspections require sign-off by the OND Division Director and forwarding through the Director, DSI.

IV. Tables of Specific Data to be Verified (if applicable)

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- Verify that potential endpoint events were reported to the sponsor; of particular interest is the reporting of transient ischemic attacks (TIAs), strokes and non-CNS systemic embolism events, myocardial infarctions, as well as deaths
- Verify the integrity of the sponsor-monitor audits; during the IND phase of the NDA, DSI was unable to verify the allegations made by the sponsor at a site that was closed for cause (site 251); a site investigator at another site closed for cause also made allegations against the sponsor-monitor (site 354)
- Verify that important adverse events were reported to the sponsor; the focus should be on the reporting of clinically significant bleeding events and liver function abnormalities; the reported follow-up of these patients (date beyond which follow-up information no longer available if patient withdrew from study) should also be confirmed
- Verify the integrity of the INR data submitted for patients assigned to warfarin; the data should be reviewed for its accuracy, the completeness of reporting (e.g. was additional monitoring done/were additional values obtained that were not reported), adherence to the protocol specified frequency of INR monitoring; the reported action taken with regard to warfarin dose adjustment/changes should also be verified
- Verify study medication (dabigatran and warfarin) start and stop dates (of note, patients could go on and off therapy during the course of the trial); verify the reasons given for temporary/permanent study medication discontinuation

Should you require any additional information, please contact Alison Blaus at 301-796-1138 or Aliza Thompson at 301-796-1957.

Concurrence:

Aliza Thompson
Norman Stockbridge

Medical Reviewer
Division Director (for foreign inspection requests or requests
for 5 or more sites only)

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22512	ORIG-1	BOEHRINGER INGELHEIM PHARMACEUTICA LS 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/

ALISON L BLAUS
01/26/2010

ALIZA M THOMPSON
01/26/2010

NORMAN L STOCKBRIDGE
01/26/2010