

MEMORANDUM
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DEPARTMENT OF HEALTH AND HUMAN SERVICES

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.

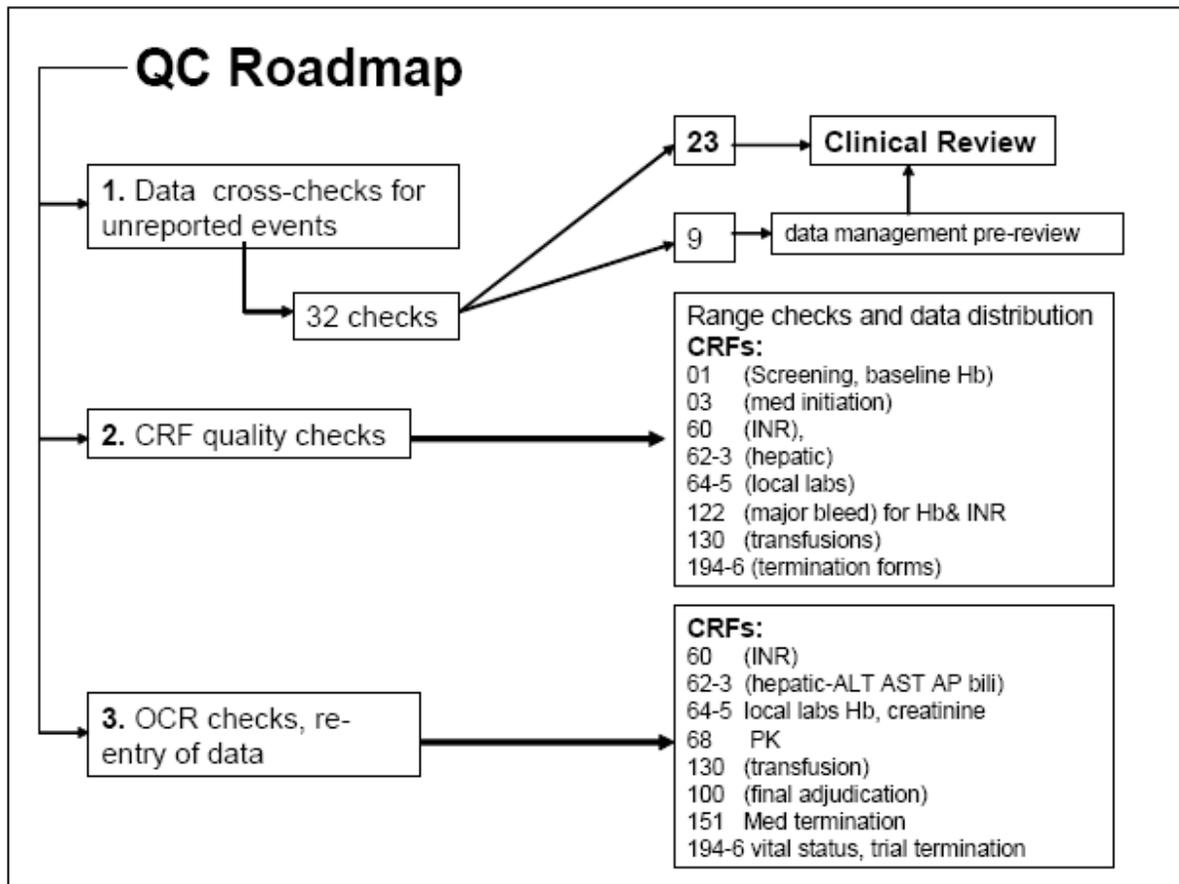


Figure 2.1: Overview of Post-trial QC process of RE-LY

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 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."

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 Iggabel 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 Wynnewood, 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 [REDACTED] ^{(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 Pionniers Terrebonne
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 Warfarin 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}

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