CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022406Orig1s000

OTHER REVIEW(S)

Attachment B: Sample PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

PMR/PMC Description: PMR for Rivaroxaban:
Perform a clinical trial to evaluate the effect of renal impairment (i.e., mild, moderate, severe)
plus the concurrent use of P-gp and moderate inhibitors of CYP3A4 on the pharmacokinetics, pharmacodynamics, and safety of rivaroxaban in volunteers so that appropriate dosing recommendations can be developed in these populations.

PMR/PMC Schedule Milestones:		
	Final Protocol Submission:	Submitted 02/04/11
	Study/Ttrial Completion:	2/29/2012
	Final Report Submission:	6/30/2012
	Other: _____	MM/DD/YYYY

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

   ☒ Unmet need
   ☒ Life-threatening condition
   ☐ Long-term data needed
   ☐ Only feasible to conduct post-approval
   ☐ Prior clinical experience indicates safety
   ☒ Small subpopulation affected
   ☐ Theoretical concern
   ☐ Other

   Affects patients with renal impairment (i.e., mild, moderate, severe) plus the concurrent use of P-gp and moderate inhibitors of CYP3A4 in combination with renal impairment

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

The applicant reports that based on its simulations using a population pharmacokinetic approach, it anticipates that combined use of a drug that would inhibit non-renal clearance by 30% and inhibit active renal clearance by 45% in patients with mild or moderate renal impairment may result in an approximate 2 and 2.4 fold increase in plasma AUC, respectively, when compared to subjects which is considered significant. Using a physiologically based (PBPK) modeling approach FDA reached similar results, but also found that this complex DDI may be more pronounced in the elderly.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

- **Which regulation?**

☐ Accelerated Approval (subpart H/E)
☐ Animal Efficacy Rule
☐ Pediatric Research Equity Act
☒ FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

☒ Assess a known serious risk related to the use of the drug?
☐ Assess signals of serious risk related to the use of the drug?
☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

☐ Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

☐ Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

☒ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

A multicenter, open-label, sequential design trial in both healthy subjects with normal renal function, and otherwise healthy subjects with mild or moderate renal impairment to compare the pharmacokinetics (PK) and pharmacodynamics (PD) of rivaroxaban (administered as a single 5 mg and 10 mg dose) in subjects with mild or moderate renal impairment receiving multiple doses of erythromycin, to the pharmacokinetics and pharmacodynamics of a single 10 mg dose of rivaroxaban administered alone in subjects with normal renal function.

The Applicant agreed to conduct this study following a October 14, 2010, with the Agency. A protocol synopsis was included in this CR response.

Required

☐ Observational pharmacoepidemiologic study
☐ Registry studies
☐ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☒ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials
☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

Agreed upon:

☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

☐ Other

5. Is the PMR/PMC clear, feasible, and appropriate?

☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
☒ Are the objectives clear from the description of the PMR/PMC?
☒ Has the applicant adequately justified the choice of schedule milestone dates?
☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

_____

(signature line for BLAs)

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/s/

TYREE L NEWMAN
07/01/2011

ROBERT C KANE
07/01/2011

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

PMR/PMC Description: PMR for Rivaroxaban:
A postmarketing pharmacovigilance study of the risk factors, clinical management, and outcome of cases of major bleeding in association with Xarelto® (rivaroxaban) use.
You agree to conduct an "Enhanced Pharmacovigilance Plan" that will consist of the collection, analysis, and reporting of events termed "major bleeding," to consist of active solicitation of the events and associated risk factors, subsequent therapy, and outcomes. Major bleeding is defined as in the clinical protocols and current drug labeling.
You agree to provide reports quarterly for the first three years following drug approval, then annually. The final plan will be submitted by October 30, 2011.
Submit summary information (total cases and summary of key facts in those cases, with pertinent expert analysis of clinically relevant information from the case series and any potential regulatory implications such as labeling changes) quarterly for three years, then annually.

PMR/PMC Schedule Milestones:		
	Final Protocol Submission:	11/30/2011
	Study/Trial Completion:	06/30/2016
	Final Report Submission:	12/30/2016

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- ☐ Unmet need
- ☐ Life-threatening condition
- ☒ Long-term data needed
- ☐ Only feasible to conduct post-approval
- ☐ Prior clinical experience indicates safety
- ☐ Small subpopulation affected
- ☐ Theoretical concern
- ☐ Other

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

The protocol should include:

- Definition of major bleeding (as per your protocol, transfusion of 2 units of blood or loss of 2 units is acceptable)
- Methods to be used for data collection and analysis, including your solicitation of reports of bleeding events,
- Plan for enhanced follow-up with reporters – you will actively query and ascertain key facts about the bleeding event, including:
  - Demographics (age, gender, race, location of bleeding)
  - Underlying diagnoses including specific reason for rivaroxaban treatment
  - Other relevant risk factors for bleeding
  - Dose and duration of rivaroxaban therapy
  - Concomitant medications
  - Treatment given for the bleeding (names of products, doses and duration of treatment)
  - Any laboratory monitoring tests performed
- Outcome information on:
  - Bleeding outcome – time to cessation and opinion on the role of therapy given on the bleeding cessation
  - Survival / disability / further complications

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

- **Which regulation?**

☐ Accelerated Approval (subpart H/E)
☐ Animal Efficacy Rule
☐ Pediatric Research Equity Act
☒ FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

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☐ Assess signals of serious risk related to the use of the drug?
☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

☐ Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

☒ Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

"Enhanced Pharmacovigilance Plan" that will consist of the collection, analysis, and reporting of events termed "major bleeding," to consist of active solicitation of the events and associated risk factors, subsequent therapy, and outcomes. Major bleeding as defined in the clinical protocols and current drug labeling.

Required

☒ Observational pharmacoepidemiologic study
☐ Registry studies
☐ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

☒ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☐ Pharmacokinetic studies or clinical trials
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☐ Dosing trials
☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

Agreed upon:

☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

_____

☐ Other

_____

5. Is the PMR/PMC clear, feasible, and appropriate?

☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
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PMR/PMC Development Coordinator:

☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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/s/

TYREE L NEWMAN
07/01/2011

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:	June 14, 2011
To:	Ann Farrell, MD, Director Division of Hematology Products
Through:	Todd Bridges, RPh, Acting Deputy Director Carol Holquist, RPh, Director Division of Medication Error Prevention and Analysis (DMEPA)
From:	Denise V. Baugh, PharmD, BCPS, Safety Evaluator Division of Medication Error Prevention and Analysis
Subject:	Label and Labeling Review
Drug Name:	Xarelto (Rivaroxaban) Tablets 10 mg
Application Number:	NDA 22406
Applicant:	Johnson & Johnson Pharmaceutical Research & Development
OSE RCM #:	2011-513

1 BACKGROUND

1.1 INTRODUCTION

This review evaluates the container labels, carton and insert labeling for Xarelto (Rivaroxaban) Tablets (NDA 022406). We provide recommendations in Section 4 for improvements to the labels and labeling.

2 METHODS AND MATERIALS

The Division of Medication Error Prevention and Analysis uses Failure Mode and Effects Analysis (FMEA)[1], principals of human factors, and lessons learned from post marketing experience in our evaluation of labels and labeling of drug products. For this application, we evaluated the following:

Carton labeling (b) (4) – submitted December 23, 2010
Container label (30 count) - submitted December 23, 2010
Blister label – submitted July 29, 2008 and
Insert labeling – substantially complete as of June 7, 2011

See Appendix A for the carton labeling, container and blister labels. There is no image for the insert labeling.

3 RESULTS

Our review of the proposed container and blister labels, carton and insert labeling is discussed below.

3.1 LABEL AND LABELING

In our evaluation of the insert labeling, we recommended: revising the Dosage and Administration sections to state that the product should always be taken with food and deletion of error prone abbreviations. In our evaluation of the carton labeling, container and blister labels, we made recommendations to relocate certain statements and increase the prominence of the established name.

4 CONCLUSIONS AND RECOMMENDATIONS

Our evaluation of the proposed container and blister labels, carton and insert labeling identified areas of improvement to minimize medication errors. Section 4.1, *Comments to the Division of Hematology Products*, contains our recommendation for the proposed insert labeling for Xarelto. We have provided our recommendations on the container labels and carton labeling below in Section 4.2, *Comments to the Applicant*. Please forward these recommendations 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 any further questions or need clarifications on this review, please contact Sue Kang, OSE Project Manager, at 301-796-4216.

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

4.1 COMMENTS TO THE DIVISION OF HEMATOLOGY PRODUCTS

1. The Dosage and Administration sections indicate that the 10 mg dose can be taken with or without food [redacted (b) (4)]. These instructions are likely to lead to confusion and medication errors as administration of a product with or without food is typically based upon the active ingredient(s) of the product and not the dose being administered. We recommend revision of the labeling to indicate that the proposed product should always be taken with food.
2. We recommend using the terms "greater than" or "less than" instead of the ">" and "<" symbols throughout the insert labeling as these symbols have been mistaken as the opposite of their intended meaning. FDA launched a campaign on June 14, 2006, warning healthcare practitioners and consumers not to use error prone abbreviations, acronyms, dose designations, or symbols. As part of the campaign, FDA agreed not to use such error prone designations in their approved product labeling.
3. Define the abbreviation "P-gp" the first time it is used in the insert labeling.
4. We note a typographical error in Section 8.7, Renal Impairment. The words 'with' and 'and' (following "n = 8") should appear in reverse order.
5. Add the units of measurement to Creatinine Clearance throughout the labeling and avoid using dashes to reflect the range (e.g., revise "CrCL 30 – 50 mL/min" in Section 8.7 to read "CrCL 30 mL/min to CrCL 50 mL/min").
6. The last statement in Section 2 Dosage and Administration (in Full Prescribing Information) regarding administration of this product via feeding tube appears to contradict the statement in Section 12.3 under Clinical Pharmacology. Please clarify the appropriateness of administration of this drug product via feeding tube.

4.2 COMMENTS TO THE APPLICANT

1. Blister Label, Container Label and Carton Labeling

   In accordance with 21 CFR 201.10(g)(2), increase the prominence of the established name to be commensurate with the proprietary name taking into account all pertinent factors, including typography, layout, contrast, and other printing features.

2. Container Label and Carton Labeling

   a. Reduce the size of the graphic which appears to the left of the 'X' so that it does not distract from the proprietary name.

   b. Relocate the strength, "10 mg" to come after the dosage form so that it reflects the traditional sequence of information.

3. Carton Labeling (for Hospital Unit Dose Tablets)

   a. Relocate the net quantity to appear in the upper right hand corner of the panels and away from the statement of strength.

   b. Delete storage statements from principal display panel and top panel to reduce clutter on the label and decrease redundant statements

   c. Relocate the 'each tablet contains' statement from the side panel to the principal display panel.

3 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

TODD D BRIDGES on behalf of DENISE V BAUGH
06/14/2011
signing for Denise Baugh also.

CAROL A HOLQUIST
06/15/2011

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

NDA REVIEW AND EVALUATION OF CARCINOGENICITY DATA

Application numbers:	22406, 202439
Supporting documents:	In Electronic Document Room (EDR)
Applicant's letter dates:	22406: resubmission on 12/30/2010 202439: original submission 01/04/11
CDER stamp dates:	22406: resubmission on 01/03/11 202439: original submission on 01/05/11
Product:	Rivaroxaban (Bay 59-7939)
Indication:	Prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation.
Applicant:	Ortho McNeil Janssen Pharmaceuticals Inc [Bayer Schering Pharma AG (Bayer) and Johnson & Johnson Pharmaceutical Research and Development, L.L.C. (J&JPRD)]
Review Division:	Division of Cardiovascular and Renal Products
Reviewer:	Patricia P. Harlow, Ph.D.
Supervisor/Team Leader:	Thomas Papoian, Ph.D., D.A.B.T.
Division Director:	Norman Stockbridge, M.D., Ph.D.
Project Manager:	Alison Blaus

Template Version: September 1, 2010

Disclaimer
Except as specifically identified, all data and information discussed below and necessary for approval of NDAs 22406 and 202439 are owned by Ortho McNeil Janssen Pharmaceuticals Inc or are data for which Ortho McNeil Janssen Pharmaceuticals Inc has obtained a written right of reference. Any information or data necessary for approval of NDAs 22406 and 202439 that Ortho McNeil Janssen Pharmaceuticals Inc does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as reflected in the drug's approved labeling. Any data or information described or referenced below from reviews or publicly available summaries of a previously approved application is for descriptive purposes only and is not relied upon for approval of NDA 22406 and 202439.

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1 Executive Summary

1.1 Introduction

Rivaroxaban is a direct factor Xa inhibitor being developed for the prevention and treatment of multiple thrombosis-mediated conditions, including short-term prophylaxis of deep vein thrombosis in patients undergoing knee or hip replacement surgery under NDA 22406 and for the longer-term prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation under NDA 202439.

According to the ICH Guideline S1A (1996), “Carcinogenicity studies should be performed for any pharmaceutical whose expected clinical use is continuous for at least 6 months. For the longer-term indication under NDA 202439, the study reports of the carcinogenicity studies were submitted and reviewed. However, this document was written separately from the remainder of the nonclinical review for NDA 202439 to support similar incorporation of the carcinogenicity results into the label for the shorter-term indication under NDA 22406.

1.2 Brief Discussion of Nonclinical Findings

Two year carcinogenicity studies were conducted in CD-1 mice and Wistar rats.

In an adequate 104-week study using 60 CD-1 mice/sex/group, daily doses of 0, 10, 20, and 60 mg/kg/day of rivaroxaban in ethanol/solutol HS/tap water (10/40/50% v/v) were administered by oral gavage. The systemic exposures (AUCs) of unbound rivaroxaban in male and female mice at the highest dose tested (60 mg/kg/day) were 1- and 1.6 times, respectively, the human exposure of unbound drug at the human dose of 20 mg per day, and 3- and 5-times, respectively, the human exposure of unbound drug at the human dose of 10 mg daily.

No significant treatment-related effects were observed in mice on mortality, bodyweight gain or food consumption. At study end, slight decreases in hemoglobin concentration and hematocrit, slightly prolonged thromboplastin times, and increased incidences of microscopic pigment deposits were consistent with the pharmacodynamic action of rivaroxaban as a factor Xa inhibitor. Consistent with the increase in liver nodules macroscopically, hepatocellular tumors (adenoma and carcinoma) increased with rivaroxaban dosage in the male, but not in the female mice. However, the incidences of hepatocellular tumors were within historical ranges, and the attained p values do not reach the thresholds to classify these tumors as drug-related.. Similarly, the incidences of a few other tumors, including histiocytic sarcoma, malignant lymphoma, ovarian cystadenoma, uterine hemangiosarcoma, and testicular Leydig cell tumors, were numerically increased in the higher dose groups compared to those in the control groups. However, the incidences were within historical ranges, and the attained p values do not reach the thresholds to classify these tumors as drug-related.

In an adequate 104-week study using 50 Wistar rats/sex/group, daily doses of 0, 10, 20, and 60 mg/kg/day of rivaroxaban in ethanol/solutol HS/tap water (10/40/50% v/v) were administered by oral gavage. The systemic exposures (AUCs) of unbound rivaroxaban

in male and female rats at the highest dose tested (60 mg/kg/day) were 1.5- and 3.7 times, respectively, the human exposure of unbound drug at the human dose of 20 mg per day, and 4- and 10-times, respectively, the human exposure of unbound drug at the human dose of 10 mg daily.

No significant treatment-related effect was observed in rats on mortality, bodyweight gain, and food consumption. Although only slight effects were observed on red cell parameters on Days 184, 366, 548, and 716 , the mean values for thromboplastin time for all treated groups on all sampling days were significantly greater (up to 1.9 and 2.5-fold in males and females, respectively) than those for the control groups. Likewise, the incidence of pigment deposition increased in some organs and across all organs in the high dose groups consistent with the pharmacodynamic action of BAY 59-7939. However, the incidence of valvular fibrosis in the heart increased with dose in both male and female rats with the incidence in females statistically significant ($p = 0.0048$) in a trend test, but not in a pair-wise test ($p = 0.0587$).

The incidences of a few tumors in rats, including squamous cell carcinoma of the clitoral glands, adrenal cortical adenoma, adrenal pheochromocytoma, mammary fibroadenoma, histocytic sarcoma, and skin fibroma, were numerically increased in the higher dose groups compared to those in the control groups. However, these incidences were within historical ranges, and the attained p values do not reach the thresholds to classify these tumors as drug-related according to the CDER statistical criteria.

The nonclinical and statistical reviewers concurred with the sponsor that no significant evidence of neoplasia related to BAY 59-7939 treatment was observed either in Wistar rats or CD-1 mice. The Executive Carcinogenicity Assessment Committee also concluded that there were no clear drug-related neoplasms in either study.

1.3 Recommendations

1.3.1 Approvability

The results of the carcinogenicity studies support approvability of rivaroxaban.

1.3.2 Additional Non Clinical Recommendations

No additional nonclinical recommendation is necessary.

1.3.3 Labeling

For Section 13.1 of the label for NDA 22406 and NDA 202439; however, the exposure ratios below are for NDA 22406.

Rivaroxaban was not carcinogenic when administered by oral gavage to mice or rats for up to 2 years. The systemic exposures (AUCs) of unbound rivaroxaban in male and female mice at the highest dose tested (60 mg/kg/day) were 3- and 5-times, respectively, the human exposure of unbound drug at the human dose of 10 mg per

day. Systemic exposures of unbound drug in male and female rats at the highest dose tested (60 mg/kg/day) were 4- and 10-times, respectively, the human exposure.

2 Drug Information

2.1 Drug

CAS Registry Number: 366789-02-8

Generic Name: Rivaroxaban (Xarelto™)

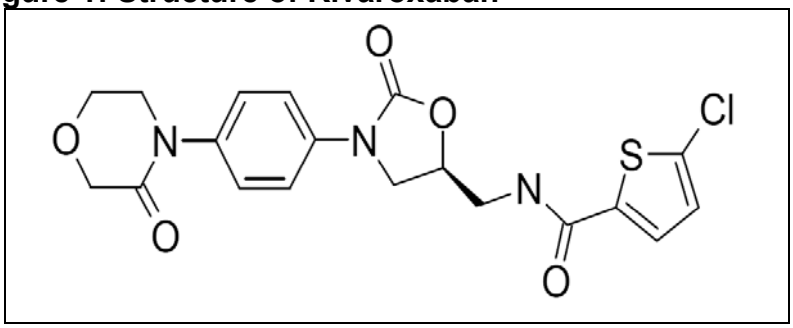
Code Names: JNJ-39039039, BAY 59-7939

Chemical Name: 5-chloro-*N*-({(5*S*)-2-oxo-3-[4-(3-oxomorpholin-4-yl) phenyl]-1,3-oxazolidin-5-yl}methyl)thiophene-2-carboxamide

Molecular Formula/Molecular Weight: $C_{19}H_{18}ClN_3O_5S$/ 435.89 g/mol

Structure or Biochemical Description:

Figure 1: Structure of Rivaroxaban



Pharmacologic Class: Rivaroxaban is a direct Factor Xa inhibitor.

2.2 Relevant INDs, NDAs, BLAs and DMFs

NDA-022406 (DHP)
IND-064892 (DHP)

(b) (4)

2.3 Drug Formulation

Rivaroxaban is formulated for oral administration as immediate release, film-coated tablets containing either (b) (4) of active compound. The tablets also contain microcrystalline cellulose (b) (4) NF, croscarmellose sodium NF, hypromellose (b) (4) (b) (4)) USP), lactose monohydrate NF, magnesium stearate (b) (4) NF, sodium lauryl sulfate NF, (b) (4) as excipients. The commercially available film coating for the (b) (4) tablet is Opadry (b) (4) containing hypromellose (b) (4) 15 cp USP, polyethylene glycol (Macrogol) 3350 NF, ferric oxide red NF, and titanium dioxide USP. (b) (4)

(b) (4)

2.4 Comments on Novel Excipients

All of the excipients are commonly used in oral commercial pharmaceutical dosage forms. The CMC Review of NDA 22406 indicates that the formulation excipients are conventional.

2.5 Comments on Impurities/Degradants of Concern

Impurities and degradants will be discussed in the nonclinical review of NDA 202439.

2.6 Proposed Clinical Population and Dosing Regimen

Rivaroxaban is being developed for the prevention and treatment of multiple thrombosis-mediated conditions. Under NDA 22406, rivaroxaban at 10 mg daily is proposed for the prophylaxis of deep vein thrombosis (DVT) in patients undergoing knee or hip replacement surgery. Under NDA 202439, rivaroxaban at 20 mg daily is proposed for the prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation.

2.7 Regulatory Background

The carcinogenicity protocols were submitted and reviewed under IND 64,892. In April 2005, the Exec CAC reviewed rat and mouse carcinogenicity protocols that proposed dietary administration of rivaroxaban (b) (4) . The Exec CAC did not concur with the proposed protocols and made recommendations to the sponsor. In January 2006, the Exec CAC reviewed additional data submitted by the sponsor and concurred with the sponsor's originally proposed dietary doses. However, a subsequent addendum to the January 2006 meeting minutes indicates the Exec CAC rescinded this concurrence, because the sponsor failed to submit the stability and pharmacological activity data (b) (4) as requested by DMIHP in a teleconference on February 6, 2006. The carcinogenicity protocols and the Exec CAC's action were discussed with the sponsor in a teleconference on February 23, 2006. Subsequently, in a teleconference on June 1, 2006, the sponsor

revealed that [redacted] (b) (4) . Consequently, the sponsor proposed to use micronized rivaroxaban [redacted] (b) (4) as the drug product for development. On August 1, 2006, the Exec CAC evaluated carcinogenicity protocols that used micronized rivaroxaban. For both the rat and mouse protocols, the Exec CAC did not concur with the sponsor's proposed doses [redacted] (b) (4) and instead recommended doses of 0, 10, 20, and 60 mg/kg/day by oral gavage, based on saturation of absorption in 13-week gavage studies.

3 Studies Submitted

The following study reports for the carcinogenicity studies were submitted under NDA 202439 and are reviewed in Section 4 below

Document Number	Study Number	Study Title
PH-36243	T3076596	BAY 59-7939: Carcinogenicity Study in CD-1 Mice (2 Years Administration by Gavage)
PH-36242	T8076429	BAY 59-7939: Carcinogenicity Study in Wistar Rats (2 Years Administration by Gavage)

4 Carcinogenicity

Two year carcinogenicity studies were conducted in CD-1 mice and Wistar rats. The nonclinical reviews of the study reports are below. The complete statistical review by Dr. Matthew Jackson dated May 11, 2011 is in DARRTS.

Study title: BAY 59-7939: Carcinogenicity Study in CD-1 Mice (2 Years Administration by Gavage)

Document no.:	PH-36243
Study no.:	T3076596 (AT05917)
Study report location:	EDR, Module 4
Conducting laboratory and location:	Bayer Schering Pharma AG GDD-GED Toxicology, Wuppertal Germany
Date of study initiation:	October 17, 2006
GLP compliance:	Indicated
QA statement:	Present
Drug, lot #, and % purity:	BAY 59-7939 (rivaroxaban) a) Lot BXO23BS, purity 100% b) Lot BXA18UX, purity > 99.7%
CAC concurrence - protocol:	On August 1, 2006, the Executive CAC did not concur with the sponsor's proposed doses (b) (4) and instead recommended doses of 0, 10, 20, and 60 mg/kg/day by oral gavage, based on saturation of absorption. The Executive CAC meeting minutes are in Appendix 1.
CAC concurrence – study results:	On April 15, 2011, the Executive CAC concurred that the study was adequate and there were no clear drug-related neoplasms. The Executive CAC meeting minutes are in Appendix 2.

Key Study Findings

Introduction

CD-1 mice received oral doses of BAY 59-7939 (rivaroxaban) for up to 104 weeks. At dosages of 10, 20 and 60 mg/kg/day the mean $AUC_{(0\text{-}24h)}$ during Week 52 was 980, 1540, and 2520 ng.hr/mL in males and 1710, 3290, and 4240 ng.hr/mL in females, respectively.

Summary of Non-neoplastic Findings

Consistent with the anti-coagulant pharmacodynamic action of BAY 59-7939, the mean thromboplastin time at 1 hour after dosing was significantly prolonged in all treated groups of males and females on all sampling days; however, not all members of each treated group had values above the normal range. Some of the non-neoplastic microscopic findings, such as increased pigment deposits, were also related to the pharmacodynamic action of BAY 59-7939. The combined incidence of necrosis in the liver slightly increased in the high dose males. In addition, the incidence of biliary cysts in the liver and dilation/atrophy in the preputial gland increased in mid and high dose male groups.

Adequacy of Carcinogenicity Study

The mouse carcinogenicity study used the doses (0, 10, 20, and 60 mg/kg/day) that were recommended by the Exec CAC based on saturation of exposure at the high-

dose. The study length was acceptable since the male and female mice were treated for up to 104 weeks. No statistically significant difference in mortality was observed between control and treated groups for either sex.

Appropriateness of Test Model
The Crl: CD-1™ (ICR) BR strain is an appropriate model because this strain is known to be responsive to known carcinogens and historical control data have been established. The proposed metabolic pathway of BAY 59-7939 in mice and man is similar involving structural cleavage and hydroxylation, although a minor metabolite, M-5, is not formed in mice.

Summary of Tumor Findings
Consistent with the increase in liver nodules macroscopically, hepatocellular tumors (adenoma and carcinoma) increased with BAY 59-7939 dosage in the males, but not in the females. If the hepatocellular tumors are combined, the statistical evaluations by the sponsor and the FDA statistician indicated p values in the trend test (p_t) of 0.0076 and 0.036, respectively. Since hepatocellular tumors are common tumors in mice, no p value for hepatocellular tumors attains the significance level ($p < 0.005$) necessary for the tumors to be considered positive, according to current CDER guidance. Furthermore, the incidence of either basophilic foci or total foci of alterations in the liver was similar across control and treated groups. The incidences of hepatocellular tumors for the male treated groups in the current study are within historical ranges.

The incidences of a few other tumors were increased in the higher dose groups compared to those in the control groups. The tumors with overall incidences greater than 1% in the (b) (4) listing (2003) for spontaneous tumors in CD-1 mice include histocytic sarcoma in the high dose females (incidence of 1.6%, sponsor's p_t = 0.176, FDA p_t = 0.174), malignant lymphoma in the high dose males ((incidence of 4.5%, sponsor's p_t = 0.136, FDA p_t = 0.043) and in mid- and high dose females (incidence of 9.9%, sponsor's p_t = 0.071, FDA p_t = 0.164). The tumors with overall incidences less than 1% in the (b) (4) listing (2003) for spontaneous tumors in CD-1 mice include ovarian cystadenoma in the high dose females (incidence of 0.74%, sponsor's p_t = 0.032, FDA p_t = 0.055), testicular Leydig cell tumor in mid and high dose males ((incidence of 0.85%, sponsor's p_t = 0.070, FDA p_t = 0.155) and uterine hemangiosarcoma in the high dose females ((incidence of 0.47%, sponsor's p_t = 0.086, FDA p_t = 0.058). In RITA historical control database, the mean incidences of testicular Leydig cell tumor and ovarian cystadenoma are 3.2% and 1.7%, respectively. However, no p value for these tumors attained the significance level of $p < 0.025$ required for even a rare tumor to be considered positive. In addition, the incidences are within historical ranges.

Evaluation of Tumor Findings
The FDA nonclinical and statistical reviewers concur with the sponsor that no significant evidence of neoplasia related to BAY 59-7939 treatment was observed in CD-1 mice.

Methods

Doses:	0, 10, 20, and 60 mg/kg/day
Frequency of dosing:	Daily for up to 729 days
Dose volume:	10 mL/kg
Route of administration:	Orally by gavage
Formulation/Vehicle:	Ethanol/Sotutol HS 15/Tap Water (10/40/50 v/v/v)
Basis of dose selection:	A 13-week dose range finding study in the same strain of mice indicated that absorption of BAY 59-7939 saturated at 60 mg/kg
Species/Strain:	Mice (Mus musculus)/ Crl:CD-1(ICR) BR (b) (4)
Number/Sex/Group:	Main: 60 animals/sex/dose Satellite: 20 animals/sex/dose
Age:	6-7 weeks on first day of treatment
Animal housing:	Individual cages
Paradigm for dietary restriction:	None; food was administered ad libitum
Dual control employed:	None
Interim sacrifice:	None
Satellite groups:	Yes, for clinical laboratory and toxicokinetic measurements
Deviation from study protocol:	Not indicated

Observations and Results

Mortality

The animals were examined visually for mortality and morbidity twice daily, except on weekends and holidays when they were examined once daily.

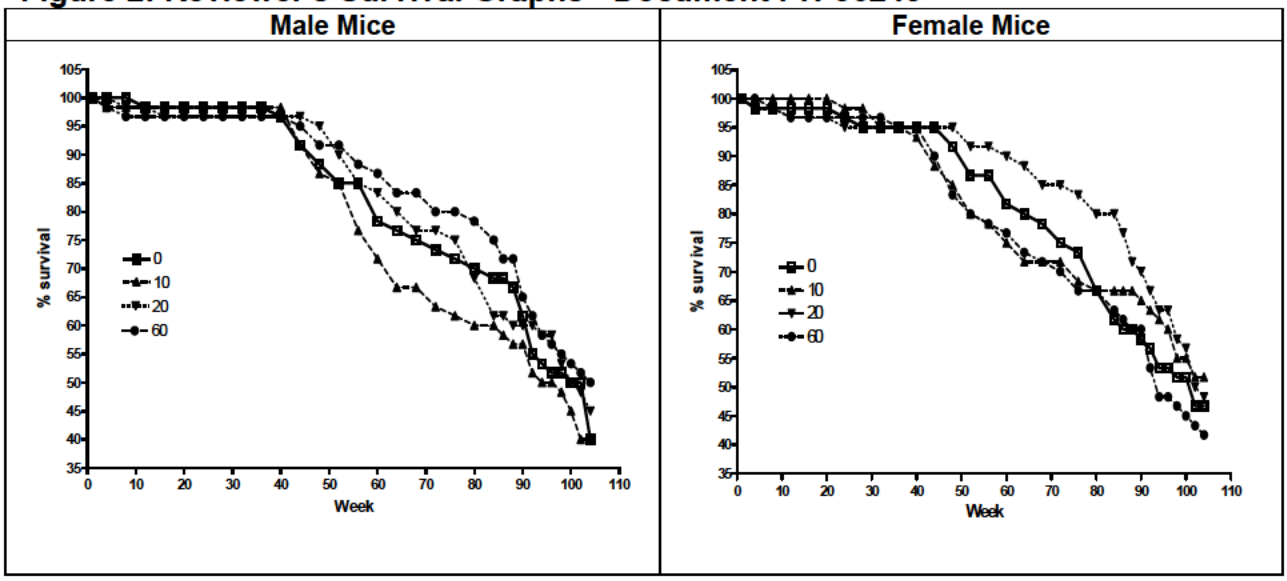
Although no statistically significant difference in mortality was observed (Table 1), the high dose males showed a slight decrease in mortality compared to the control males and the high dose females showed a slight increase in mortality compared to control females at the end of the study.

Table 1: Reviewer's Table Summarizing Mortality in Mice - Document PH-36243

	Males				Females			
Dose, mg/kg	**0**	**10**	**20**	**60**	**0**	**10**	**20**	**60**
Main animals								
Total number/group	60	60	60	60	60	60	60	60
Intercurrent deaths	37	36	34	31	32	29	31	36
% mortality	61.6	60	56.6	51.6	53.3	48.3	51.6	60
Satellite animals								
Total number/group	20	20	20	20	20	20	20	20
Intercurrent deaths	15	11	11	9	12	13	11	13
% mortality	75	55	55	45	60	65	55	65

The sponsor did not provide Kaplan-Meier survival graphs. The reviewer's graphs (Figure 2) below indicate survival was greater in the high dose male group compared to control male group beginning at Week 50. The survival in the mid dose female group was greater than that in the control female group during Weeks 50 to 104.

Figure 2: Reviewer's Survival Graphs - Document PH-36243



The pathologist noted two factors, malignant lymphoma and amyloidosis, that contributed to mortality of some decedents. The percentage of mid and high dose female decedents (30-47%) with moderate to severe amyloidosis in the duodenum, liver, kidneys and spleen was lower than the percentage of control female decedents (57-60%) with amyloidosis. However, the percentage of male decedents with amyloidosis generally was similar across dose groups, except in a few organs, such as the heart (control: 29%, high dose: 11%) and stomach (control 32%, high dose: 7%). The percentage of mid and high dose female decedents (17-23%) with malignant lymphoma was higher than the percentage of control female decedents (6.7%) with malignant lymphoma. Likewise, the percentage of high dose male decedents (21%) with malignant lymphoma was higher than the percentage of control male decedents (2.9%) with malignant lymphoma.

Clinical Examinations

Detailed clinical examinations were made once before the start of treatment and once weekly in all groups during treatment.

The most frequent clinical signs included increased urine excretion, piloerection, pallor, and increased girth (Table 2). The incidence of animals with increased girth was greater in the low, mid and high dose male groups and the mid and high dose female groups compared to the incidence in the control groups. However, the finding of increased girth did not correlate with the numbers of animals with palpable masses. Importantly, the incidence of signs associated with bleeding (vaginal, discolored feces, and blood in bedding) was low and did not show a dosage relationship.

Table 2: Reviewer's Summary of Clinical Findings - Document PH-36243

	Cumulative number of animals in main groups (in satellite groups)							
	Male mice				Female mice			
Finding/Dose (mg/kg)	0	10	20	60	0	10	20	60
Number of animals	60 (20)	60 (20)	60 (20)	60 (20)	60 (20)	60 (20)	60 (20)	60 (20)
Increased urine excretion	25 (14)	29 (9)	31 (8)	25 (12)	25 (11)	27 (10)	26 (9)	19 (11)
Piloerection	28 (15)	21 (15)	32 (10)	22 (13)	23 (8)	20 (8)	22 (3)	19 (10)
Pallor	23 (14)	27 (13)	24 (6)	23 (6)	20 (9)	24 (12)	22 (8)	18 (10)
Increased girth	7 (8)	19 (2)	17 (1)	16 (3)	12 (7)	12 (5)	16 (7)	17 (8)
Palpable masses	2 (1)	5 (0)	6 (0)	3 (1)	4 (2)	0 (0)	2 (0)	1 (0)

Body Weights

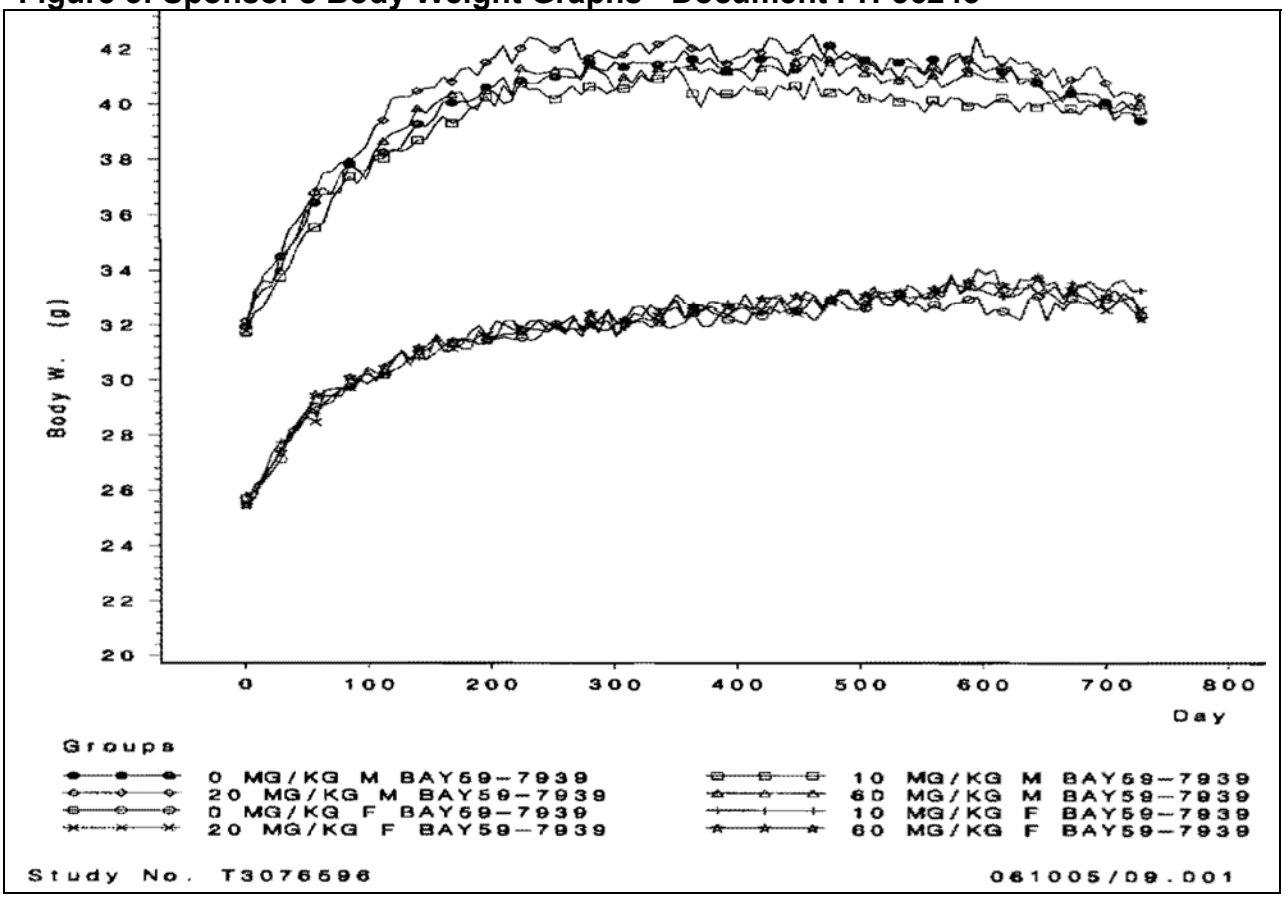
The animals in all groups were weighed on Day 1 of treatment and weekly up to scheduled necropsy and immediately before necropsy.

Body weight and body weight gain in the main study groups were not significantly affected by treatment with BAY 59-7939 (Table 3, Figure 3).

Table 3: Reviewer's Summary of Body Weights - Document PH-36243

Main Study	Dose (mg/kg)							
	Male mice				Female mice			
Day Dose (mg/kg)	0	10	20	60	0	10	20	60
Mean body weight (gm)								
1	31.9	31.7	32.1	31.7	25.7	25.8	25.5	25.5
92	37.6	37.1	38.1	37.6	30.0	29.9	30.1	29.9
183	40.1	39.8	41.3	39.9	31.1	31.7	31.3	31.4
274	41.0	40.3	41.6	40.8	31.8	31.9	31.7	31.6
365	41.6	40.4	42.0	41.4	32.4	32.6	32.5	32.7
456	41.3	40.1	42.2	41.7	32.4	32.6	33.2	32.9
547	41.4	40.0	41.3	40.6	32.7	33.0	33.2	33.0
631	40.7	39.7	41.4	40.9	32.1	33.6	33.1	33.3
722	39.6	40.0	40.4	39.8	32.5	33.2	32.9	33.0
729	39.4	39.7	40.2	40.0	32.3	33.2	32.5	32.2
Body weight gain (gm)								
Day 1 – Day 183	8.2	8.1	9.2	8.2	5.4	5.9	5.8	5.9
Day 1 – Day 365	9.7	8.7	9.9	9.7	6.7	6.8	7.0	7.2
Day 1 – Day 729	7.5	8.0	8.1	8.3	6.6	7.4	7.0	6.7

Figure 3: Sponsor's Body Weight Graphs - Document PH-36243



Food and Water Consumption

Food and water consumption were determined weekly for individual main group animals.

The sponsor's summary tables below (Table 4) indicate that no treatment effect was observed on group mean food or water intake relative to the control group.

Table 4: Sponsor's Summaries of Food and Water Intake - Document PH-36243

	Male mice					Female mice				
	Group means					Group means				
Dose mg/kg	Days	g/animal total	g/animal per day	g/kg body weight total	g/kg body weight per day	Days	g/animal total	g/animal per day	g/kg body weight total	g/kg body weight per day
Food intake										
0	728	4084	5.61	102692	141.06	728	3524	4.84	112076	153.95
10	728	3946	5.42	100668	138.28	728	3574	4.91	112556	154.61
20	728	4040	5.55	99998	137.36	728	3545	4.87	111668	153.39
60	728	3997	5.49	100588	138.17	728	3560	4.89	112214	154.14

Water intake									
0	728	5176	7.11	130443	179.18	728	5016	6.89	158952	218.34
10	728	4950	6.80	126301	173.49	728	4929	6.77	154867	212.73
20	728	4929	6.77	122348	168.06	728	4834	6.64	152356	209.28
60	728	4827	6.63	121896	167.44	728	4834	6.64	152640	209.67
Reviewer's modification of sponsor's tables										

Hematology

Blood samples for hematology were collected from 10 non-fasting satellite animals per group during weeks 50, 77, and 103. The following parameters were measured: hematocrit, hemoglobin concentration, erythrocyte count, erythrocyte morphology, reticulocyte count, mean cell hemoglobin (MCH), mean cell hemoglobin concentration (MCHC), mean cell volume, platelet count, total white cell count, and differential white cell count, including lymphocytes, eosinophils, monocytes, segmented neutrophils, banded neutrophils, and atypical lymphocytes. Additional blood samples taken for measurement of thromboplastin time (Hepato Quick) were collected from 10 satellite animals per group during weeks 51, 78, and 104 approximately 1 hour after drug administration. Samples for blood smears were collected satellite groups during weeks 49, 76, and 101 as well as from all animals killed in moribund condition and the surviving main study animals in the control and high dose groups near the end of the study.

The sponsor concluded that no treatment-related effects on red blood cell parameters were observed in either males or females at any dose of BAY 59-7939 after 49 and 76 weeks of treatment. Evaluation of hematology parameters at these timepoints is complicated by some control animals having values outside of the reference range (Table 5). For males on Day 347 the aberrant values were close to the reference range. For males on Day 535 and females on Day 347 the aberrant control value could be rejected on the basis of a statistical Q test (Dean and Dixon, 1951). For females on Day 536, two control females had values below the reference range and the concurrent control range for some parameters was narrower than the reference range. On Days 716 and 717 only the concurrent control values were available for comparison. Some values for individual animals in the treated groups were below the concurrent control range and some values were above the concurrent control range. However, the erythrocyte count, hemoglobin concentration, and hematocrit values were significantly lower for the high dose females and a dose relationship was evident. Mean values for these parameters for the high dose females on Days 347 and 536 were also lower, but were not statistically significant. The high dose males had non-statistically significant increases in these parameters on Days 535 and 716.

Although statistically significant increases were observed on Day 346 for MCH in the low dose males and for MCHC in the low and mid dose males, these increases were not considered toxicologically significant because of a lack of a dose response relationship with the high dose group. Increased leucocyte counts on Day 716 in the mid and high dose females were attributable to the very high values for single females (617 and 632) in each group. Platelet and differential blood counts showed no significant treatment-related effects.

Table 5: Reviewer's Summary - Hematology Results - Document PH-36243

			Mean (# outside reference range) [# outside concurrent control range]					
	Day	Dose Mg/kg	ERY 10e12/L	HB Gm/L	HCT L/L	MCH pg	MCHC Gm/L ERY	RETI %
Male mice	346	0	8.52	131 (1)	0.410 (1)	15.4 (2)	319 (1)	31
		Min., Max	7.32,10.08	**96**,153	0.339, 0.459	**13.3**, 16.4	**288**, 332	24, 35
		10	8.20	134	0.403	***16.4**** (2)[4]	***332****[5]	32 [4]
		20	8.58 [1]	139	0.414	16.2 (3)[3]	***335****(3)[6]	27
		60	8.51 [2]	137 (1)	0.416 (1) [1]	16.2 (3)[3]	330 (1)[3]	28
		2SD-	7.03	107	0.352	13.9	294	6
		2SD+	10.52	163	0.492	16.6	343	58
	535	0	7.55 (1){8.1}	113 (1){122}	0.393 (1){0.373}	14.9 (2)	283 (1) {293}	68 (1) {28}
		Min., Max	**2.61**, 9.63	**33**, 129	**0.180**, 0.438	**13.0,** 16.0	**190**, 307	21, **426**
		10	7.56 (1)	113 (2)[1]	0.390 (2)[2]	14.9 (1)	289	33 (4)[1]
		20	8.17 (2)	121 (1)[5]	0.419 (1)[4]	14.8 (3)[2]	288	35 (2)[1]
		60	8.49	127 [3]	0.434 (1)[5]	14.9	292	29 (2)[1]
		2SD-	6.56	102	0.343	14.2	266	21
		2SD+	9.80	150	0.490	16.7	341	35
	716[§]	0	7.72	115	0.381	14.7	298	49
		Min., Max	7.02, 8.76	105, 129	0.351, 0.435	14.1, 16.1	294, 308	26, 73
		10	7.64 [5]	115 [7]	0.373 [6]	14.9 [3]	303 [9]	55 [7]
		20	8.13 [5]	125 [4]	0.401 [3]	15.4 [3]	308 [6]	43 [3]
		60	8.78 [5]	128 [5]	0.421 [5]	14.6 [1]	305 [4]	46 [4]
Female mice	347	0	8.54 (1){8.82}	132 (2){138}	0.415 (1){431}	15.4 (1){15.7}	318 (1)	28
		Min., Max	**6.0**, 9.27	**75**, 147	**0.264**, 0.441	**12.7,** 16.4	**290,** 336	**15**, 41
		10	8.65 (1)[3]	138 (2)[3]	0.427 (2)[3]	16.0 (1)[2]	324	29 (2)[2]
		20	8.42 (2)[1]	133 (1)	0.413 (2)[2]	15.8 (1)[3]	320	27
		60	8.23 (4)[1]	128 (2)[2]	0.390 (4)[2]	15.4 (2)[2]	324 (2)[2]	33 (2)[2]
		2SD-	8.21	129	0.404	14.5	294	17
		2SD+	9.74	152	0.493	16.8	334	41
	536	0	7.98 (2)	119 (2)	0.411 (2)	15.0	290	45 (3)
		Min., Max	**5.19**, 9.84	**75**, 141	**0.267**, 0.486	14.4, 15.4	284, 300	17, **99**
		10	7.92	121 (1)	0.417 (1)	15.4 (1)[5]	291 (2)[3]	30
		20	7.75 (1)[1]	119 (2)	0.413 (3)	15.3 (1)[7]	286 (2)[3]	59 (1)[1]
		60	7.53 (2)	111 (2)	0.385 (5)	14.8 (2)[3]	288 (2)[3]	44 (2)
		2SD-	6.99	112	0.376	14.4	281	12
		2SD+	9.99	153	0.508	16.9	320	58
	717[§]	0	8.70	128	0.428	14.7	298	35
		Min., Max	7.38, 10.02	102, 141	0.345, 0.471	13.9, 15.5	286, 313	12, 58
		10	7.38 [3]	113 [2]	0.380 [2]	15.3 [3]	295 [1]	53 [3]
		20	7.06 [5]	104 [3]	0.354 [2]	14.5 [5]	283 [4]	87 [4]
		60	***5.82**** [5]	***86****[4]	***0.296**** [4]	14.6 [2]	286 [3]	74 [4]

* $p < 0.05$, HD = high dose, ERY = erythrocytes, HB = hemoglobin concentration, HCT = hematocrit,
MCV = mean cell volume, MCH = mean cell hemoglobin, MCHC = mean cell hemoglobin concentration,
RETI = % reticulocytes, 2SD+ = 2 standard deviations above the mean, 2SD- = 2 standard deviations below the mean
Min. = minimum, Max. = maximum, [§] Only concurrent control range available

Although the mean thromboplastin time was significantly prolonged in all treated groups of males and females on all sampling days (Table 6), examination of individual values indicates that not all members of each treated group had values above the normal range. Despite collection of blood samples at 1 hour after dose administration or close to the T_{max}, the maximum individual value on each sampling day was at most 1.8-fold the mean of the respective control group. Furthermore, the maximum individual value did not always occur in the highest dose group.

Table 6: Reviewer's Summary Thromboplastin Times - Document PH-36243

		Dose	HQUICK, sec			Reference range		Number	
	Day	Mg/kg	Mean	Min.	Max.	3SD-	3SD+	≤ 3SD+[†]	>3SD+[‡]
Male mice	345	0	18.0	16.3	20.6	13.3	22.7	10	0
		10	21.9**	19.5	25.0			7	3
		20	22.0**	19.7	27.2			8	2
		60	22.2**	18.3	16.7			6	4
	535	0	19.9	16.9	22.0	15.0	24.7	10	0
		10	24.0**	20.7	26.3			7	3
		20	24.1**	20.6	31.4			7	3
		60	23.1**	21.9	24.5			10	0
	716	0	20.0	16.7	23.5	16.7	23.5	5[§]	0
		10	23.2**	21.1	25.3			5[§]	4
		20	27.0**	23.4	35.6			1[§]	8
		60	24.4**	21.7	28.2			4	6
Female mice	347	0	19.5	16.2	21.4	15.1	23.8	10	0
		10	24.5**	20.4	33.6			5	5
		20	24.0**	18.1	28.5			3	7
		60	25.6**	21.9	29.6			3	7
	536	0	19.0	16.3	20.5	15.1	22.9	10	0
		10	23.2**	21.0	25.6			4	6
		20	23.6**	20.2	27.0			2	8
		60	24.2**	19.3	28.3			4	6
	717	0	19.8	17.6	21.1	17.6	21.1	8[§]	0
		10	25.6**	19.7	28.9			1[§]	6
		20	24.6**	22.2	27.0			0[§]	9
		60	24.9**	16.2	32.7			1[§]	6

[†] Number of values <3 standard deviations above mean, [‡] Number of values ≥ 3 standard deviations above mean, [§] Less than 10 animals/groups

Gross Pathology

The surviving satellite animals were sacrificed for scheduled necropsy during week 105. The surviving main study animals were sacrificed for scheduled necropsy during weeks 105-107. Animals found dead during the study were necropsied at the earliest opportunity. The animals were subjected to systematic examination and the organs listed in Table 7 were fixed in 10% neutral buffered formalin. The urinary bladder and lungs were initially inflated with 10% neutral buffered formalin prior to fixation by immersion.

Table 7: Reviewer's List of Organs Collected - Document PH-36243

Abnormal tissues	Kidneys	Seminal vesicles with coagulating glands
Adrenal glands	Larynx	Skeletal muscle (thigh)+
Aorta	Liver[#]	Skin (mammary area)
Brain (cerebrum, cerebellum, brain stem)	Lungs	Spinal cord (cervical, thoracic, lumbar)
Cecum	Lymph nodes (mandibular, mesenteric)	Spleen
Clitoral gland	Nasal cavity/nasopharynx	Sternum with bone marrow
Colon	Optic nerves	Stomach
Duodenum	Ovaries	Testes
Epididymides	Oviduct	Thymus
Esophagus	Pancreas	Thyroid with parathyroids
Eyes and eyelids	Peyers patches	Tongue
Extraorbital lacrimal glands	Pharynx	Trachea
Femur with joint	Pituitary	Ureters
Gall bladder[#]	Preputial gland	Urethra
Harderian glands	Prostate	Urinary bladder
Head with skull cap	Rectum	Uterus with cervix
Heart	Salivary glands (submandibular, sublingual and parotid)	Vagina
Ileum	Sciatic nerve	Zymbal's glands
Jejunum		

[#] Satellite animals were also examined by histopathology.

The principal gross lesions were nodules, cysts, dilations and discolorations (Table 8). Although nodules were found in many tissues, the highest incidence of nodules was in the liver, lung, ovaries, and uterus. The incidence of nodules was increased in the livers of mid and high dose males, the uteri of high dose females and the ovaries of mid and high dose females. Lower incidences of nodules were found in mesenteric lymph node, skin, spleen, heart, testes, thymus, body cavity and Harderian gland. The incidence of nodules was increased in spleen of high dose males, hearts of high dose males, skin of treated male groups, and mesenteric lymph node of mid and high dose male and females. The incidence of nodules in other tissues (adrenal glands, gallbladder, kidney, pancreas, pituitary, preputial glands, seminal vesicles, skull cap, sternum, and stomach) was limited to a single incidence per group. Higher incidences of cysts in the liver were observed in mid and high dose males compared to the incidence in the control group. Higher incidences of lung discoloration were observed in mid and high dose females compared to that in the control group. Higher incidence of gallbladder dilations were observed in the high dose females compared to that in the control group. Necropsy findings in the satellite animals confirm the increased cysts in the high dose male livers, increased nodules in the mid and high dose male livers, and increased nodules in the mid and high dose female ovaries.

Table 8: Reviewer's Summary of Necropsy Findings - Document PH-36243

		Male mice				Female mice			
	Dose, mg/kg	0	10	20	60	0	10	20	60
Number of animals	Main study (decedents)	60 (37)	60 (36)	60 (34)	60 (31)	60 (32)	60 (29)	60 (31)	60 (36)
Finding	Tissue								
Cyst	Liver	0	0	3 (2)	3	0	1	1	1
	Ovaries	-	-	-	-	18 (7)	24 (9)	18 (7)	18 (10)
Dilations	Gallbladder	2 (2)	0	2 (2)	0	6 (4)	5 (1)	6 (3)	**12 (8)**
	Uterus	-	-	-	-	0	0	2 (1)	2 (1)
Discoloration	Lung	4 (4)	4 (4)	6 (6)	7 (6)	6	6	**12**	**12**
Nodules	Liver	4 (4)	8 (4)	**12 (7)**	**12 (6)**	3 (2)	1 (0)	3 (3)	1 (1)
	Lung	6 (3)	10 (4)	5 (2)	8 (4)	5 (1)	3	**6 (3)**	**6 (1)**
	Ovaries	-	-	-	-	2 (2)	2 (2)	**5 (3)**	**4 (2)**
	Uterus	-	-	-	-	4 (3)	3	5 (3)	**9 (7)**
	Testes	0	0	3 (1)	1	-	-	-	-
	Spleen	0	1 (1)	0	**3** (1)	0	0	0	0
	Thymus	1 (1)	2 (2)	0	2 (2)	2 (2)	3 (1)	1 (1)	1 (1)
	Lymph node mesenteric	0	1 (1)	**3 (1)**	**2 (2)**	1	1 (1)	**2 (1)**	**2**
	Skin	0	**2 (2)**	**2 (2)**	**2 (2)**	1	0	1 (1)	1
	Body cavity	1 (1)	0	0	0	2 (2)	0	3 (1)	0
	Harderian gland	2	0	1	1 (1)	2	0	0	0
	Heart	0	0	1 (1)	**2** (2)	0	0	0	0
Satellite animals	Number	23	24	26	29	28	31	29	24
Cyst	Liver	0	0	**1**	**3**	0	1	1	1
	Ovaries	-	-	-	-	11	18	11	8
Dilations	Gallbladder	0	0	0	0	2	4	3	4
Discoloration	Lung	0	0	0	0	0	2	2	0
Nodules	Lung	3	6	3	4	4	3	3	5
	Liver	0	4	**5**	**6**	1	1	0	0
	Ovaries	-	-	-	-	0	0	**2**	**2**
	Uterus	-	-	-	-	2	3	3	0

Organ Weights

The following organs were weighed before fixation: adrenals, brain, kidneys, liver, spleen, and testes.

Sponsor concluded that no treatment-related effect was observed on organ weights (Table 9). However, the reviewer notes a slight increase in absolute and relative liver weights in the high dose male group. This is best illustrated by a comparison of the median liver weights. Some correlation of liver weight with the presence of nodules and cysts exists in that 13 of the 19 males for whom liver weights were available had liver weights above the median of the group.

Table 9: Sponsor's Summaries of Organ Weights - Document PH-36243

Dose mg/kg	Body W. G	Brain mg	Adrenals mg	Liver mg	Spleen mg	Kidneys mg	Testes mg	Median Liver Weight
Mean Absolute Organ Weights								
m	Terminal Sacrifice							
0	39	497	8	2331	106	780	212	2297
10	40	512	8	2480	120	783	203	2403
20	40	501	7	2303	137	730	217	2224
60	40	507	7	2579	137	771	215	2431
f	Terminal Sacrifice							
0	33	508	10	1962	146	509		1847
10	33	496	9	1901	120	477		1759
20	33	488 +	8	1920	122	487		1795
60	33	497	9	1904	145	486		1872
Mean Relative Organ Weights								
Dose mg/kg	Body W. G	Brain mg/100g	Adrenals mg/100g	Liver mg/100g	Spleen mg/100g	Kidneys mg/100g	Testes mg/100g	
m	Terminal Sacrifice							
0	39	1273	20	5939	273	1996	547	5724
10	40	1291	19	6252	299	1967	513	5894
20	40	1264	18	5690	349	1812	547	5583
60	40	1288	17	6524	343	1947	544	6331
f	Terminal Sacrifice							
0	33	1571	30	6001	439	1561		5684
10	33	1505	26	5765	360	1439		5301
20	33	1497	25	5803	369	1480		5551
60	33	1537	27	5861	452	1494		5692

Histopathology

Tissue samples from all main study animals were dehydrated, embedded in Paraplast, sectioned, and stained with hematoxylin and eosin. All tissues listed in Table 7 and gross abnormalities identified at macroscopic examination from all animals sacrificed at the end of the scheduled treatment period and from all animals killed or dying during the study were examined by histology. In addition, the liver and gallbladder were examined microscopically from animals in all satellite groups.

Peer Review

Peer review included examination of the liver, pituitary glands and mesenteric lymph nodes as well as all tumors and pre-neoplastic lesions of all groups. In addition, approximately 25% of frequent lesions and all slides of six animals per sex from the high dose group were also examined.

Neoplastic Lesions

The incidences of the most notable tumors in the mouse carcinogenicity study are summarized in Table 10 below. The sponsor's listing of tumor incidences is in Appendix 3. The statistical evaluations of the sponsor and the FDA statistician are in Appendix 4 and 5, respectively. Historical control data provided by the sponsor are in Appendix 9.

Consistent with the increase in liver nodules macroscopically, hepatocellular tumors (adenoma and carcinoma) increased with BAY 59-7939 dosage in the males, but not in the females. The sponsor's evaluation of hepatocellular adenoma and hepatocellular carcinoma indicated p values in the trend test of 0.052 and 0.046, respectively. The FDA statistician's evaluation of hepatocellular adenoma and hepatocellular carcinoma indicated p values in the trend test of 0.128 and 0.143, respectively. If the hepatocellular tumors are combined, the statistical evaluations by the sponsor and the FDA statistician indicated p values in the trend test (p_t) of 0.0076 and 0.036, respectively. Since hepatocellular tumors are common tumors in mice, no p value attains the significance level ($p < 0.005$) necessary for the tumors to be considered positive, according to current CDER guidance. Furthermore, the incidence of either basophilic foci or total foci of alterations in the liver was similar across control and treated groups. The incidences of hepatocellular tumors for the male treated groups in the current study are within historical ranges.

The incidences of a few other tumors were increased in the higher dose groups compared to those in the control groups. The tumors with overall incidences greater than 1% in the [redacted] (b) (4) listing (2003) for spontaneous tumors in CD-1 mice include histocytic sarcoma in the high dose females (incidence of 1.6%, sponsor's p_t = 0.176, FDA p_t = 0.174), malignant lymphoma in the high dose males (incidence of 4.5%, sponsor's p_t = 0.136) and in mid- and high dose females (incidence of 9.9%, sponsor's p_t = 0.071). The tumors with overall incidences less than 1% in the [redacted] (b) (4) listing (2003) for spontaneous tumors in CD-1 mice include ovarian cystadenoma in the high dose females (incidence of 0.74%, sponsor's p_t = 0.032, FDA p_t = 0.055), testicular Leydig cell tumor in mid and high dose males (incidence of 0.85%, sponsor's p_t = 0.070) and uterine hemangiosarcoma in the high dose females (incidence of 0.47%, sponsor's p_t = 0.086, FDA p_t = 0.058). In RITA historical control database, the mean incidences of testicular Leydig cell tumor and ovarian cystadenoma are 3.2% and 1.7%, respectively. However, no p value for these tumors attained the significance level of $p < 0.025$ required for even a rare tumor to be considered positive. In addition, the incidences are within historical ranges.

Table 10: Reviewer's Summary of Neoplastic Findings – Document PH-36243

Mouse Carcinogenicity Study		BAY 59-7939 Dose level (mg/kg/day)							
Neoplastic Findings†		Male				Female			
All main study animals		0	10	20	60	0	10	20	60
Organ/Tissue Finding	#/group	60	60	60	60	60	60	60	60
Liver	#	58	60	58	57	58	60	59	58
Hepatocellular Adenoma – B	#	0	3	**4**	**4**	0	0	0	0
(RITA range: Male, 0-21.7%) (p_t = 0.053)	%	0	5.0	6.9	7.0	0	0	0	0
(CR maximum: Male, 28%)	p_e				0.057				
Hepatocellular Adenocarcinoma – M	#	2	4	**7**	**7**	1	1	0	0
(RITA range: Male, 4-22%) (p_t = 0.046)	%	3.5	6.7	12.1	12.3	1.7	1.7	0	0
(CR maximum: Male, 16%)	p_e				0.077				
Hepatocellular Adenoma + Adenocarcinoma	#	2	7	**11**	**11**	1	1	0	0
(RITA range: 8.0-36.1%) (p_t = 0.0076)	%	3.5	11.7	19.0	19.3	1.7	1.7	0	0
	p_e								
Systemic tumors	#	58	60	58	57	58	60	59	58
Histocytic sarcoma - M (F: p_t = 0.176)	#	2	0	0	2	3	3	4	**5**
(CR maximum: Male: 8.0, Female: 18.3%)	%	3.5	0	0	3.5	5.2	5.0	6.8	8.6
Lymphoma - M (M: p_t = 0.111; F: p_t = 0.059)	#	3	3	3	**7**	4	4	**11**	**7**
(RITA range: Male: 0-17.6%, Female: 4-43.3%)	%	5.2	5.0	5.2	12.3	6.9	6.7	18.6	12.1
(CR maximum: Male: 21.7%, Female: 50%)	p_e				0.14			0.05	0.26

Mouse Carcinogenicity Study		BAY 59-7939 Dose level (mg/kg/day)							
Neoplastic Findings†		Male				Female			
All main study animals		0	10	20	60	0	10	20	60
Organ/Tissue Finding	#/group	60	60	60	60	60	60	60	60
Ovaries	#	0	0	0	0	54	54	54	63
Cystadenoma - B (p_t = 0.033)	#	-	-	-	-	0	0	1	**2**
(RITA range: 0-5.0%) (CR maximum: 7.3%)	%	-	-	-	-	0	0	1.8	3.5
	p_e								0.248
Luteoma - B	#	-	-	-	-	0	0	2	1
(CR maximum: 4.0%)	%	-	-	-	-	0	0	3.5	1.8
Granulosa cell - B	#	-	-	-	-	0	0	2	0
(CR maximum: 2.9%)	%	-	-	-	-	0	0	3.5	0
Granulosa cell - M	#	-	-	-	-	0	0	1	0
(CR maximum: 1.7%)	%	-	-	-	-	0	0	1.7	0
Granulosa cell - combined	#	-	-	-	-	0	0	3	0
	%					0	0	5.2	0
Testes	#	57	60	58	57	0	0	0	0
Granulosa cell - B	#	0	0	1	0	-	-	-	-
	%	0	0	1.7	0	-	-	-	-
Leydig cell – B (p_t = 0.07)	#	0	2	**3**	**3**	-	-	-	-
(RITA range: Male, 0-10%)	%	0	3.3	5.2	5.3	-	-	-	-
Vascular system									
Hemangiosarcoma									
Liver	#	1/58	2/60	0	2/57	0	0	1/59	0
	%	1.7	3.3	0	3.5	0	0	1.7	0
Spleen	#	1/58	0	0	0	1/58	0	1/59	0
	%	1.7	0	0	0	1.7	0	1.7	0
Skin	#	0	0	0	0	1/58	0	0	0
	%	0	0	0	0	1.7	0	0	0
Uterus (p_e = 0.248, Trend p_t = 0.086)	#	-	-	-	-	0	0	1/58	**2**/58
(CR maximum: 4.1%)	%	-	-	-	-	0	0	1.7	3.5
Body cavity	#	0	0	0	0	0	0	1/4	0
	%	0	0	0	0	0	0	N<10	0
Combined hemangiosarcomas	#	2	2	0	2	2	0	4	2
	%	3.4	3.3	0	3.5	3.4	0	>6.8	3.5
Hemangioma									
Spleen	#	0	0	1/58	0	0	0	0	0
	%	0	0	1.7	0	0	0	0	0
Skin	#	0	0	0	1/57	0	0	0	0
	%	0	0	0	1.8	0	0	0	0
Uterus	#	-	-	-	-	2/58	0	1/58	0
(CR maximum: 4.6%)	%	-	-	-	-	3.5	0	1.7	0
Spinal Cord	#	0	1/60	0	0	0	0	0	0
	%	0	1.7	0	0	0	0	0	0
Combined hemangiomas	#	0	1	1	1	2	0	1	0
	%	0	1.7	1.7	1.8	3.5	0	1.7	0
Total hemangiosarcomas + hemangiomas	#	2	3	1	3	4	0	5	2
	%	3.4	5.0	1.7	5.3	7.0	0	>8.5	3.5

† All p values are from the sponsor's study report for T3076596. p_e = Exact p value, p = Trend p value, RITA(Registry of International Toxicology Animal) Data, 2009, [redacted] (b) (4), March 2005

Non Neoplastic Lesions

The study pathologist considered the significant increases in biliary cysts in the liver of males and dilation/atrophy in the preputial gland to be background variation (Table 11). The pathologist noted non-statistically significant increases in ovarian hemorrhages often associated with large cyst formation in the treated females groups and a statistically significant increase in ovarian pigment deposits. Likewise, extramedullary hematopoiesis in the spleen and liver increased in incidence and severity in the treated male groups and reached statistical significance for the mid-dose group. The pathologist considered the observations of hemorrhage, pigment deposits and hematopoiesis to be related to the pharmacodynamic effect of BAY 59-7939.

Although the reviewer agrees that these observations could be related to the anti-coagulant effects of BAY 59-7939, the reviewer notes that the incidence of hemorrhage in other organs did not always increase with dose. In the urinary bladder, the incidence of hemorrhage decreased with dose. Furthermore, the incidence of hemorrhage across all organs did not increase with dose. However, the incidence of pigment deposits increased in male liver, female ovaries, and female lungs. Also, the incidence of pigment deposits across all organs did increase in the mid and high dose males and the high dose females.

Table 11: Reviewer's Summary Non-neoplastic Lesions – Document PH-36243

Mouse Carcinogenicity Study			BAY 59-7939 Dose level (mg/kg/day)							
	All animals		Male				Female			
			0	10	20	60	0	10	20	60
Organ/Tissue	Finding	#/group	60	60	60	60	60	60	60	60
Liver		#	58	60	58	57	58	60	59	58
	Amyloidosis	#	25	23	19	25	22	28	14	19
		%	43.1	38.3	32.8	43.9	37.9	46.7	23.7	32.8
	Basophilic foci	#	2	2	2	4	0	0	0	1
		%	3.4	3.4	3.4	6.8	0	0	0	1.7
	Clear cell foci	#	3	1	1	1	1	0	0	0
		%	5.2	1.7	1.7	1.7	1.7	0	0	0
	Eosinophilic foci	#	0	0	4	1	0	0	0	1
		%	0	0	6.8	1.7	0	0	0	1.7
	Total foci	#	5	3	7	6	1	0	0	2
		%	8.6	5.0	12.1	10.5	1.7	0	0	3.4
	Biliary cysts	#	0	0	**3**	**3**	0	1	2	2
		%	0	0	5.2	5.2	0	1.7	3.4	3.4
					p = 0.012					
	Increased hemopoiesis	#	0	1	**5**	3	7	3	4	4
		%	0	1.7	8.6	5.2	12.0	5.2	6.8	6.8
					p = 0.022					
	Increased pigment deposit	#	2	1	3	4	0	2	0	1
		%	3.5	1.7	5.2	7.0	0	3.3	0	1.7
	Focal necrosis	#	10	9	13	12	11	10	8	10
		%	17.2	15.0	22.4	21.1	19.0	16.7	13.6	17.2
	Diffuse necrosis	#	0	1	0	0	0	0	0	0
		%	0	1.7	0	0	0	0	3.4	0
	Single cell necrosis/degeneration	#	5	5	2	8	1	3	0	1
		%	8.6	8.3	3.5	14.0	1.7	5.0	0	1.7
	Total necrosis	#	15	15	15	20	12	13	8	11
		%	25.8	25.0	25.8	35.0	20.6	21.6	13.6	19.0
Gall bladder		#	58	60	58	57	58	60	59	58
	Amyloidosis	#	1	1	0	1	3	4	0	1
		%	1.8	1.8	0	1.9	5.4	6.8	0	1.9
	Dilation	#	2	1	3	0	5	5	6	10
		%	3.5	1.8	5.5	0	8.9	9.5	10.3	18.5
Urinary bladder			57	60	57	57	58	59	57	57
	Hemorrhage		4	1	0	1	0	0	0	0
			7.0	1.7	3.5	3.5	0	0	0	0
Ovaries		#	-	-	-	-	57	60	57	57
	Amyloidosis	#	-	-	-	-	11	17	5	9
		%	-	-	-	-	19.3	*28.3*	8.8	15.9
	Hemorrhage	#	-	-	-	-	4	10	10	8
		%	-	-	-	-	7.0	16.7	17.5	14.0
	Pigment deposits	#	-	-	-	-	0	0	**1**	**3**
		%	-	-	-	-	0	0	1.8	5.3
		p							p = 0.012	
Testes		#	57	60	58	57	-	-	-	-
	Hemorrhage	#	0	1	1	0	-	-	-	-
		%	0	1.7	1.7	10	-	-	-	-
	Leydig cell hyperplasia, diffuse	#	17	17	21	19	-	-	-	-
		%	29.9	28.3	36.7	33.0	-	-	-	-
	Leydig cell hyperplasia, focal	#	1	0	1	1	-	-	-	-
		%	1.8	0	1.7	1.8	-	-	-	-

Mouse Carcinogenicity Study		BAY 59-7939 Dose level (mg/kg/day)							
All animals		Male				Female			
		0	10	20	60	0	10	20	60
Organ/Tissue Finding	#/group	60	60	60	60	60	60	60	60
Total Leydig cell hyperplasia	#	18	17	22	20	-	-	-	-
	%	31.6	28.3	37.9	35.0	-	-	-	-
Epididymides	#	58	60	58	57	-	-	-	-
Hemorrhage	#	0	1	0	1	-	-	-	-
	%	0	1.7	0	1.8	-	-	-	-
Oligospermia	#	2	6	5	7	-	-	-	-
	%	3.5	10.0	8.6	12.3	-	-	-	-
Prostate	#	58	60	58	57	-	-	-	-
Hemorrhage	#	1	0	0	0	-	-	-	-
	%	1.8	0	0	0	-	-	-	-
Lymphoid infiltrates	#	3	6	4	6	-	-	-	-
	%	5.3	10.2	6.9	10.5	-	-	-	-
Preputial gland	#	58	60	58	57	-	-	-	-
Dilation/atrophy	#	43	43	**47**	**50**	-	-	-	-
	%	74.1	71.7	81.0	87.7	-	-	-	-
	p			p = 0.019					
Lungs	#	58	60	58	57	57	60	59	58
Alveolar hemorrhage	#	5	8	6	7	5	3	3	8
	%	8.6	13.3	10.3	12.3	8.8	5.0	5.1	
Pigment deposits	#	1	1	1	0	1	0	0	3
	%	1.7	1.7	1.7	0	1.8	0	0	5.2
Urinary bladder	#	57	60	57	57	58	59	57	57
Hemorrhage	#	4	1	2	2	0	0	0	0
	%	7.0	1.7	3.5	3.5	0	0	0	0
Stomach	#	57	60	58	55	57	60	56	58
Amyloidosis	#	11	13	5	2	9	15	5	7
	%	29.3	21.7	8.6	3.6	15.8	25.0	8.9	12.1
Hyperplasia, squamous cell	#	3	1	5	5	6	4	2	0
forestomach	%	5.3	1.7	8.6	9.1	10.5	6.7	3.6	0
Hyperplasia, fundic mucosal	#	11	18	20	14	8	12	10	12
	%	19.3	30.0	34.5	25.5	14.0	20.0	17.9	20.7
Pancreas	#	57	60	58	55	57	60	56	58
Amyloidosis	#	1	1	0	0	2	1	2	0
	%	1.9	1.7	0	0	3.5	1.7	3.5	0
Heart	#	58	60	58	57	58	60	59	58
Amyloidosis	#	10	12	5	3	6	7	4	6
	%	17.2	20.0	8.6	5.3	10.3	11.7	6.8	10.3
Cardiomyopathy	#	6	7	8	8	5	6	3	4
	%	10.3	11.7	13.8	14.0	8.6	10.0	5.1	6.9
Spleen	#	58	60	58	57	58	60	59	58
Amyloidosis	#	27	28	24	28	25	27	20	22
	%	46.6	46.7	41.4	49.1	43.1	45.0	33.9	37.9
Pigment deposits	#	0	2	2	1	0	1	1	1
	%	0	3.3	3.5	1.8	0	1.7	1.7	1.7
Increased hemopoiesis	#	6	13	**14***	10	10	11	14	9
	%	10.3	21.7	24.1	17.5	17.2	18.3	23.7	15.5
				P = 0.042					
All organs Hemorrhage/hematoma	#	10	9	9	6	13	13	14	11
	%	17.6	15.1	15.6	10.7	22.7	21.7	24.4	19.1
Pigment deposits	#	3	4	7	8	3	4	4	8
	%	5.2	6.7	12.1	14.1	5.2	6.7	6.9	13.9

Toxicokinetics

Blood samples were obtained and plasma was prepared from three satellite animals/sex/group at 0.5, 1, 2, 4, 7, and 24 hours after dosing on Days 1 and 361 of treatment. On Day 710, blood samples were obtained from three satellite animals/sex/group at 0.5 hour after dosing. After addition of an internal standard and protein precipitation with acetonitrile, analysis of BAY 59-7939 was performed using a validated LC-MS/MS assay with a lower limit of quantification of 0.002 mg/L. The

concentration of BAY 59-7939 in control animals was below the limit of quantification on all three sampling days.

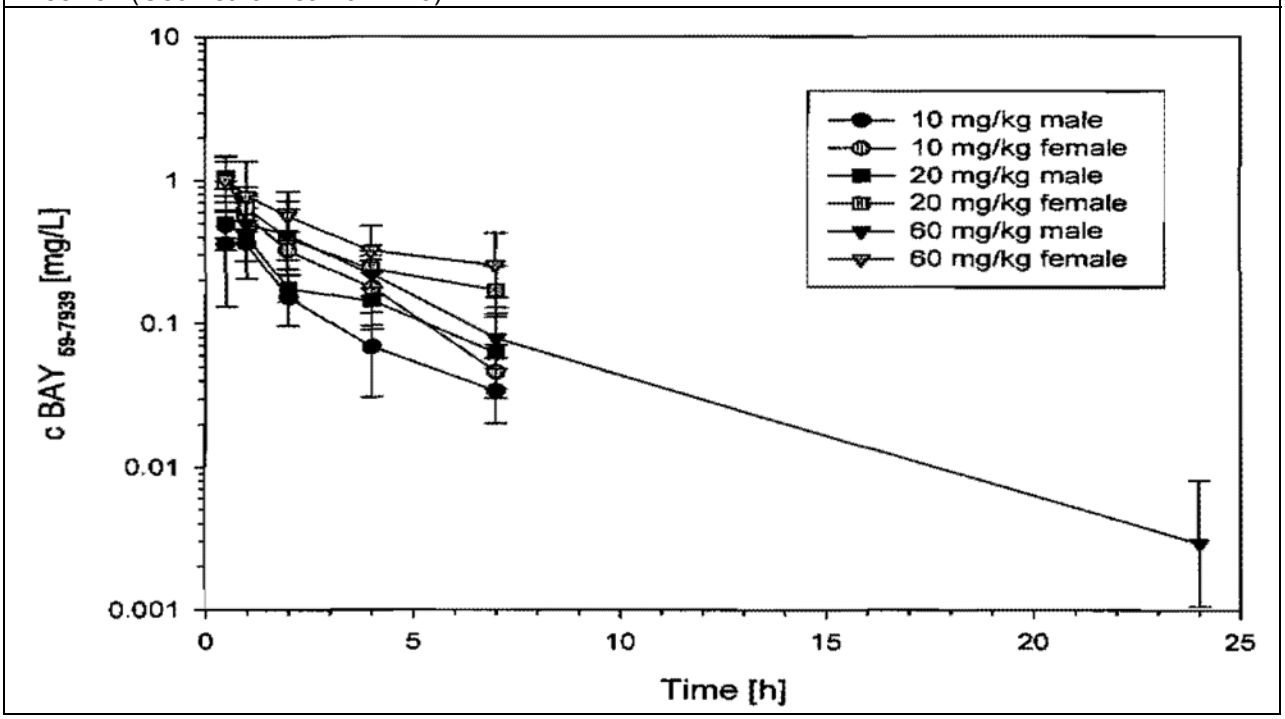
The t_{max} was 0.5 - 1 hour, indicating rapid absorption of BAY 59-7939. Exposure to BAY 59-7939 on Day 1 was only slightly lower in males than in females; however, exposure during Week 52 was lower in males by a factor of 0.5 to 0.8 (Table 12). Although exposure increased with dose in both males and females, the increase was less than dose-proportional. Exposure decreased with repeated dosing for 52 weeks by a factor of 0.3 to 0.5 in males and 0.65 to 0.7 in females. Plasma concentrations at 0.5 hour after dosing during Week 102 were not significantly different from plasma concentrations at 0.5 hour after dosing during Week 52. Since the human exposure at the highest recommended daily dose of 20 mg/day was 3.3 mg*hr/L, the exposure multiples for male and female mice were 0.76 and 1.28 times, respectively, the human exposure based on total AUC values. These multiples of the human exposure for male and female mice increase to 1.0 and 1.6 based on unbound AUC values.

Table 12: Reviewer's Summary of Toxicokinetics in Mice - Document PH-36243

Pharmacokinetic Parameters – Day 1 versus Week 52							
		Male			Female		
Dose (mg/kg)		10	20	60	10	20	60
Day 1							
$AUC_{(0-24)}$	mg*hr/L	2.47	4.95	4.79	2.61	NC	6.15
C_{max}	mg/L	0.806	1.25	1.38	1.13	1.28	2.33
t_{max}	hr	0.5	0.5	1.0	0.5	0.5	0.5
Week 52							
$AUC_{(0-24)}$	mg*hr/L	0.98	1.54	2.52	1.71	3.29	4.24
C_{max}	mg/L	0.363	0.503	1.09	0.568	0.963	1.02
t_{max}	hr	1.0	0.5	0.5	1.0	0.5	0.5
Plasma concentrations (mg/L) at 0.5 hour after drug administration							
		Male			Female		
Dose (mg/kg)		10	20	60	10	20	60
Day 1	Mean (SD)	0.826 (0.222)	1.26 (0.129)	1.29 (0.122)	1.16 (0.298)	1.34 (0.457)	2.35 (0.318)
Week 52	Mean SD	0.469 (0.313)	0.536 (0.237)	1.11 (0.241)	0.495 (0.110)	1.03 (0.495)	1.07 (0.404)
Week 102	Mean SD	0.321 (0.119)	0.446 (0.031)	0.809 (0.164)	0.739 (0.220)	0.706 (0.271)	0.956 (0.316)

Figure 4: Sponsor's Concentration-Time Profiles in Mice - Document PH-36243

Plasma concentrations of BAY 59-7939 versus time after oral administration to male and female mice in Week 52 (Geometric mean of n = 3)



Dosing Solution Analysis

Prior to the start of the study, test article formulations at concentrations above 6 mg/mL and below 1 mg/mL were shown to be homogenous and stable for 15 days at room temperature. During the study test article formulations were prepared as needed based on the 15 day stability. Analysis of the dose formulations on eleven days throughout the study showed the formulations were homogenous and the measured concentrations ranged from 84% to 114% of nominal (Table 13).

Table 13: Reviewer's Summary of Formulation Analysis - Document PH-36243

	Nominal concentration, mg/mL		
	1	2	6
Number	11	11	11
Mean recovery, %	101.2	103.5	101.1
SD	3.7	4.6	6.0
Maximum	107	114	107
Minimum	93	97	84

Study title: BAY 59-7939: Carcinogenicity Study in Wistar Rats (2 Years Administration by Gavage)

Document no.:	PH-36242
Study no.:	T8076429 (AT05916)
Study report location:	EDR, Module 4
Conducting laboratory and location:	Bayer Schering Pharma AG GDD-GED Toxicology, Wuppertal Germany
Date of study initiation:	September 6, 2006
GLP compliance:	Indicated
QA statement:	Present
Drug, lot #, and % purity:	BAY 59-7939 (rivaroxaban) a) Lot BXO23BS, purity 100% b) Lot BXA18UX, purity > 99.7%
CAC concurrence - protocol:	On August 1, 2006, the Executive CAC did not concur with the sponsor's proposed doses (b) (4) and instead recommended doses of 0, 10, 20, and 60 mg/kg/day by oral gavage, based on saturation of absorption. The Executive CAC meeting minutes are in Appendix 1
CAC concurrence – study results:	On April 15, 2011, the Executive CAC discussed the study results and concurred that the study was adequate and there were no clear drug-related neoplasms. The Executive CAC meeting minutes are in Appendix 2.

Key Study Findings

Introduction

Wistar rats received oral doses of BAY 59-7939 for up to 104 weeks. At dosages of 10, 20, and 60 mg/kg/day, the mean $AUC_{(0\text{-}24h)}$ was 13.4, 15.4, and 20.3 mg.hr/L in males and 34.7, 47.5, and 48.2 mg.hr/L in females, respectively, during week 54 of treatment.

Summary of Non-neoplastic Findings

Consistent with the pharmacodynamic action of BAY 59-7939, the mean values for thromboplastin time for all treated groups at 1 hour after dosing on all sampling days were significantly greater than those for the control groups. Likewise, the incidence of increased pigment deposition increased in some organs and across all organs in the high dose groups. The incidence of valvular fibrosis in the heart increased with dose in both males and females and the incidence was statistically significant in females ($p = 0.0048$) by the trend test.

Adequacy of Carcinogenicity Study

The rat carcinogenicity study used the doses (0, 10, 20 and 60 mg/kg/d) that were recommended by the Executive CAC. The study length was acceptable since the rats were treated for up to 104 weeks. No treatment-related effect on mortality was observed.

Appropriateness of Test Model
The Wistar strain is an appropriate model because this strain is known to be responsive to known carcinogens and historical control data are available. The most predominant form of BAY 59-7939 in both rat and human plasma was unchanged compound. The proposed metabolic pathway of BAY 59-7939 in rats and man is similar involving structural cleavage and hydroxylation, although a minor metabolite, M-7, is not formed in rats.

Summary of Tumor Findings
Squamous cell carcinoma was present in the clitoral gland of two high dose females. Statistical evaluations by the sponsor and the FDA statistician indicated p values in the trend test (pt) of 0.030 and 0.070, respectively. Neither p value attain the significance in the trend test ($p_t < 0.025$) required for this finding of a rare tumor to be considered positive, according to current CDER guidance. Additionally, squamous cell papilloma was present in both a control female and a high dose female. Although the incidence of squamous cell carcinoma was statistically significant (p = 0.03), squamous cell papilloma was present in both a control female and a high dose female. Therefore, statistical significance for squamous cell carcinoma plus papilloma is lacking.

Adrenal cortical adenomas were present only in treated animals with the incidence significantly higher in the mid and high dose females (p = 0.012, trend test). No adrenal adenocarcinoma was found in any group. Since adrenal cortical adenoma is a common tumor, the p value for females did not attain the significance in the trend test (p< 0.005) required for this common tumor to be considered positive.

Evaluation of Tumor Findings
The nonclinical and statistical reviewers concur with the sponsor that no significant evidence of neoplasia related to BAY 59-7939 treatment was observed in Wistar rats.

Methods

Doses:	0, 10, 20, and 60 mg/kg/day
Frequency of dosing:	Daily for up to 732 days
Dose volume:	10 mL/kg
Route of administration:	Orally by gavage
Formulation/Vehicle:	Ethanol/Sotutol HS 15/Tap Water (10/40/50 v/v/v)
Basis of dose selection:	A 13-week dose range finding study in the same strain of rats indicated that absorption of BAY 59-7939 saturated at 60 mg/kg
Species/Strain:	Rat (Rattus norvegicus)/(Hsd Cpb:WU, Wistar) [redacted] (b) (4)
Number/Sex/Group:	50
Age:	6-7 weeks at study initiation
Animal housing:	2-3 rats/cage
Paradigm for dietary restriction:	None; food was administered ad libitum
Dual control employed:	None

Interim sacrifice: None
Satellite groups: Yes, for clinical laboratory and toxicokinetic measurements
Deviation from study protocol: Not indicated

Observations and Results

Mortality

The animals were examined visually for mortality and morbidity twice daily, except on weekends and holidays when they were examined once daily.

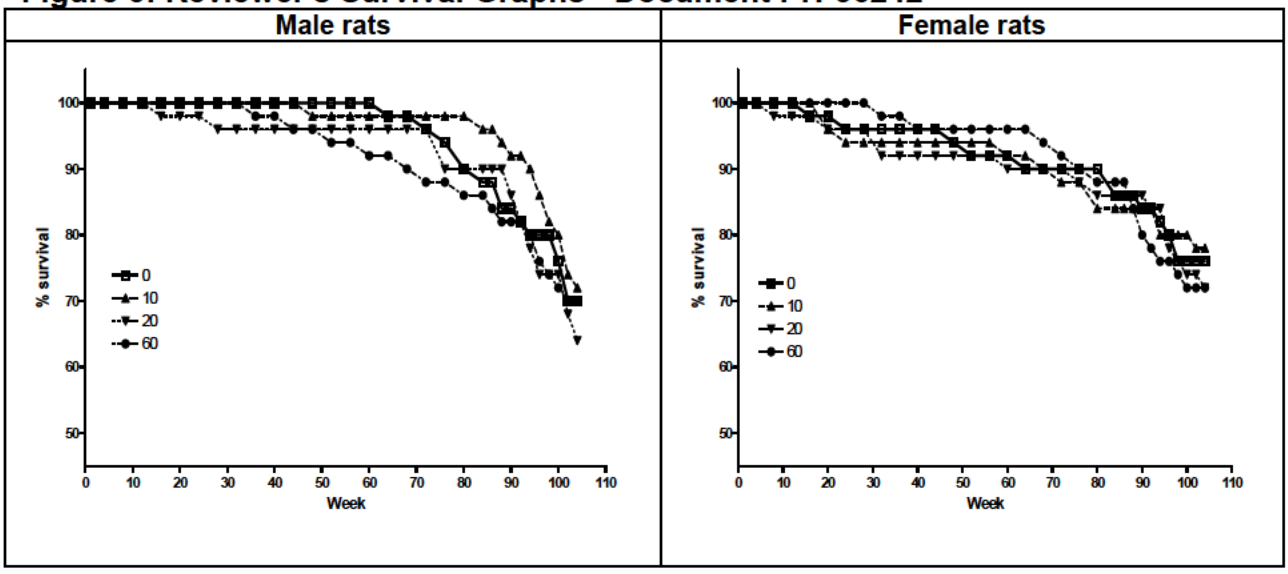
Mortality was not related to treatment (Table 14).

Table 14: Reviewer's Summary of Rat Mortality – Document PH-36242

	Males				Females			
Dose, mg/kg	**0**	**10**	**20**	**60**	**0**	**10**	**20**	**60**
Main animals								
Total number/group	50	50	50	50	50	50	50	50
Intercurrent deaths	15	14	19	16	12	11	14	14
% mortality	30	28	38	32	24	22	28	28
Satellite animals								
Total number/group	20	20	20	20	20	20	20	20
Total intercurrent deaths	5	12	5	9	4	10	7	6
% total mortality	25	60	25	45	20	50	35	30
Deaths during blood sampling	0	3	1	0	1	1	0	1

The sponsor did not provide Kaplan-Meier survival graphs. The reviewer's graphs (Figure 5) below indicate survival was reduced in the high dose male group compared to control male group during Weeks 40 to 80. The survival in the female groups was similar across all dose groups.

Figure 5: Reviewer's Survival Graphs - Document PH-36242



The pathologist noted that chronic progressive nephropathy contributed to mortality of the male decedents and gross lesions in the uterus or mammary gland contributed to the mortality of female decedents.

Clinical Signs
Detailed clinical examinations were made once before the start of treatment and once weekly in all groups during treatment.

The most frequent clinical signs included piloerection, hair loss, bloody eye, and palpable masses (Table 15). Although the incidence of main study animals with palpable masses was slightly higher in the mid and high dose male groups than the incidence in the control group, the incidence of satellite animals with palpable masses was slightly lower in the mid and high dose male groups than the incidence in the control group. Importantly, bleeding (general or vaginal) did not increase with dose.

Table 15: Reviewer's Summary of Notable Clinical Signs – Document PH-36242

	Cumulative number of animals in main groups (in satellite groups)							
	Male rats				Female rats			
Finding/Dose (mg/kg)	0	10	20	60	0	10	20	60
Number of animals	50 (20)	50 (20)	50 (20)	50 (20)	50 (20)	50 (20)	50 (20)	50 (20)
Piloerection	22 (5)	18 (4)	15 (2)	15 (6)	11 (1)	7 (2)	14 (3)	11 (3)
Hair loss	17 (4)	17 (5)	11 (7)	18 (7)	10 (11)	15 (9)	17 (10)	18 (7)
Bloody eye	7 (2)	5 (4)	7 (5)	5 (7)	8 (5)	7 (5)	5 (1)	7 (8)
Palpable masses	6 (5)	2 (5)	9 (2)	10 (2)	14 (4)	16 (9)	15 (8)	16 (8)

Body Weights
The animals in all groups were weighed on Day 1 of treatment and weekly up to scheduled necropsy and immediately before necropsy.

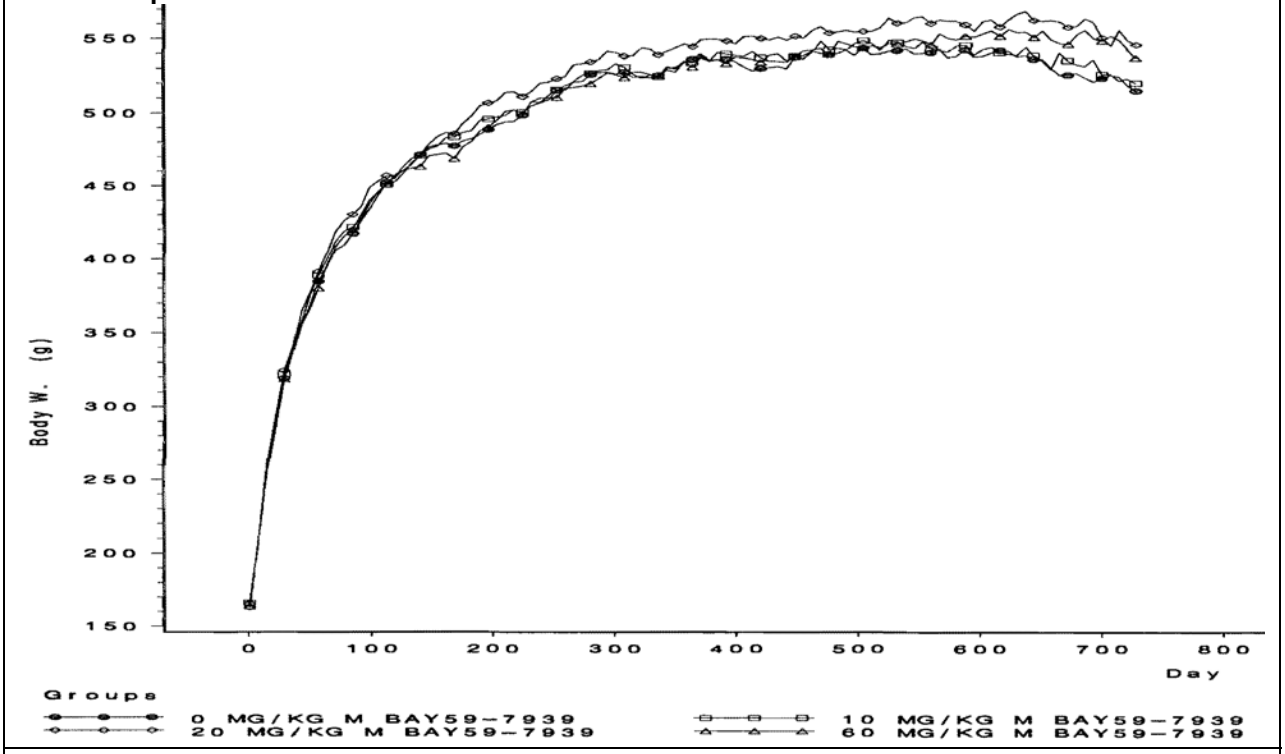
Body weight and body weight gain in the main study groups were not significantly affected by treatment with BAY 59-7939 (Table 16, Figure 6).

Table 16: Reviewer's Summary of Body Weights – Document PH-36242

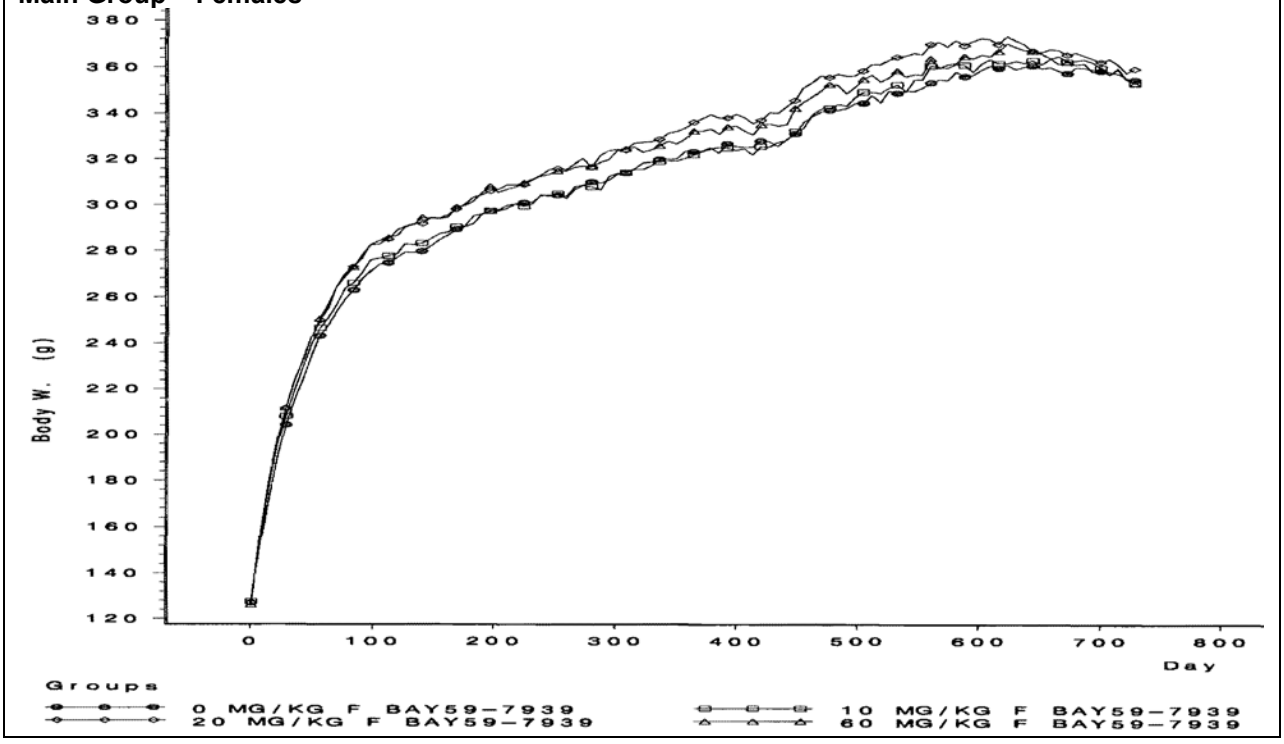
Main Study	Dose (mg/kg)							
	Male rats				Female rats			
Day Dose (mg/kg)	0	10	20	60	0	10	20	60
Mean body weight (gm)								
1	165	165	163	164	127	127	127	126
92	426	427	435	430	268	270	276	278
183	482	487	497	480	292	295	303	301
274	521	525	533	518	308	308	320	317
365	536	533	544	534	323	322	336	332
456	537	535	550	541	336	333	351	344
547	539	543	564	548	349	354	365	356
631	538	543	568*	554	359	362	371	368
722	518	522	548	542	354	354	357	355
729	514	519	545	536	354	353	359	352
Body weight gain (gm)								
Day 1 – Day 183	317	322	334	316	165	168	176	175
Day 1 – Day 365	371	368	381	370	196	195	209	206
Day 1 – Day 729	349	354	382	372	227	226	232	226

Figure 6: Sponsor's Body Weight Graphs – Document PH-36242

Main Group – Males



Main Group – Females



Food and Water Consumption
Food and water consumption were determined weekly for individual main group animals.

The sponsor's summary tables (Table 17) indicate no treatment effect was observed for group mean food or water intake relative to the control group.

Table 17 : Sponsor's Summaries of Food and Water Intake – Document PH-36242

	Males					Females				
	Group means					Group means				
Dose mg/kg	Days	g/animal total	g/animal per day	g/kg body weight total	g/kg body weight per day	Days	g/animal total	g/animal per day	g/kg body weight total	g/kg body weight per day
Food intake										
0	1-730	15732	21.6	32706	44.9	1-730	11733	16.1	38574	52.9
10	1-730	15612	21.4	32281	44.3	1-730	11605	15.9	37901	52.0
20	1-730	16052	22.0	32380	44.4	1-730	11922	16.4	37950	52.1
60	1-730	15528	21.3	31963	43.9	1-730	11847	16.3	37964	52.1
Water intake										
0	1-730	22936	31.5	47329	64.9	1-730	18674	25.6	60612	83.1
10	1-730	22907	31.4	47042	64.5	1-730	18819	25.8	60745	83.3
20	1-730	23941	32.8	48016	65.9	1-730	19259	26.4	60486	83.0
60	1-730	22927	31.5	47056	64.5	1-730	19407	26.6	61692	84.6

Reviewer's modification of sponsor's tables

Ophthalmology
The eyes of all main study animals were examined before treatment initiation. Only the eyes of control and high dose animals were examined during weeks 53/54, 79, and 103-105. After testing papillary reflex, the eyes were dilated and examined using an indirect ophthalmoscope and a photo slit-lamp.

No treatment related findings were observed for the ophthalmoscopic parameters.

Hematology
Blood samples for hematology were collected from 10 fasting satellite animals per group during weeks 27/28, 53/54, 79/80, and 103/104. The following parameters were measured: hematocrit, hemoglobin concentration, erythrocyte count, erythrocyte morphology, reticulocyte count, mean cell hemoglobin, mean cell hemoglobin concentration, mean cell volume, platelet count, total white cell count, and differential white cell count, including lymphocytes, eosinophils, monocytes, neutrophils, basophils, and atypical lymphocytes. Additional blood samples taken for measurement of thromboplastin time (Hepato-Quick, (b) (4)) were collected from 10 satellite animals per group during weeks 51, 78, and 104 approximately 1 hour after drug administration. Samples for blood smears were collected satellite groups during weeks 54, 80, and 103 as well as from all animals killed in moribund condition and the surviving main study animals in the control and high dose groups near the end of the study.

Most of the statistically significant changes in means for red cell parameters in treated groups were less than 6% of the control means (Table 18) and individual values were within or close to the reference range. For example, statistically significant decreases in

erythrocytes, hemoglobin and hematocrit in the mid-dose group on Day 717 were attributed to Male 448, whose values (8.07, 140, and 0.418, respectively) are within the reference ranges for these parameters. Although none of the group means for hematology parameters for the high dose females on Day 716 were significantly different from the control means, the reviewer notes that the values for all hematology parameters for Female 544 are considerably outside the reference range. This female had the clinical sign of pallor from Day 715 to 729. At necropsy at study termination, she had pale liver and red nodules in her uterus. These findings and changes in hematology parameters are consistent with bleeding, a pharmacodynamic effect of rivaroxaban.

Table 18: Reviewer's Summary of Hematology Parameters – Document PH-36242

	Day	Dose Mg/kg	ERY 10e12/L	HB Gm/L	HCT L/L	MCV fL	MCH pg	MCHC Gm/L ERY	RETI %	Platelet 10e9/L
Males	185	0	9.33	157	0.466	50.0	16.8	337	13	1204
		10	9.01	156	0.452	50.2	17.4	**347***	13	1145
		20	8.93	155	0.452	50.7	17.3	342	14	1220
		60	8.96	155	0.451	50.4	17.3	**343***	14	1127
	367	0	8.88	154	0.452	51.0	17.4	341	12	1220
		10	8.92	156	0.455	51.1	17.5	343	13	1191
		20	8.81	154	0.452	51.3	17.5	341	13	1238
		60	9.00	155	0.453	50.3	17.2	342	13	1201
	550	0	9.12	156	0.494	54.3	17.2	316	14	1438
		10	8.68	153	0.478	55.1	17.6	320	16	1369
		20	8.69	151	0.472	54.4	17.4	320	14	1412
		60	8.94	153	0.477	53.4	17.1	320	14	1360
	717	0	9.01	157	0.469	52.2	17.5	336	14	1195
		10	8.75	156	0.461	52.8	17.9	339	14	1245
		20	**8.48***	**150***	**0.442***	52.2	17.6	338	13	1250
		60	8.65	153	0.452	52.2	17.7	339	14	1264
Reference range for Day 717		2SD+	10.09	171	0.517	56.8	18.4	346	26	1810
		2SD-	6.98	122	0.374	46.8	15.5	310	10	858
Female	184	0	8.74	156	0.47	53.8	17.8	332	15	1209
		10	8.57	154	0.46	53.7	18.0	335	16	1166
		20	8.51	154	0.462	54.3	18.1	334	17	1171
		60	8.49	152	**0.452***	53.3	18.0	**337***	16	1121
	366	0	8.03	152	0.442	55.0	19.0	345	18	1128
		10	7.91	149	0.434	54.9	18.8	343	17	1107
		20	7.86	150	0.432	55.0	19.1	347	18	1152
		60	8.04	150	0.433	54.0	18.7	347	16	1112
	548	0	8.16	151	0.475	58.2	18.6	319	19	1187
		10	8.05	149	0.457	56.9	18.5	**326***	16	1203
		20	8.03	153	0.464	57.9	19.0	**329***	17	1261
		60	7.96	149	**0.453***	57.0	18.7	**328***	16	1243
	716	0	7.68	148	0.436	57.1	19.4	340	24	1123
		10	7.70	148	0.428	55.6	19.2	346	17	1114
		20	7.77	150	0.427	55.1	19.3	**351***	18	1176
		60	7.24	139	0.407	57.0	19.3	340	45	1200

Reference range for Day 717	2SD+	9.16	163	0.493	59.4	19.7	350	29	1419
	2SD-	7.43	138	0.412	49.9	16.8	318	7	792
717	F544	**3.83**	**78**	**0.257**	**67.3**	**20.5**	**304**	**284**	**1644**
Remaining	Max.	8.82	154	0.451	58.8	19.9	351	24	1267
HD females	Min.	7.1	138	0.404	51.2	18.6	338	13	1056

* $p < 0.05$, HD = high dose, ERY = erythrocytes, HB = hemoglobin concentration, HCT = hematocrit, MCV = mean cell volume, MCH = mean cell hemoglobin, MCHC = mean cell hemoglobin concentration, RETI = % reticulocytes, 2SD+ = 2 standard deviations above the mean, 2SD- = 2 standard deviations below the mean

Since blood samples for measurement of coagulation times were collected 1 hour after dosing, the values for thromboplastin time were expected to indicate prolonged coagulation times. The mean values for thromboplastin time for all treated groups on all sampling days were significantly greater (1.5 to 1.9-fold in males, 1.8 to 2.5-fold in females) than those for the control groups (Table 19). Individual values of all treated animals, except one (low dose female 507 on Day 723), were greater than three standard deviations above the reference mean. Dose dependence is more evident in the females compared to the males. However, the reviewer notes that the mean value and all individual values for control males on Day 192 were greater than three standard deviations above the reference mean. Individual values for other control males and females were also greater than three standard deviations above the reference mean. These included control males on Day 375, control males on Day 724, control females on Day 191 and one control female on Day 723.

Table 19: Reviewer's Summary of Thromboplastin Times – Document PH-36242

		Dose	HQUICK, sec			Reference range		Number	
	Day	Mg/kg	Mean	Min.	Max.	3SD-	3SD+	< 3SD+[†]	>3SD+[‡]
Males	192	0	44.9	**42.8**	**49.1**	26.8	41.5	0	10
		10	**71.9***	53.5	86.4			0	10
		20	**71.3***	56.9	86.6			0	10
		60	**82.4***	56.7	105.8			0	10
	375	0	39.3	35.8	**43.7**	24.3	39.2	7	3
		10	**61.8***	46.2	69.9			0	10
		20	**63.1***	49	84.6			0	10
		60	**74.7***	52	109.7			0	10
	556	0	38.7	33.4	42.6	18.8	47.2	10	0
		10	**68.3***	51.9	88.1			0	8[§]
		20	**66.3***	49.9	88.9			0	10
		60	**73.5***	57.2	95.6			0	10
	724	0	39.1	33.6	**43.9**	22.5	39.6	5	5
		10	**63.7***	49.7	88.8			0	10
		20	**67.5***	50.8	81.6			0	10
		60	**68.7***	61.6	95.5			0	10

	Day	Dose Mg/kg	HQUICK, sec Mean	Min.	Max.	Reference range 3SD-	3SD+	Number < 3SD+[†]	>3SD+[‡]
Females	191	0	37.9	34.3	**41.1**	25.2	40.6	8	2
		10	**70.4***	56.6	86.2			0	10
		20	**72.2***	57.8	87.2			0	10
		60	**86.5***	72.9	103.4			0	10
	373	0	34.1	30.2	36.3	23.3	36.4	10	0
		10	**61.8***	52.6	81.1			0	10
		20	**72.3***	59.9	81.3			0	10
		60	**85.6***	69.6	95.8			0	10
	555	0	36.8	33.3	38.9	21.1	42.4	10	0
		10	**70.8***	55.9	83.9			0	10
		20	**77.5***	70	85.6			0	10
		60	**88.3***	72.6	101.5			0	10
	723	0	36.1	33.1	**38.3**	23.4	37.6	9	1
		10	**66.2***	**36.9**	81.9			1	9
		20	**70.1***	57.3	85.6			0	10
		60	**79.4***	59.9	104			0	10

[†] Number of values <3 standard deviations above mean, [‡] Number of values > 3 standard deviations above mean, [§] Only 8 animals

Clinical Chemistry

Blood samples for clinical chemistry were collected from 10 fasting satellite animals per group during weeks 27, 53, 79, and 103. The following parameters were measured: alkaline phosphatase, alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma glutamyl transferase, glucose, total bilirubin, total cholesterol, triglycerides, creatinine, urea, total protein, sodium, potassium, chloride, calcium, and inorganic phosphate.

The findings are summarized in the sponsor's tables below (Table 20, Table 21). No significant changes were observed in plasma enzyme activities, including ALT or AST. Glucose, urea, total protein, and sodium are parameters for which a treated group exhibited a statistically significant difference from the concurrent control group. For these parameters, no dose or time-dependence was observed and values for individual animals were within the sponsor's reference ranges (± 2 SD) or within the range of concurrent control values.

However, other parameters (chloride, phosphate, and potassium) with a statistically significant difference from the concurrent control group had individual values outside the reference range. On Day 717, the high dose male group exhibited statistically significant higher chloride concentration than the control males Although five of ten high dose males had individual values above the reference range (94-102), only one had a value (106) that was more than 7% above the mean of the reference range. Furthermore, this increase was not observed in the high dose female group.

The high dose male group on Days 367 and 717 also showed a statistically significant decrease in phosphate. However, only one high dose male had a phosphate value (1.12) below the reference range (1.19 – 1.93) and all individual values for females were within the reference range.

Statistically significant decreases in potassium were observed in the high dose males on Day 550 and mid- and high dose females on Day 548. Table 22 summarizes these results with respect to the time-matched reference range and individual animal values. On Day 550, not only were the values for six high dose males less than two standard deviations below the reference mean, but also the mean potassium value for the high dose male group was less than two standard deviations below the reference mean. Interestingly, the values for six low dose males were also less than two standard deviations below the reference mean, but all values for control males were within the reference range. In contrast, the values for individual mid- and high dose females on Day 548 were within the reference range, but the values for five control females were above two standard deviations above the reference mean. Additionally, although no statistically significant difference was observed among the male groups on Day 717, one, three and two individual values in the control, mid, and high dose groups, respectively, were less than two standard deviations below the reference mean. Furthermore, values for two control males (401 and 405) of 9.2 and 7.1 mmole/L, respectively, were greater than three standard deviations above the reference mean. No explanation was provided for these excessive values for control animals, although hemolysis of these control samples is a potential explanation.

Table 20: Sponsor's Summary of Clinical Chemistry - A – Document PH-36242

Dose mg/kg	GLUCOSE mmol/l	CHOL mmol/l	TRIGL mmol/l	CREA mcmol/l	UREA mmol/l	BILIt mcmol/l	PROT g/l	ALBUMIN g/l
m	**Day 185**							
0	3.18	2.21	0.82	57	6.29	2.1	71.8	35.7
10	3.01	2.30	0.98	54	5.23 ++	1.9	69.3	35.9
20	3.08	2.19	1.00	55	5.77	1.8	69.4	35.9
60	3.19	2.21	0.88	55	5.57	1.9	69.9	36.6
m	**Day 367**							
0	3.48	2.87	1.34	56	6.03	1.7	70.9	32.8
10	3.36	2.84	1.50	54	5.57	1.8	69.0	33.1
20	3.53	2.78	1.38	55	6.19	1.5	70.2	33.2
60	3.57	3.09	1.54	54	5.89	1.7	72.0	34.1
m	**Day 550**							
0	3.85	3.71	2.13	59	7.61	1.9	73.3	32.7
10	3.66	3.39	1.77	57	6.73	1.7	69.7 +	32.9
20	3.66	3.35	1.57	56	6.74	1.7	70.3	33.3
60	3.96	3.83	1.88	59	7.59	2.0	72.8	34.1
m	**Day 717**							
0	3.44	3.96	1.89	60	7.24	2.1	70.5	33.1
10	3.59	3.58	2.01	55	6.14	1.9	69.1	33.3
20	3.46	3.71	2.24	59	7.11	1.8	69.4	32.6
60	3.53	4.26	2.40	58	6.56	2.0	72.2	33.7
f	**Day 184**							
0	3.54	2.08	1.11	56	6.53	2.4	72.5	40.9
10	3.30	1.75	0.86	56	6.56	2.3	70.8	40.5
20	3.27 +	2.11	0.93	56	7.06	2.2	72.4	41.6
60	3.33	1.66	0.94	61	7.61	2.0	70.1	39.6
f	**Day 366**							
0	3.31	2.01	1.51	57	6.46	1.8	73.2	38.3
10	3.13	1.86	1.33	57	6.69	1.6	70.5	37.3
20	3.25	1.97	1.50	56	6.94	1.7	71.5	38.0
60	3.37	1.71	1.55	56	6.63	1.9	71.3	37.4
f	**Day 548**							
0	3.96	2.28	1.52	54	6.27	2.2	75.1	37.7
10	3.64	2.18	1.28	53	6.16	1.9	75.3	39.1
20	3.63 +	2.22	1.49	52	6.86	2.2	74.2	39.2
60	3.80	2.22	1.55	55	6.80	2.3	75.1	39.2
f	**Day 716**							
0	4.07	2.55	2.16	57	6.30	1.7	77.8	38.2
10	3.69	2.81	2.23	55	6.31	2.2	76.4	38.6
20	3.80	2.69	2.78	55	6.31	1.8	75.3	37.5
60	3.93	2.71	3.41	56	6.31	1.8	77.0	38.0

Table 21: Sponsor's Summary of Clinical Chemistry - Part B - Document PH-36242

Dose mg/kg	ASAT (GOT) U/l	ALAT (GPT) U/l	APh U/l	GLDH U/l	GGT U/l
m	Day 185				
0	66.4	58.6	67	8.8	1
10	64.8	61.1	63	8.8	1
20	64.0	67.1	60	8.6	1
60	62.0	51.1	63	8.5	1
m	Day 367				
0	72.3	62.4	62	15.4	0
10	74.5	72.2	62	14.6	1
20	59.9	59.1	57	11.8	0
60	58.9	58.2	57	12.7	1
m	Day 550				
0	80.1	53.5	60	14.4	3
10	65.7	46.2	57	17.5	2
20	57.7	48.1	58	12.4	3
60	60.0	53.1	59	10.1	3
m	Day 717				
0	75.7	58.7	67	8.9	3
10	67.7	62.8	62	12.4	3
20	55.2 +	61.3	61	7.4	4
60	59.3	67.5	61	7.4	4
f	Day 184				
0	62.1	47.8	34	7.2	0
10	66.4	46.3	33	4.0	0
20	64.6	44.0	32	6.0	0
60	68.6	49.1	35	14.2	1
f	Day 366				
0	75.6	55.5	33	15.1	1
10	66.0	48.6	24	9.4	1
20	62.0	51.4	27	9.5	0
60	75.2	56.3	31	15.4	1
f	Day 548				
0	81.8	47.0	31	19.8	0
10	83.4	49.0	29	15.5	0
20	82.6	44.1	27	12.7	0
60	78.8	43.2	25	15.9	0
f	Day 716				
0	80.5	47.3	33	20.5	0
10	72.4	50.6	29	11.7	0
20	60.8	50.0	31	8.2	0
60	67.3	49.5	27	18.2	0

Dose mg/kg	Na mmol/l	K mmol/l	Cl mmol/l	Ca mmol/l	P mmol/l
m	Day 185				
0	144	5.0	97	2.45	1.70
10	143	4.9	98	2.42	1.64
20	143	4.9	98	2.42	1.73
60	143	4.7	97	2.46	1.77
m	Day 367				
0	144	4.8	97	2.44	1.69
10	143	5.0	96	2.43	1.57
20	144	4.9	97	2.43	1.53
60	143	4.9	98	2.47	1.52 +
m	Day 550				
0	141	5.0	99	2.44	1.44
10	141	4.6	98	2.41	1.50
20	140	4.8	99	2.43	1.49
60	140	4.4 ++	99	2.47	1.47
m	Day 717				
0	144	5.6	99	2.54	1.59
10	142	4.9	97	2.51	1.47
20	143	4.5	99	2.55	1.47
60	142 ++	4.6	102 ++	2.57	1.33 ++
f	Day 184				
0	142	4.4	100	2.52	1.43
10	142	4.2	100	2.45	1.28
20	142	4.2	100	2.49	1.35
60	141 +	4.2	100	2.45	1.30
f	Day 366				
0	142	4.4	97	2.49	1.30
10	141	4.3	97	2.48	1.26
20	141 ++	4.5	96	2.54	1.41
60	141 ++	4.4	98	2.49	1.26
f	Day 548				
0	139	4.8	98	2.43	1.12
10	139	4.4	99	2.44	1.00
20	139	4.3 ++	99	2.48	1.19
60	139	4.2 ++	97	2.50	1.16
f	Day 716				
0	140	4.4	97	2.53	1.12
10	140	4.4	98	2.53	1.14
20	139 +	4.3	96	2.57	1.20
60	140	4.3	98	2.59	1.19

\+ significantly different at $p \leq 0.05$

++ significantly different at $p \leq 0.01$

Table 22: Reviewer's Summary of Serum Potassium Values - Document PH-36242

		Dose	K, mmole/L			Reference range		Number	
	Day	Mg/kg	Mean	Min.	Max.	2SD-	2SD+	< 2SD-[†]	>2SD+[‡]
Males	185	0	5.0	4.4	**5.7**	4.3	5.6	0	1
		10	4.9	4.6	5.2			0	0
		20	4.9	4.4	5.5			0	0
		60	4.7	4.3	5.2			0	0
	367	0	4.8	4.6	5.0	4.4	5.5	0	0
		10	5.0	4.5	**5.6**			0	1
		20	4.9	**4.3**	5.4			2	0
		60	4.9	4.4	5.5			0	0
	550	0	5.0	4.6	5.7	4.5	5.8	0	0
		10	4.6	**3.8**	5.8			**6**	0
		20	4.8	4.4	5.4			0	0
		60	**4.4***	**3.8**	5.0			**6**	0
	717	0	5.6 [5.0]	**4.1**	**9.2** [5.5]	4.3	5.9	1	2 [§]
		10	4.9	4.5	5.6			0	0
		20	4.5	**4.0**	5.0			**3**	0
		60	4.6	**4.0**	4.9			**2**	0
Females	184	0	4.4	3.9	5.0	3.7	5.1	0	0
		10	4.2	3.7	4.6			0	0
		20	4.2	3.9	4.6			0	0
		60	4.2	**3.5**	4.6			1	0
	366	0	4.4	4.0	4.8	3.5	5.0	0	0
		10	4.3	3.8	4.7			0	0
		20	4.5	4.0	4.7			0	0
		60	4.4	3.8	4.7			0	0
	548	0	4.8	4.4	**5.2**	3.5	4.9	0	5
		10	4.4	3.8	**6.2**			0	1
		20	**4.3***	3.8	4.6			0	0
		60	**4.3***	3.8	4.6			0	0
	716	0	4.4	3.9	**5.3**	3.4	5.0	0	1
		10	4.4	4.1	4.8			0	0
		20	4.3	3.9	4.9			0	0
		60	4.3	4.1	4.8			0	0

[†] Number of values < 2 standard deviations below mean, [‡] Number of values >2 standard deviations above mean, [§] Control males 401 and 405 had values of 9.2 and 7.1, respectively. [ ] Values omitting males 401 and 405.

Urinalysis

Urine samples were collected for a period of 16 hours from 10 fasting satellite animals per group during weeks 26, 52, 78, and 102. The following parameters were measured: volume, density, pH, blood, bilirubin, protein, glucose, ketone bodies, and urobilinogen. The urine sediment was examined microscopically for epithelial cells, leucocytes, erythrocytes, bacteria, amorphous salts, triple phosphate crystals, and other abnormal components.

Although the low and high dose males on Day 180 showed a statistically significant decrease in urine density compared to the density for the control group, urinalysis

parameters were considered to be unaffected by treatment, because all individual values were within the reference range.

Gross Pathology

The surviving satellite animals were sacrificed for scheduled necropsy during week 105. The surviving main study animals were sacrificed for scheduled necropsy during weeks 105-107. Animals found dead during the study were necropsied at the earliest opportunity. The animals were subjected to systematic examination and the organs listed in Table 23 were fixed in 10% neutral buffered formalin. The urinary bladder and lungs were initially inflated with 10% neutral buffered formalin prior to fixation by immersion.

Table 23: Reviewer's Summary of Tissues Collected - Document PH-36242

Abnormal tissues	Kidneys	Seminal vesicles with coagulating glands
Adrenals	Larynx	Skeletal muscle - thigh
Aorta	Liver	Skin (mammary area)
Brain (cerebrum, cerebellum, brain stem)	Lungs	Spinal cord (cervical, thoracic, lumbar)
Cecum	Lymph nodes (mandibular – mesenteric, popliteal)	Spleen
Clitoral gland	Nasal cavity/nasopharynx	Sternum with bone marrow
Colon	Optic nerves	Stomach
Duodenum	Ovaries with oviduct	Testes
Epididymides	Pancreas	Thymus
Esophagus	Peyers patches	Thyroid with parathyroids
Eyes and eyelids	Pharynx	Tongue
Extraorbital lacrimal glands	Pituitary	Trachea
Femur with joint	Preputial gland	Ureters
Harderian glands	Prostate	Urethra
Head with skull cap	Rectum	Urinary bladder
Heart	Salivary glands (submandibular, sublingual and parotid)	Uterus with cervix
Ileum	Sciatic nerve	Vagina
Jejunum		Zymbal's glands

The pathology report commented on kidney discoloration, nodules in the pituitary and preputial glands, and cysts in the ovary. A decreased incidence of kidney discoloration was found in the mid and high dose males. However, the reviewer notes that discoloration of the adrenal glands was present in a few treated animals from all dose groups, but not in the control group (Table 24). In contrast, discoloration in the liver was similar across groups and discoloration in the lungs was slightly decreased in the mid and high dose females. Although lung discoloration occurred primarily in decedents, discoloration in the other tissues did not.

The pathologist noted the absence of nodules of the pituitary glands of high dose females and the increased incidence of nodules in the preputial glands of high dose males. The reviewer also noted the decreased incidence of nodules in uteri of the treated female groups. In contrast, the incidence of nodules in the skin was increased in the high dose females and the mid and high dose males. However, the incidence of nodules in other tissues was generally evenly distributed across groups.

The pathologist noted a decreased incidence of ovarian cysts in the high dose females. The reviewer noted the incidence of cysts in other tissues, exemplified by the liver and kidney, was generally similar across groups.

Table 24: Reviewer's Summary of Gross Pathology - Document PH-36242

		Male				Female			
	Dose, mg/kg	0	10	20	60	0	10	20	60
Finding	Number (decedents)	50 (5)	50 (12)	50 (5)	50 (9)	50 (4)	50 (10)	50 (7)	50 (6)
Discoloration	Kidney	9 (3)	8 (4)	**3 (1)**	**2 (0)**	2 (1)	2 (1)	3 (2)	2 (2)
	Adrenal glands	0	2 (0)	1 (0)	2 (1)	0	1 (0)	2 (0)	1 (0)
	Lungs	9 (8)	7 (6)	10 (8)	8 (8)	6 (5)	5 (5)	3 (3)	3 (3)
	Liver	7 (3)	9 (1)	6 (0)	6 (2)	6 (2)	12 (3)	3 (2)	10 (3)
Nodules	Preputial glands	1 (0)	0	0	**4 (1)**	-	-	-	-
	Pituitary	0	0	0	1 (0)	6 (1)	5 (1)	7 (3)	**0**
	Lung	0	0	1 (1)	3 (2)	0	1 (0)	0	1 (1)
	Liver	2 (1)	1 (0)	0	1 (0)	2 (1)	0	0	2 (0)
	Pancreas	0	2 (0)	0	1 (0)	0	0	0	0
	Kidney	1 (1)	1 (0)	0	0	0	1 (0)	1 (0)	2 (2)
	Uterus	-	-	-	-	16 (4)	**9 (4)**	**10 (2)**	**11 (3)**
	Adrenal glands	3 (0)	4 (2)	5 (2)	2 (0)	1 (0)	2 (1)	3 (1)	2 (1)
	Skin	3 (1)	0	**6 (2)**	**6 (3)**	6 (1)	9 (3)	5 (2)	**11 (5)**
Cyst	Ovaries	-	-	-	-	6 (0)	6 (2)	7 (0)	**2 (1)**
	Liver	5 (0)	3 (0)	1 (1)	3 (0)	4 (1)	10 (1)	5 (1)	6 (2)
	Kidney	7(2)	4(2)	6(0)	5(2)	1(0)	0	0	0
Enlarged	Liver	1 (0)	5 (3)	4 (2)	1 (0)	2 (1)	1 (0)	0	0
Decreased size	Testes	1 (0)	1 (0)	4 (0)	2 (0)	-	-	-	-

Organ Weights

The following organs were weighed before fixation: adrenals, brain, kidneys, liver, spleen, and testes. The methods indicate that the weights of organs exhibiting a severe pathological alteration (e.g. nodule, tumor, cyst) were excluded from the calculation of the mean value, if the individual weight was at least three times higher than the median value of the respective group. The rationale for these criteria was not provided.

Most of these exclusions were for male adrenal weights, which had a 32 to 85 fold intra-group variation consistent with the high overall incidence of pheochromocytoma in male adrenal glands. Intra-group variation of female adrenal weights was less (6 to 28 fold) and fewer values were excluded.

The testes weight (12006 mg) for low dose male 53 was excluded, since the testes had nodules and Leydig cell tumor. However, testes weight (10110 mg) for control male 23 was not excluded, although those testes also had Leydig cell tumor. The low testes weight for mid-dose male 103 (812 mg) was included and was attributable to severe (Grade 5) atrophy of the testes and other sexual organs. Likewise, the low testes weight for mid-dose male 111 (1752 mg) was included and was attributable to severe (Grade 5) atrophy of the testes.

No absolute kidney weights were excluded. Although no significant difference in mean absolute kidney weights was observed for either males or females, the high dose males showed a statistically significant decrease in mean relative kidney weight (Table 25). The mean relative kidney weight in the low and mid-dose males was also decreased, but was not statistically significant. The decreases in mean relative kidney weight in male treated groups correlated best with combined incidence of hyperplasia in the kidney.

Although mean absolute and relative spleen weights for female treated groups were lower than those in the control group, the differences were not statistically significant and a clear dose relationship was not evident (Table 26). The spleen absolute weight for control female 244 (17028 mg, 26 times the group median of 652 mg) was excluded even though severe pathology was not noted, probably because this value was a clear outlier. However, the spleen absolute weight for control female 207 (3582 mg, 5.5 times the group median of 652 mg) was included even though this organ was noted as being enlarged at necropsy, because the enlargement was consistent with markedly (grade 4) increased hematopoiesis found microscopically, not the presence of a nodule, tumor, or cyst. Similarly, the spleen absolute weight for high dose female 382 (2411 mg, 3.6 times median of 670 mg) was included, even though this spleen was noted as being enlarged at necropsy, because the enlargement was consistent with moderate (grade 3) increased hematopoiesis found microscopically. If values for females 207 and 382 are omitted, the decrease in mean female spleen weights is no longer evident.

In contrast, statistically significant decreases in absolute spleen weight were found for the low and mid-dose males (15%) and decreases in relative spleen weight were found for all treated male groups (16%, 20% and 14%). However, the sponsor discounted these changes because they were considered small and lacking in a dose relationship. The spleen of high dose male 165 (2549 mg, 2.8 times group median of 912 mg) was included even though nodules (0.8 cm diameter) were found at necropsy and lymphoma grade 3 was found microscopically. Likewise, the spleen of high dose male 175 (1807 mg, 2 times group median of 912 mg) was included even though nodules were found at necropsy and a grade 4 histocytic sarcomatous infiltrate was found microscopically. Omission of the values for these two high dose males results in a dose-dependent decrease spleen absolute and relative weights in the males. However, this decrease did not correlate with a specific histopathological finding.

Table 25: Sponsor's Summaries of Organ Weights - Document PH-36242

Absolute organ weights

Dose mg/kg	Body W. G	Brain mg	Adrenals mg	Liver mg	Spleen mg	Kidneys mg	Testes mg
m							
0	512	2189	73	19851	1095	3856	3744
10	517	2180	77	18757	928 ++	3667	3558
20	546	2182	86	20183	926 ++	3856	3414
60	546	2168	70	19824	991	3725	3672
f							
0	352	1998	69	13981	772	2708	
10	353	2042	73	13627	692	2706	
20	355	2003	73	13425	665	2711	
60	354	2008	74	13046	723	2662	

Relative organ weights

Dose mg/kg	Body W. G	Brain mg/100g	Adrenals mg/100g	Liver mg/100g	Spleen mg/100g	Kidneys mg/100g	Testes mg/100g
m							
0	512	431	15	3882	215	759	731
10	517	426	15	3634	180 ++	717	695
20	546	407	16	3734	171 ++	727	630 ++
60	546	401 +	13	3649	185 ++	690 +	676
f							
0	352	571	20	3982	221	772	
10	353	582	21	3857	197	770	
20	355	570	20	3798	188	767	
60	354	573	21	3690	205	754	

\+ significantly different at $p \leq 0.05$ ++ significantly different at $p \leq 0.01$

Table 26: Reviewer's Summary of Spleen Weights - Document PH-36242

	Dose	Spleen Absolute Weight, mg				Spleen Relative, mg/100 gm			
	mg/kg	Mean	SD	Min.	Max.	Mean	SD	Min.	Max.
Males	0	1095	202	727	1446	215	43	153	319
	10	928*	164	549	1423	180*	29	127	236
	20	926*	156	477	1222	171*	30	109	236
	60	991	336	676	2549	185*	72	113	522
	60, omit M165 & M175	917*	121	676	1160	169*	28	113	212
Females	0	772	499	520	3582	221	152	143	1093
	10	692	120	490	981	197	38	144	312
	20	665	113	456	1003	188	30	137	235
	60	723	317	482	2411	205	90	138	691
	0, omit F207	694	162	520	1267	197	42	138	294
	60, omit F382	675	113	482	1046	191	30	138	296

Histopathology

Tissue samples from all main study animals were dehydrated, embedded in Paraplast, sectioned, and stained with hematoxylin and eosin. All tissues listed in Table 23 and gross abnormalities identified at macroscopic examination from all main animals sacrificed at the end of the scheduled treatment period and from all main animals killed or dying during the study were examined by histology. Tissues of the satellite groups were not examined microscopically.

Peer Review

The peer review included examination of all tumors and pre-neoplastic/hyperplastic lesions of all groups. In addition, approximately 25% of frequent lesions and all slides of 5 animals per sex from the high dose group were also examined.

Neoplastic lesions

The incidences of the most notable tumors in the rat carcinogenicity study are summarized in Table 27 below. The sponsor's listing of tumor incidences is in Appendix

6. The statistical evaluations of the sponsor and the FDA statistician are in Appendix 7 and 8, respectively. Historical control data provided by the sponsor are in Appendix 9.

Squamous cell carcinoma was present in the clitoral gland of two high dose females. Statistical evaluations by the sponsor and the FDA statistician indicated p values in the trend test (p_t) of 0.030 and 0.070, respectively. Neither p value attains the significance in the trend test ($p_t < 0.025$) required for this finding of a rare tumor to be considered positive, according to current CDER guidance. Additionally, squamous cell papilloma was present in both a control female and a high dose female. Therefore, statistical significance for squamous cell carcinoma plus papilloma is also lacking. Furthermore, squamous cell hyperplasia in the clitorial gland was present in females of the control, low and mid-dose groups, but not the high dose group further confirming the lack of a treatment relationship.

Adrenal cortical adenomas were present only in treated animals with the incidence significantly higher in the mid and high dose females (sponsor's pt = 0.0126). However, no adrenal adenocarcinoma was found in any group. The FDA statistician's evaluation indicated a p value for the trend test of 0.041. Based on a mean background incidence of 3.5% in the RITA database, adrenal cortical adenoma is a common tumor. Therefore, neither p value for females attained the significance in the trend test ($p < 0.005$) required for this finding to be considered positive, according to current CDER guidance. In addition, cortical adrenal hyperplasia (zona fasciculata and zona glomerulosa) did not show a dose relationship.

The incidence of benign and malignant pheochromocytoma in the adrenal medulla was higher in males than in females. The incidence in males was similar across all groups. However, the incidence in females slightly increased in the treated groups, but was without statistical significance. In addition, focal medullary hyperplasia was similar across control and treated groups in both males and females.

The incidence of adenoma and adenocarcinoma in the mammary gland of females did not show a positive dose relationship. However, the incidence of fibroadenoma increased in the high dose females. The sponsor's statistical analysis for fibroadenoma indicated a p value of 0.0526 for the trend test. The FDA statistician's analysis indicated a p value of 0.031 for the pairwise test and 0.062 for the trend test. Based on a mean background incidence of 14% in the RITA database, mammary fibroadenoma in female rats is a common tumor. Therefore, the p value for fibroadenoma in females did not attain the significance in the trend test ($p< 0.005$) required for this finding of a common tumor to be considered positive. Even if fibroadenomas and fibromas are combined, the p value would not attain the required significance level. Furthermore, hyperplasia in the mammary gland did not show a positive dose relationship.

The sponsor's evaluation indicated that histiocytic sarcoma (pt = 0.0268) and skin fibroma (p_t = 0.0294) were statistically significant in males. The FDA statistician's evaluation indicated p values in the trend test of 0.056 and 0.18 for histiocytic sarcoma and skin fibroma, respectively. Based on the (b) (4) (2011) listing of spontaneous tumors in Wistar rats, the overall incidences of histiocytic sarcoma and skin fibroma are 0.74% and 0.41%, respectively. Neither p value attains the

significance in the trend test ($p_t < 0.025$) required for these findings of rare tumors to be considered positive, according to current CDER guidance.

In contrast to the mouse carcinogenicity study in which hepatocellular tumors in males increased with dose, only two hepatocellular tumors were observed in rats, one in a low dose male and another in a high dose female. Leydig cell tumors in rats decreased with dose in contrast to an increase in Leydig cell tumors in mice.

Table 27: Reviewer's Summary – Neoplastic Lesions - Document PH-36242

Rat Carcinogenicity Study		BAY 59-7939 Dose level (mg/kg/day)							
Neoplastic Findings		Male				Female			
All main study animals		0	10	20	60	0	10	20	60
Organ/Tissue Finding	#/group	50	50	50	50	50	50	50	50
Liver	#	50	50	50	49	50	50	50	50
Hepatocellular adenoma - B	#	0	1	0	0	0	0	0	1
(CR max.: M 17.5%, F 9.2%)	%	0	2	0	0	0	0	0	2
Pancreas	#	49	50	50	49	50	50	50	50
Acinar adenoma – B	#	0	0	2	1	0	1	0	1
(CR max.: M 1.8%)	%	0	0	4	2	0	2	0	2
Acinar adenocarcinoma – M	#	0	1	0	0	0	0	0	0
(CR max.: M 1.5%)	%	0	2	0	0	0	0	0	0
Combined acinar adenoma/carcinoma	#	0	1	2	1	0	1	0	1
	%	0	2	4	2	0	2	0	2
Islet cell adenoma	#	0	1	1	1	0	0	1	0
(CR max.: M 7.0%, F 2.0%)	%	0	2	2	2	0	0	2	0
Testes		50	50	50	49	0	0	0	0
Leydig cell tumor - B	#	6	6	3	3	-	-	-	-
(CR max.: M 6.7%)	%	12	12	6	6	-	-	-	-
Clitorial glands	#	-	-	-	-	43	40	42	45
Squamous cell carcinoma – M (p = 0.03)	#	-	-	-	-	0	0	0	**2***
	%	-	-	-	-	0	0	0	4.4
Squamous cell papilloma - B	#	-	-	-	-	1	0	0	1
	%	-	-	-	-	2.3	0	0	2.2
Squamous cell carcinoma + papilloma	#	-	-	-	-	1	0	0	3
	%	-	-	-	-	2.3	0	0	6.6
Basal cell tumor - B	#	-	-	-	-	0	0	1	0
	%	-	-	-	-	0	0	2.4	0
Basal cell carcinoma - M	#	-	-	-	-	1	0	2	0
	%	-	-	-	-	2.3	0	2.4	0
Adenoma - B	#	-	-	-	-	0	0	1	0
	%	-	-	-	-	0	0	1.2	0
Adenocarcinoma - M	#	-	-	-	-	0	1	0	0
	%	-	-	-	-	0	2.5	0	0
Pituitary gland	#	50	49	48	49	50	50	50	50
Adenoma pars distalis - B	#	3	7	6	5	9	7	13	3
(CR max.: M 37.3%, F 75%)	%	6	14.2	12.5	10.2	18	14	26	6
Adenocarcinoma pars distalis - M	#	0	0	0	0	2	0	0	0
(CR max.: M 6.7%, F 5.4%)	%	0	0	0	0	4	0	0	0
Combined Adenoma + Adenocarcinoma	#	3	7	6	5	11	7	13	3
	%	6	14.2	12.5	10.2	22	14	26	6
Adrenal gland		50	49	50	49	50	50	50	50
Cortical Adenoma – B (p_t = 0.012)	#	0	2	2	1	0	1	**4***	**4***
RITA range: Male: 0-5.9%, Female: 0-8%	%	0	4.1	4	2	0	2	8	8
(CR max.: M 6.7%, F 3.0%)									
Pheochromocytoma -B	#	20	22	12	18	1	3	4	3
	%	40	44.8	24	36.7	2	6	8	6
Pheochromocytoma -M	#	1	4	4	2	0	0	1	0
	%	2	8.2	8	4.1	0	0	2	0
Combined Pheochromocytoma	#	21	26	16	20	1	3	5	3
	%	42	53.0	32	40.8	2	6	10	6
Hemolymphoreticular System	#	50	50	50	50	50	50	50	50
Sarcoma histiocytic (p_t = 0.026)	#	0	0	0	**2***	1	0	0	0
(CR max.: M 2.0%, F 1.3%)	%	0	0	0	4	2	0	0	0
Malignant f brous histiocytoma - M	#	0	0	0	1	0	0	0	0
	%	0	0	0	2	0	0	0	0
Mammary gland	#	50	50	50	49	50	50	50	50

Rat Carcinogenicity Study		BAY 59-7939 Dose level (mg/kg/day)							
Neoplastic Findings		Male				Female			
All main study animals		0	10	20	60	0	10	20	60
Organ/Tissue Finding	#/group	50	50	50	50	50	50	50	50
Adenoma - B	#	0	0	0	0	1	2	0	0
(CR max.: F 8.0%)	%	0	0	0	0	2	4	0	0
Adenocarcinoma - M	#	0	0	0	0	3	1	1	1
(CR max.: F 12.0%)	%	0	0	0	0	6	2	2	2
Adenoma + Adenocarcinoma	#	0	0	0	0	4	3	1	1
	%	0	0	0	0	8	6	2	2
Fibroadenoma – B (p_t= 0.052)	#	0	0	0	0	4	7	4	**11***
(RITA range: 5-28%, CR max.: F 32%)	%	0	0	0	0	8	14	8	**22**
Fibroma - B	#	0	0	0	0	0	0	0	1
	%	0	0	0	0	0	0	0	2
Fibroadenoma + Fibroma	#	0	0	0	0	4	7	4	**12***
	%	0	0	0	0	8	14	8	**24**
Skin	#	50	50	50	49	50	50	50	50
Papilloma - B	#	1	0	0	1	0	0	0	0
(CR max.: M 2.0%)	%	2	0	0	2	0	0	0	0
Basal cell carcinoma, basosquamous - M	#	1	0	0	0	0	0	0	0
(CR max.: M 1.3%)	%	2	0	0	0	0	0	0	0
Fibroma - B (p = 0.029)	#	0	0	**2***	**2***	0	0	0	0
(CR max.: M 2.0%)	%	0	0	4	4	0	0	0	0
Fibrosarcoma – M	#	0	0	0	1	0	0	0	0
(CR max.: M 0.67%)	%	0	0	0	2	0	0	0	0
Keratoacanthoma – B	#	1	0	1	1	0	0	0	0
(CR max.: M 10%)	%	2	0	2	2	0	0	0	0
Liposarcoma - M	#	1	0	1	0	0	0	0	0
	%	2	0	2	0	0	0	0	0
Squamous cell carcinoma - M	#	0	0	1	0	0	0	0	0
(CR max.: M 2.7%, F 2.0%)	%	0	0	2	0	0	0	0	0
Fibroma + F brosarcoma	#	0	0	2	3	0	0	0	0
	%	0	0	4	6	0	0	0	0
RITA: Registry of Industrial Toxicology Animal Data, [redacted] (b) (4) (March 2011)									

Non Neoplastic lesions

In the two year studies, the percentage of rats (54-84%) with chronic cardiomyopathy was higher than the percentage of mice with (5-14%) cardiomyopathy. Although the incidence of cardiomyopathy in rats was similar across male groups, a slight non-statistically significant increase in the incidence of cardiomyopathy was observed in female groups with dose (Table 28). However, the incidence of valvular fibrosis in the heart increased with dose in both males and females and was statistically significant in females by a trend test (p_t = 0.0048), but not by a pairwise test (p = 0.0587).

Although the incidence of hemorrhage did not increase significantly with dose in any organ or across all organs, the incidence of pigment deposition increased with dose in some organs. The increased pigment deposition representing the remains of previous micro-hemorrhages was attributed to the pharmacological action of BAY 59-7939. In the pancreas, peri-vascular and/or peri-insular pigment deposition was increased of high dose rats with statistical significance attained in the high dose females. In the adrenal gland, pigment deposits increased in the high dose males, the mid- and high dose females without statistical significance. In the high dose males, the incidence of pigment deposition also increased in the mesenteric lymph nodes. In the high dose females, the incidence of pigment deposition also increased with statistical significance in the popliteal lymph nodes and the uterus. Across all organs the incidence of pigment deposition increased in the high dose males and females.

Table 28: Reviewer's Summary - Non-neoplastic Lesions - Document PH-36242

Rat Carcinogenicity Study		BAY 59-7939 Dose level (mg/kg/day)							
Non-Neoplastic Findings		Male				Female			
All main study animals		0	10	20	60	0	10	20	60
Organ/Tissue Finding	#/group	50	50	50	50	50	50	50	50
Liver	#	50	50	50	49	50	50	50	50
Hyperplasia bile duct - diffuse	#	39	39	40	38	20	20	16	22
Hyperplasia bile duct – focal/multifocal	#	4	0	2	1	5	2	3	3
Foci- Basophilic (NOS)	#	4	2	0	0	2	0	1	2
Foci- Basophilic Tigroid	#	5	8	7	9	10	5	9	9
Foci- Eosinophilic	#	1	1	0	0	0	0	0	1
Foci- Clear cell	#	33	39	34	37	10	7	13	13
Congestion/hemorrhage	#	5	6	12	7	1	3	3	3
Hemorrhage	#	0	1	0	0	0	0	0	0
Pigment deposits	#	5	1	1	1	0	0	0	2
Necrosis – focal/multi-focal	#	3	3	2	3	3	2	2	5
Necrosis – single cell	#	1	0	0	0	0	0	0	0
Heart		50	50	50	49	50	50	50	50
Cardiomyopathy		39	39	41	41	27	28	30	33
Valvular f brosis (p = 0.0048)		0	1	1	2	0	0	2	**4***
Pancreas	#	49	50	50	49	50	50	50	50
Hyperplasia – focal acinar	#	1	3	1	0	0	1	0	0
Hyperplasia – focal ductular	#	1	1	1	1	0	0	0	0
Metaplasia – focal hepatocytic	#	0	0	0	0	0	0	0	1
Hemorrhage	#	0	1	0	0	0	0	0	0
Pigment deposits – perivascular (p=0.021)	#	21	21	20	25	7	10	13	**15***
Pigment deposits – periinsular (p = 0.031)	#	12	10	8	15	3	1	5	**7***
Kidneys	#	50	50	50	49	50	50	50	50
Chronic progressive nephropathy	#	45	48	49	45	41	37	40	33
Hemorrhage/hematoma	#	1	1	0	0	0	0	0	0
Testes	#	50	50	50	49	0	0	0	0
Leydig cell hyperplasia – diffuse	#	2	0	0	0	-	-	-	-
Leydig cell hyperplasia – focal	#	8	7	4	5	-	-	-	-
Clitorial glands	#	0	0	0	0	43	40	42	45
Hyperplasia – focal squamous cell	#	-	-	-	-	1	0	1	0
Hyperplasia – diffuse squamous cell	#	-	-	-	-	1	1	1	0
Hyperplasia – focal acinar cell	#	-	-	-	-	0	1	0	1
Hyperplasia – diffuse reactive (p = 0.016)	#	-	-	-	-	0	1	0	**4***
Hyperplasia – focal reactive	#	-	-	-	-	1	1	0	0
Pituitary gland	#	50	49	48	49	50	50	50	50
Hyperplasia – pars distalis diffuse	#	1	0	0	0	2	2	0	0
Hyperplasia – pars distalis focal	#	19	16	11	13	8	6	5	4
Hyperplasia – pars intermedia diffuse	#	2	1	1	0	0	0	0	0
Pigment deposits	#	0	2	1	2	6	5	4	5
Adrenal gland	#	50	49	50	49	50	50	50	50
Hyperplasia – focal medullary	#	31	34	34	36	17	21	12	15
Hyperplasia – focal zona fasciculata	#	11	12	7	10	3	9	4	5
Hyperplasia – focal zona glomerulosa	#	0	1	0	0	0	1	0	0
Hyperplasia – cortical (combined fas + glom)	#	11	13	7	10	3	10	4	5
RITA: Male: 4.1-73, Female: 8.3-49	%	22	26.5	14	20	6	20	8	10
Hemorrhage/congestion	#	1	1	3	2	0	3	0	0
Pigment deposits/ zona reticularis	#	18	14	13	**26**	25	28	32	**32**
				p = 0.058				p = 0.055	
Mammary gland	#	50	50	50	49	50	50	50	50
Hyperplasia – diffuse	#	0	0	0	0	6	8	6	5
Hyperplasia – focal	#	0	0	0	0	4	**12***	7	2
Hyperplasia – focal with atypia	#	0	0	0	0	1	3	0	1
Hyperplasia – ductular	#	0	0	0	0	0	1	0	0
Pigment deposits (p = 0.032)	#	14	19	16	14	1	0	1	**4***
Skin	#	50	50	50	49	50	50	50	50
Hyperplasia – focal	#	0	0	0	0	0	0	2	0
Hyperplasia – squamous cell	#	0	1	0	0	0	0	0	0
Hemorrhage	#	0	0	0	0	0	1	0	0
Skeletal Muscle	#	50	50	50	49	50	50	50	50
Myodegeneration (p = 0.016)	#	0	2	**6***	4	1	1	1	1
Hemorrhage/hematoma in other tissues									
Spinal cord	#	0/50	0/50	1/50	1/49	0/50	0/50	0/50	0/50

Rat Carcinogenicity Study		BAY 59-7939 Dose level (mg/kg/day)							
Non-Neoplastic Findings		Male				Female			
All main study animals		0	10	20	60	0	10	20	60
Organ/Tissue Finding	#/group	50	50	50	50	50	50	50	50
Nose	#	0/50	0/50	0/50	2/49	0/50	1/50	0/50	0/50
Larynx	#	0/49	0/50	0/49	2/48	0/49	0/50	0/50	0/50
Trachea	#	0/50	0/50	0/49	0/48	0/49	0/50	1/50	0/50
Lungs – aveolar	#	7/50	6/50	3/50	4/49	1/50	0/50	0/50	0/50
Urinary bladder	#	0/50	0/49	0/49	0/49	1/50	0/50	0/50	0/50
Spleen – hematoma	#	0/50	0/50	0/50	0/49	0/50	0/50	0/50	1/50
Lymph node – mesenteric	#	0/49	0/50	1/49	0/49	0/50	0/50	0/50	0/50
Lymph node – mandibular	#	3/50	1/50	5/49	3/49	1/49	2/50	1/50	0/49
Total hemorrhage in other tissues		10	7	10	12	3	3	2	1
Total hemorrhage from liver, etc. above		2	4	3	2	0	4	0	0
Total hemorrhage		12	11	13	14	3	7	2	1
Increased pigment deposits in other tissues									
Lung	#	0/50	0/50	1/50	1/49	0/50	0/50	1/50	0/50
Ovaries	#	-	-	-	-	0/50	0/50	0/50	1/50
Uterus (p = 0.011)	#	-	-	-	-	1/50	3/50	4/50	**7*/50**
Spleen	#	23/50	19/50	28/50	20/49	21/50	21/50	21/50	26/50
Thymus	#	2/44	2/47	1/49	3/46	1/46	1/48	0/48	1/49
Lymph nodes – other	#	0/1	0/1	3/4	0/2	2/4	-	0/1	-
Lymph node – mesenteric (p = 0.054)	#	5/49	7/50	7/49	**11/49**	4/50	5/50	3/50	3/50
Lymph node – popliteal (p = 0.015)	#	6/48	7/44	8/48	4/46	9/50	8/48	12/50	**17*/48**
Lymph node – mandibular	#	21/50	13/50	15/49	19/49	21/49	20/50	19/50	25/49
Lacrimal glands	#	2/49	2/50	7/50	3/48	0/50	0/50	0/50	0/50
Eyes	#	0/49	1/50	0/50	0/48	0/50	0/50	0/50	0/50
Total pigment deposits in other tissues		59	51	70	61	59	58	60	80
Total pigment deposits from liver, etc. above		70	67	59	83	42	44	55	65
Total increased pigment deposits		129	118	129	144	101	102	115	145
Other statistically significant findings									
Hyperkeratosis extremities (p = 0.042)	#	0/0	0/0	0/1	**3*/3**	0/4	0/3	0/4	0/4
Lungs Inflam infiltrate (p = 0.012)	#	1/50	2/50	1/50	2/49	0/50	1/50	3/50	**4*/50**
Ovary hyperplasia sex cord stromal (p = 0.034)	#	-	-	-	-	10/50	5/50	14/50	**15*/50**
Thymus hyperplasia cord & tubule	#	7/44	5/47	5/49	2/46	12/46	**24*/48**	13/48	14/48
Lacrimal glands inflame. infiltrate (p = 0.013)	#	3/49	0/50	0/50	1/50	0/50	1/50	0/50	**4*/50**
Sternum myelofibrosis (p = 0.04)	#	1/50	1/50	3/50	**3*/49**	0/50	0/50	0/50	1/50

* p<0.05

Toxicokinetics

Blood samples were obtained and plasma was prepared from three satellite animals/sex/group at 0.5, 1, 2, 4, 7, and 24 hours after dosing on Days 1 and 381 of treatment. Blood samples were obtained from control animals at 1, 7 hours after dosing. On Day 726, blood samples were obtained from three satellite animals/sex/group at 1.0 hour after dosing. After addition of an internal standard and protein precipitation with acetonitrile, analysis of BAY 59-7939 was performed using a validated LC-MS/MS assay with a lower limit of quantification of 0.002 mg/L. The concentration of BAY 59-7939 in control animals was below the limit of quantification on all three sampling days.

The t_{max} was 1-2 hours on Day 1 and 1 hour on Day 381. Exposure to BAY 59-7939 on all sampling days was lower in males than in females with exposure on Day 381 lower in males by a factor of 0.32 to 0.42 (Table 29, Figure 7). Although exposure increased with dose, the increase was less than dose-proportional. Exposure increased with repeated dosing for 52 weeks by a factor of 1.3 to 1.7 in females. In contrast, exposure in males was essentially unchanged at the two lower dosages and decreased by a factor of 0.74 at the highest dosage. Plasma concentrations at 1.0 hour after dosing on Day 726 were not significantly different from plasma concentrations at 1.0 hour after dosing on Day 381. Since the mean human exposure at the highest recommended daily dose of 20 mg/day was 3.3 mg*hr/L, the exposure multiples for male and female rats on

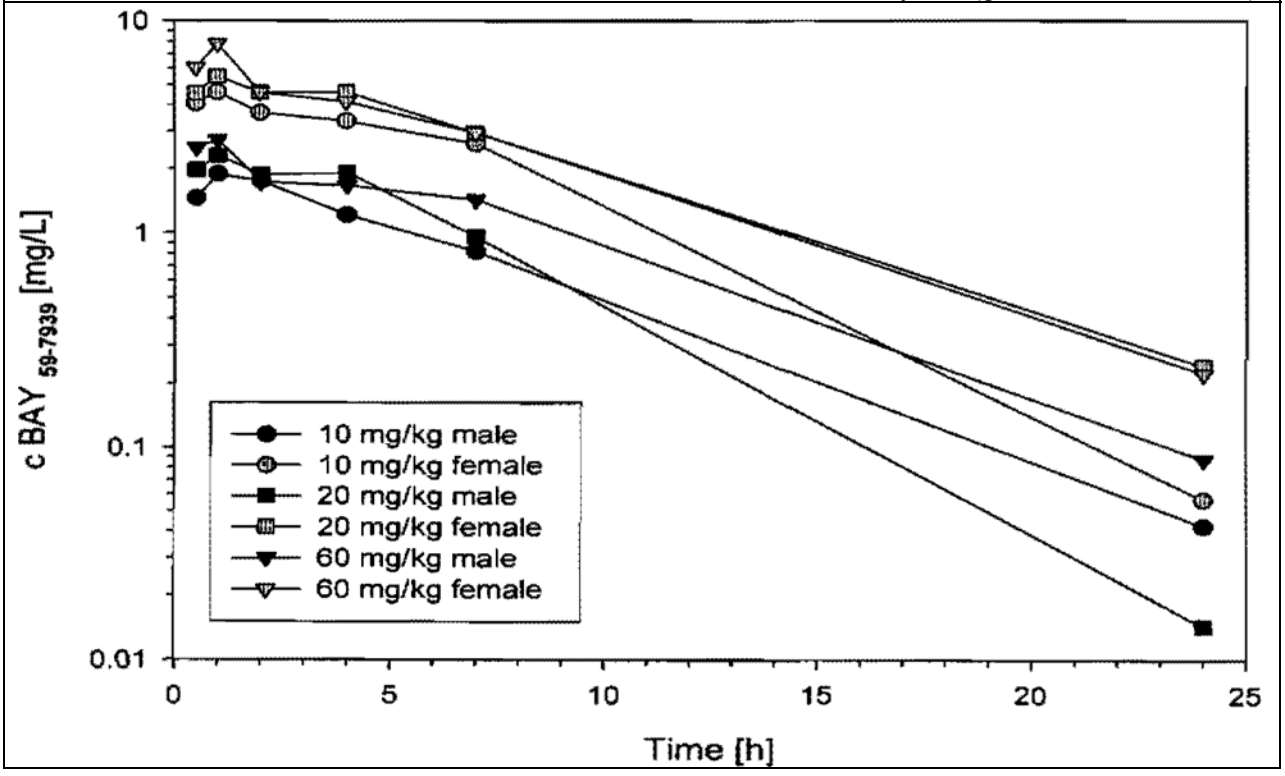
Day 381 were 6.2 and 14.6, respectively, of the human exposure based on total AUC values. These multiples of the human exposure for male and female rats decrease to 1.5 and 3.7, when correction is made for percent protein binding (i.e., amount of unbound drug).

Table 29: Reviewer's Summary of Toxicokinetic Results – Document PH-36242

Toxicokinetic Parameters – Day 1 versus Day 381							
		Male			Female		
Dose (mg/kg)		10	20	60	10	20	60
Day 1							
$AUC_{(0-24)}$	mg*hr/L	11.5	16.6	27.5	20.0	27.8	36.0
C_{max}	mg/L	1.98	2.39	2.92	2.63	3.26	4.09
t_{max}	hr	1.0	2.0	2.0	2.0	2.0	2.0
Day 381							
$AUC_{(0-24)}$	mg*hr/L	13.4	15.4	20.3	34.7	47.5	48.2
C_{max}	mg/L	1.89	2.31	2.73	4.61	5.48	7.81
t_{max}	hr	1.0	1.0	1.0	1.0	1.0	1.0
Plasma concentrations (mg/L) at 1.0 hour after drug administration							
		Male			Female		
Dose (mg/kg)		10	20	60	10	20	60
Day 1	Mean (SD)	1.98 (1.28)	1.91 (1.14)	2.33 (1.08)	2.50 (1.19)	2.65 (1.26)	3.82 (1.30)
Day 381	Mean SD	1.89 (1.19)	2.31 (1.22)	2.73 (1.08)	4.61 (1.16)	5.48 (1.55)	7.81 (1.03)
Day 726	Mean SD	2.31 (1.21)	2.61 (1.46)	2.99 (1.21)	4.05 (1.33)	5.78 (1.15)	5.70 (1.02)

Figure 7: Sponsor's Plasma Concentration Profiles – Document PH-36242

Plasma BAY 59-7939 concentrations after oral administration to rats on Day 381 (geometric mean, n = 3)



Dosing Solution Analysis
Prior to the start of the study, test article formulations at concentrations above 6 mg/mL and below 1 mg/mL were shown to be homogenous and stable for 15 days at room temperature. During the study test article formulations were prepared as needed based on the 15 day stability. Analysis of the dose formulations on eleven days throughout the study showed the formulations were homogenous and the measured concentrations ranged from 90% to 116% of nominal (Table 30).

Table 30: Reviewer's Summary of Formulation Analyses – Document PH-36242

	Nominal concentration, mg/mL		
	1	2	6
Number	11	11	11
Mean recovery, %	103.0	103.7	105.5
SD	4.6	3.8	3.5
Maximum	115	115	116
Minimum	90	95	102

5 Integrated Summary and Safety Evaluation

The nonclinical and statistical reviewers concurred with the sponsor that no significant evidence of neoplasia related to rivaroxaban treatment was observed either in Wistar rats or CD-1 mice. The Executive Carcinogenicity Assessment Committee also concluded that there were no clear drug-related neoplasms in either study.

The safety margins for the highest dosage of rivaroxaban (60 mg/kg/day) used in the carcinogenicity studies were calculated based on AUC values for exposures to total and unbound rivaroxaban. Because the protein binding of rivaroxaban differs significantly among species, the safety margins based on exposures to unbound drug are considered more relevant for comparisons between humans and different animal species.

The recommended daily dosage of rivaroxaban for patients: (a) undergoing hip and knee surgery and (b) with atrial fibrillation is 10 mg and 20 mg, respectively. Consequently, the safety margins reported in the labels for NDA 22406 and NDA 202439 will differ as indicated in Table 31 and Table 32.

Table 31: Safety Margins for Human Dose of 20 mg Rivaroxaban Daily

Study/ Species		Sex	NOAEL (mg/kg) M/F	Exposure at NOAEL		Safety Margin‡	
				Total $AUC_{(0\text{-}24\ hr)}$ (mg*hr/L)	Unbound† $AUC_{(0\text{-}24\ hr)}$ (mg*hr/L)	Based on Total AUC at NOAEL	Based on Unbound AUC
Carcinogenicity – 2 year							
Rat	Tumors	M	60	20.3	0.257	6.2	1.5
		F		48.2	0.612	14.6	3.7
Mouse	Tumors	M	60	2.52	0.162	0.76	1.0
		F		4.24	0.273	1.28	1.6

† Unbound fractions in humans, rats, mice, dogs, and rabbits are 5.07%, 1.27%, 6.45%, 10.4%, and 23.4%, respectively.
‡ Comparison to human exposure at 20 mg/day corresponding to 0.33 mg/kg in a 60 kg patient or 3.3 mg*hr/L. Human exposure to unbound drug was 0.167 mg*hr/L.

Table 32: Safety Margins for Human Dose of 10 mg Rivaroxaban Daily

Study/ Species		Sex	NOAEL (mg/kg) M/F	Exposure at NOAEL		Safety Margin‡	
				Total $AUC_{(0\text{-}24\ hr)}$ (mg*hr/L)	Unbound† $AUC_{(0\text{-}24\ hr)}$ (mg*hr/L)	Based on Total AUC at NOAEL	Based on Unbound AUC
Carcinogenicity – 2 year							
Rat	Tumors	M	60	20.3	0.257	17.4	4.3
		F		48.2	0.612	41.2	10.3
Mouse	Tumors	M	60	2.52	0.162	2.2	2.7
		F		4.24	0.273	3.6	4.6

† Unbound fractions in humans, rats, mice, dogs, and rabbits are 5.07%, 1.27%, 6.45%, 10.4%, and 23.4%, respectively.
‡ Comparison to human exposure at 10 mg/day corresponding to 0.16 mg/kg in a 60 kg patient or 1.17 mg*hr/L. Human exposure to unbound drug was 0.0593 mg*hr/L.

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

/s/

PATRICIA P HARLOW
06/10/2011

THOMAS PAPOIAN
06/13/2011
I concur.

Memorandum

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

DATE: 13 June 2011

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

TO: Ann Farrell, M.D., Acting Director, Division of Hematology Products (DHP), Office of Drug Oncology Products (ODOP)
Min Lu, M.D., Medical Reviewer, DHP
Norman Stockbridge, M.D., Director, Division of Cardio-Renal Products (DCRP), Office of New Drugs (OND)
Preston Dunnmon, M.D., Medical Reviewer (Safety), DCRP

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

SUBJECT: Hepatic effects of rivaroxaban (XARELTO®,), NDA 22-406, re-submitted 3 January 2011 by Johnson & Johnson, for the indication: prophylaxis of deep vein thrombosis and pulmonary embolism in patients undergoing hip or knee replacement (priority review); and
NDA 202-439 submitted 5 January 2011 by Ortho McNeil Janssen Pharmaceuticals, for the indication: prevention of stroke and systemic embolization in subjects with atrial fibrillation (standard review).

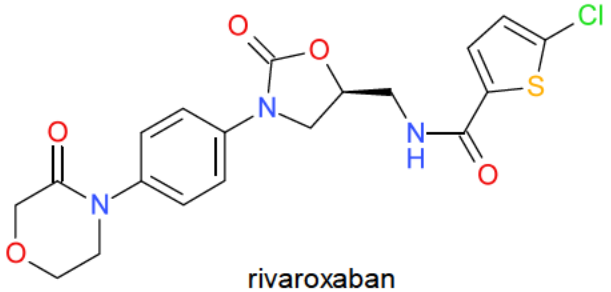
Documents reviewed:

1) Consultation request from DHP dated 11 February 2011 asking for review of findings related to liver toxicity, desired response date 30 March, assigned OSE #2011-516; and a second consultation request dated 25 May 2011 asking for comments on the draft labeling regarding hepatic effects, specifically sections 6,2 and 8.7 or other sections, desired response date 13 June, assigned OSE #2011-1858. This NDA 22-406 was granted priority review status, as a resubmission addressing deficiencies in a previous submission that had received a complete response letter from DMIHP 27 May 2009. The DCRP did not submit a formal request for consultation but asked for a copy of the response to DHP for consideration in its review of NDA 202439 for the indication of prevention of strokes in patients with atrial fibrillation and possible advisory committee discussion in November 2011.
2) Selected pertinent medical literature articles on rivaroxaban
3) Submitted data on 14,236 subjects with chronic atrial fibrillation randomized to oral rivaroxaban or warfarin in ROCKET study in studies carried out worldwide.
4) Documents submitted by the sponsor and its consultants to both NDAs.

The search continues for orally effective anticoagulants that do not require periodic monitoring of their activity (such as warfarin, which usually has a narrow range of dosing in an individual, to avoid the bleeding risk if too much or insufficient anticoagulation if too little, and therefore

must be checked periodically and dose adjusted to keep in the desired range of prothrombin time for plasma clotting or its international normalized ratio (INR) between 2 and 3. Anticoagulation is the current treatment of choice for prevention of strokes and systemic embolization in patients with chronic or recurrent atrial fibrillation, a common disorder in tens of millions of elderly people worldwide. It is also important in reducing the incidence of deep vein thrombosis (DVT) and pulmonary emboli (PE) in patients after surgery for replacement of knee or hip, procedures.

Rivaroxban was discovered by Bayer Schering Pharma (Roehrig et al. 2005; Misselwitz et al., 2011). It is an oxazolidinone derivative that exerts anticoagulant effects by directly inhibiting factor Xa in the blood coagulation cascade. The product BAY 59-7939 was licensed by Johnson & Johnson for co-development as XARELTO, JNJ 39039039 for possible marketing to prevent DVT and PE and later by Ortho McNeil Janssen Pharmaceuticals to reduce the incidence of ischemic strokes and systemic emboli in patients with non-valvular atrial fibrillation. Rivaroxaban was submitted for indication of "prophylaxis of deep vein thrombosis and pulmonary embolism in patients undergoing hip or knee replacement surgery" on 3 January 2011 as N 022406 for priority review by the Division of Hematology Products (DHP). A second application was submitted at the same time for review by the Division of CardioRenal Products (DCRP) as NDA 202439, and was accepted for standard review for the indication of preventing strokes and systemic emboli in patients with non-valvular atrial fibrillation.



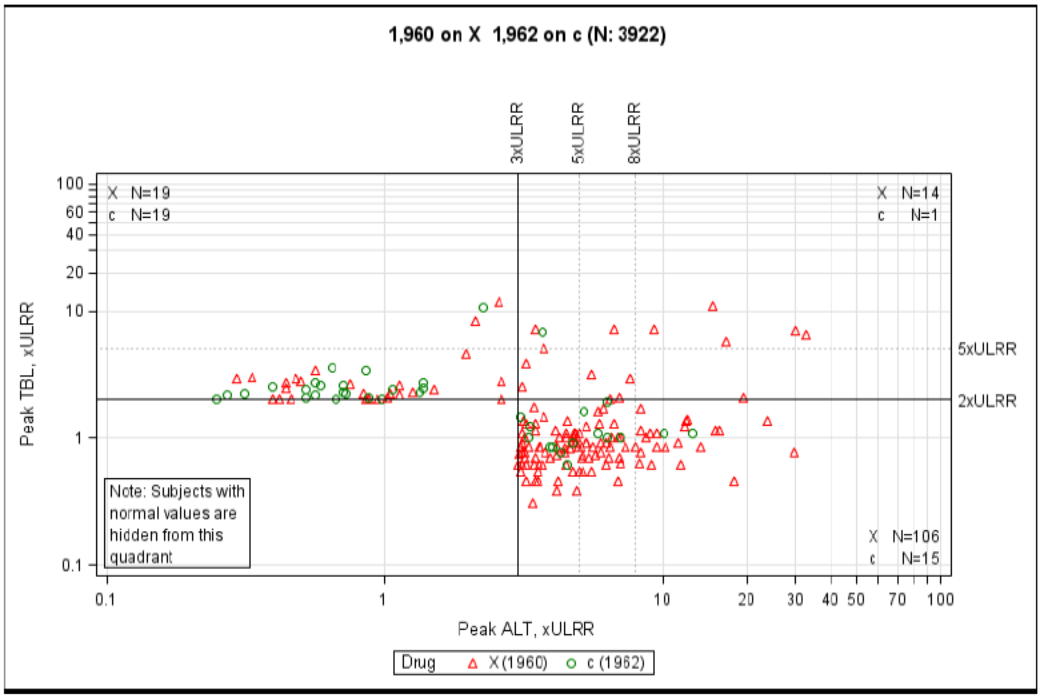
rivaroxaban

Because of earlier experience with ximelagatran (EXANTA®, AstraZeneca) whose NDA 21-686 was not approved 8 October 2004 because of hepatotoxicity, Boehringer Ingelheim proceeded a bit more slowly (Ezekowitz, 2004) and amassed a huge total of 18,113 patients with chronic atrial fibrillation enrolled in the RE-LY clinical trial worldwide (Connolly et al., 2009), and anticoagulants for use in the population of people with atrial fibrillation have been scrutinized very carefully, as was done for the recently approved dabigatran (PRADEXA®, Boehringer Ingelheim).

The original submission of NDA 22-406 was made on 28 July 2008, but was found to have several deficiencies for which a complete response letter was sent 27 May 2009, despite the generally favorable opinion of the Cardiovascular and Renal Drugs Advisory Committee at its meeting on 19 March 2009. There was expressed some concern about possible hepatotoxicity if the drug was given for longer than 2 (knee) or 5 (hip) weeks, for which findings of long-term studies would be important. They did not feel that the risks could be avoided by dose reduction. The hepatotoxicity risks were addressed in presentations by Dr. Paul Watkins representing the company, and by Dr. Kate Gelperin for DCRP, slides for which may be seen (Lincoff AM, Ferguson E, 2009). Both speakers referred to the earlier experience with ximelagatran, pointed

out that for rivaroxaban in the 2 and 5-week studies carried out in the 12,383 patients randomized in the four RECORD studies there was no unfavorable imbalance in the numbers of patients showing serum enzyme activity elevations or elevations with total bilirubin (TBL) concentration increases, between those on exoxaparin and on rivaroxaban prophylaxis. Further, the sponsor had asked several consulting hepatologists to review individual patients of special interest because both peak alanine aminotransferase (ALT) activities and TBL concentrations were increased; their findings were summarized by Dr.Watkins. No signal of rivaroxaban-induced serious liver injury was found in either the group or individual reviews for the relatively short-term exposure, but because of the earlier ximelagatran experience, all were interested in findings from long-term studies. In presenting for he sponsor, Dr. Watkins used extensively the diagnostic tool invented and developed at CDER under its Regulatory Science Review research program by Drs Guo, Gelperin, and Senior and termed "eDISH" for **e**valuation of **d**rug-**i**nduced **s**erious **h**epatotoxicity. He subsequently published his opinion that it should be used by industry as well as Agency reviewers (Watkins, 2011).

The initial impetus to develop eDISH came from the ximelagatran experience, where clearly it was important to consider in close detail *individual cases* of special interest for possibly serious hepatotoxicity. A means was needed to select out of huge numbers of patients studied in clinical trials those few cases of special interest for whom detailed additional informationwas needed to permit good clinical assessment of the severity of the liver dysfunction. No pathognomonic test or procedure for diagnosis of drug-induced liver injury (DILI) is known; it remains a diagnosis of exclusion requiring adequate clinical information for the differential diagnosis. Using the eDISH analytical system (Guo et al.), we looked in 2005 at the EXANTA® results (AstraZeneca) after ximelagatran had not been approved. We displayed an x-y plot of peak ALT (abscissa) and peak TBL(ordinate) as log-log (base 10) values of multiples of the ULN for each patient, in four quadrants defined by a vertical line at ALT 3xULN and a horizontal line at TBL 2xULN. The reason for using log-log plots was to keep the relative elevations in viewable range, and so that the ALT would not swamp the TBL rises.

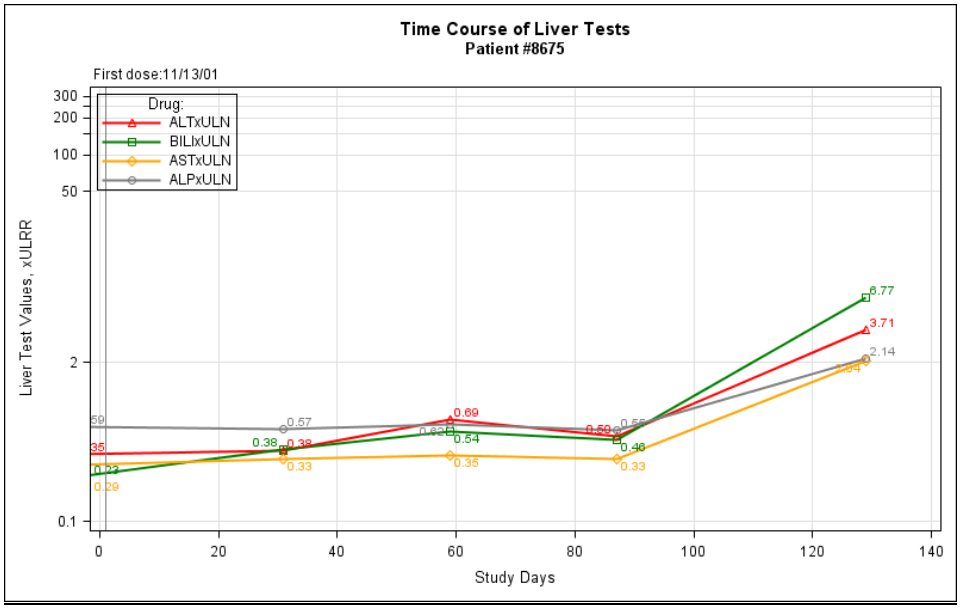


It is immediately obvious at a glance that there were 7 times more patients who showed ALT elevations on ximelagatran (X) as on Coumadin (C) in the right lower (southeast, SE) quadrant, and 14 times more who also showed bilirubin elevations as well as ALT elevations (the "Hy's Law" quadrant, upper right or "NE"). By clicking the pointer over any symbol, a time-course graph is generated showing all of the liver test data reported for that individual patient (ALT, AST, ALP, TBL), so the time relationships of the variables can be seen easily. Again, the laboratory tests values are shown and compared as the log10 values for multiples of elevation above the normal upper limit, for visual comparison without removing the magnitude of each compared to the other. Time is shown on a linear scale.

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

Of the 14 cases on ximelagatran 7 were adjudicated probable, 1 very likely, and the other 6 very unlikely (1), unlikely (4), 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 caused by hepatitis B.

Also available for inspection by the reviewers 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 xxxxxx. 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.* In the potential Hy's Law quadrant (upper right, "northeast" NE) only 1 Coumadin patient (green circle, C) was seen, versus 14 on EXANTA (red triangles, X). Time course and clinical narrative information on the lone patient on C in the NE quadrant revealed that his test abnormalities were caused by cancer of the pancreas that became recognized while he was on study, not by warfarin. In contrast, 7 patients on X had at least probable DILI, 1 more possible DILI, out of the 14 total.



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. (b) (6) *approximately* (b) (6) *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 [redacted] *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.* [redacted] *, 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* [redacted] *four months after start of study drug* [redacted] *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#)*

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):

Comment: As located by eDISH, the patient in question was 1190-8675 in the SPORTIF V study. Clicking on the symbol for that patient brought up the time course of liver tests over the period of his observation. It was 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). Retesting on 21 Mar 2002 showed elevations in bilirubin to 6.77xULN, ALT to 3.71xULN, and he was hospitalized [redacted], when it was discovered that he had pancreatic carcinoma. The work-up permitted a well supported conclusion that the tumor was the definite cause of the findings and warfarin toxicity was very unlikely. He died from inoperable pancreatic cancer [redacted]. Thus, a grading of CMP 2, INF 3, SEV 3, LIK of wILI 0 and cause definitely pancreatic cancer 5, but not warfarin 0.

Dr. Watkins had looked at the clinical trials called RECORD for the 2 and 5-week exposures to rivaroxaban for reducing DVT and PE in patients having knee or hip replacement surgery, and using eDISH did not observe any imbalance in frequency of liver test abnormalities between the patients on enoxaparin or warfarin. Interest then turned to focus on the long-term studies of patients with atrial fibrillation, as a valuable safety issue even for patients on shorter periods of exposure to rivaroxaban.

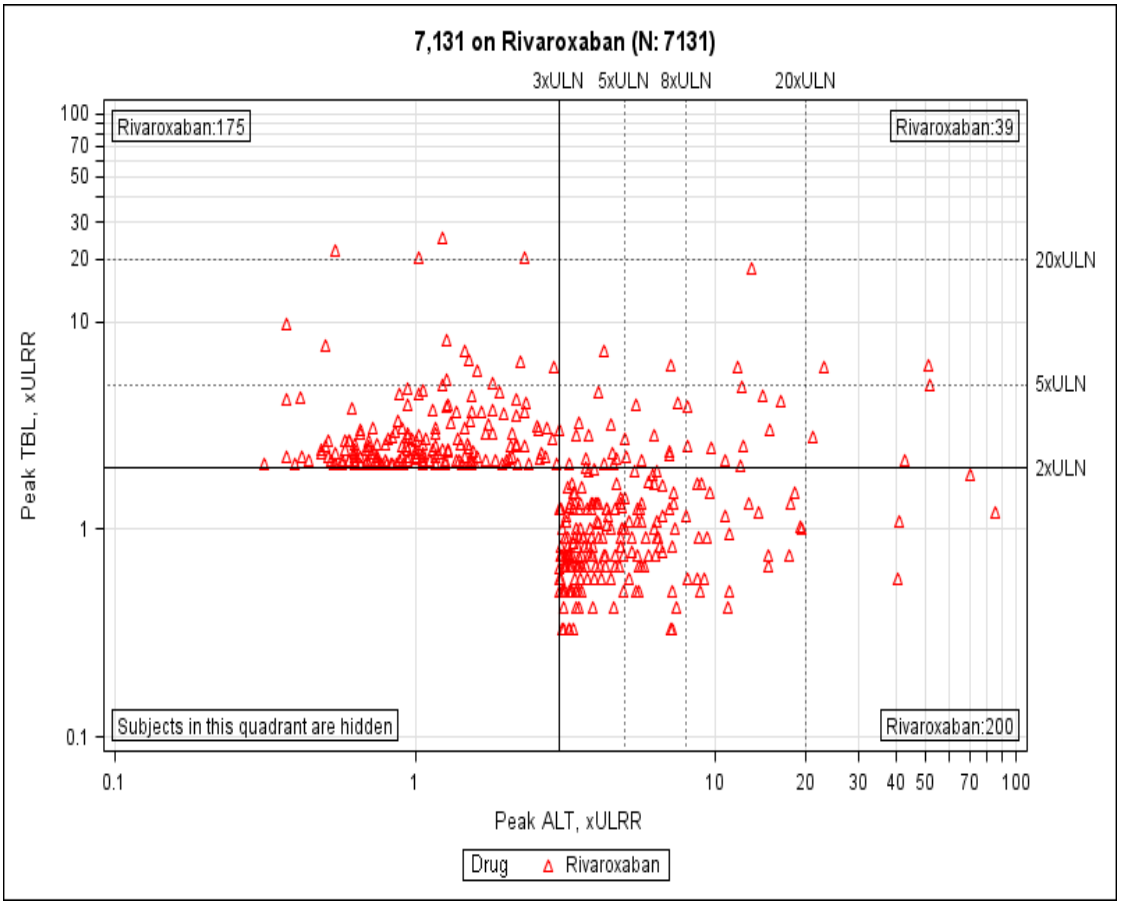
The ROCKET (**R**ivaroxaban **O**nce-daily oral direct factor Xa inhibition **C**ompared with vitamin **K** antagonist for the prevention of study of stroke and **E**mbolism Trial in atrial fibrillation) study randomized 14,264 (7,131 rivaroxaban; 7133 warfarin) subjects with atrial fibrillation (Af) for 2 years. The details of demographics and geographics, inclusion and exclusion criteria, and other protocol definitions will be found in the medical efficacy review. After some back-and-forth interactions with the sponsor, liver test data in acceptable format were obtained and entered into the database for eDISH analyses by Dr. Guo, and clinical narratives for selected cases of special interest were requested. Using eDISH system to look at the ROCKET data, the pattern was quite different from that seen for ximelagatran but fairly similar to what we had found for dabigatran.

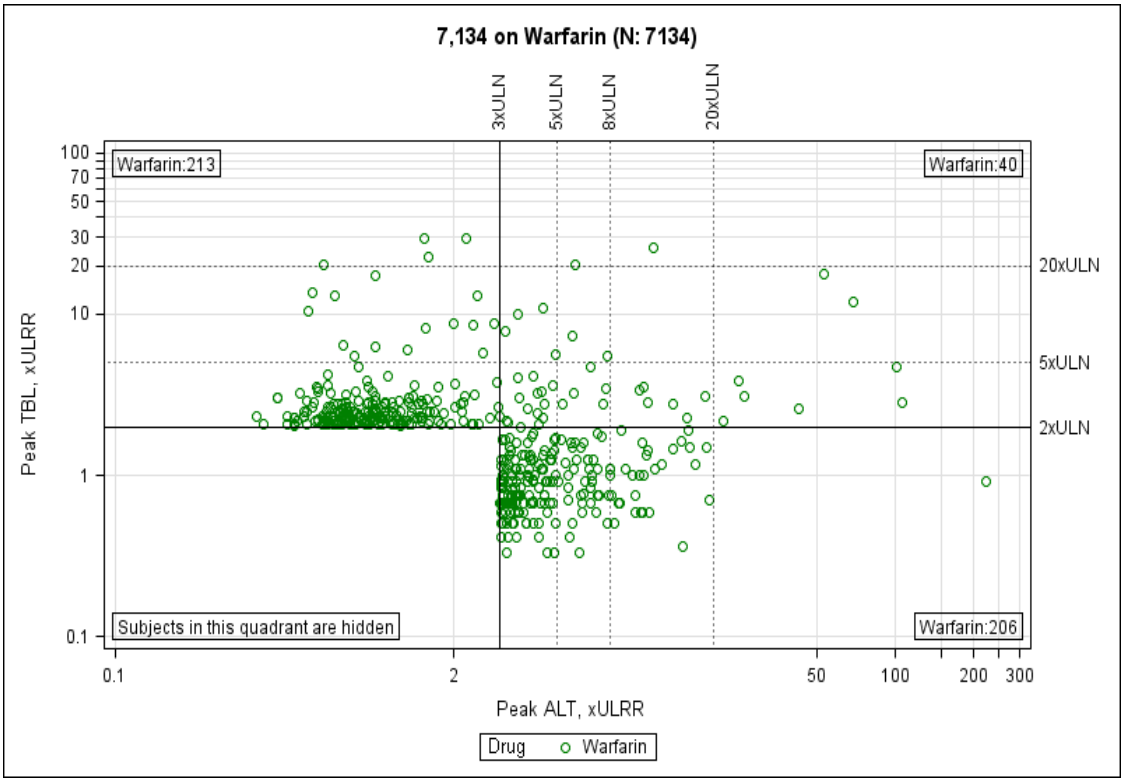
Applying what we had learned from the ximalagatran study, in a similar fashion to that used for the recent dabigatran analyses, we approached the longer-term study of rivaroxaban with a new concept of looking primarily for the probable or most likely cause of the hepatic injury or dysfunctional indicators and clinical data, rather than simply trying to rule-out drug-induced liver injury (DILI). Although we are still not able to estimate the causal likelihood with great precision or consistency, we do use the categories of percentage likelihood similar to those of the DILIN (drug-induced liver injury network), slightly modified and with greater likelihood reflected by higher scores, as follows for these analyses, and further explained and justified below:

Almost certain, definite -	>95% (96-100%)	score 5
Very likely -	>75-95% (76-95%)	score 4
Probable -	>50-75% (51-75%)	score 3
Possible -	>25-50% (26-50%)	score 2
Unlikely -	>4-25 % (5-25%)	score 1
Very unlikely -	<5% (0-4%)	score 0

We believe that serious liver dysfunction has some cause, even though we may not know or be able to find out what it is, that there is no undefined "background rate," and that uncertainty is mainly the result of insufficient information. The scores assigned may be made equivalent to DILIN scores by subtracting from 6. It is conceded that these brackets of estimated percentage likelihood are arbitray and based upon opinions, but at present no more precise estimations are possible.

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. The 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 are unambiguous are common bile duct stones 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.


7,131 on Rivaroxaban (N: 7131)
3xULN 5xULN 8xULN 20xULN
Rivaroxaban:175
Rivaroxaban:39
Subjects in this quadrant are hidden
Rivaroxaban:200
20xULN
5xULN
2xULN
Peak TBL, xULRR
Peak ALT, xULRR
Drug Rivaroxaban


7,134 on Warfarin (N: 7134)
3xULN
5xULN
8xULN
20xULN
Warfarin:213
Warfarin:40
Subjects in this quadrant are hidden
Warfarin:206
20xULN
5xULN
2xULN
Peak TBL, xULRR
Peak ALT, xULRR
Drug Warfarin

In contrast to the previous ximelagatran findings, no imbalance of peak ALT or peak (ALT&TBL) were seen in the large ROCKET study.

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 leading to liver transplant or causing death. It has been our practice to classify severity of liver injury in five grades:

1) ALT or AST >3xULN, usually transient and reversible by adaptation = mild
2) Also TBL >2xULN, after or concurrent, indicating early functional loss = Hy's Law case
3) Serious, meaning symptomatic, disabling, requiring or prolonging hospitalization
4) Acute liver failure, secondary failure of brain or kidney function due to liver dysfunction
5) Fatal (from liver failure), 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 increasing 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 >ULN – 2.5xULN; 2) moderate, if >2.5-5xULN; 3) severe, if >5-20xULN; and 4) life-threatening, if >20xULN. 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 20-30xULN 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

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.

Using this process for the patients randomized to rivaroxaban in the ROCKET study, we found:

Potential Hy's Cases Randomized to rivaroxaban (39 of 7131 exposed; 0.55% or 1/183)							
subject	Country	sex age	CMP	INF	SEV	LIK R-ILI	probable cause
100996	Bulgaria	M71	3	3	3	1	Very likely (4) heart failure
102880	Romania	F 65	2	1	3	1	CD stone (2) or uncertain (2)
104201	Taiwan	M49	3	2	3	0	Acute heart failure (5)
108923	United States	M58	4	4	3	0	Cholecystits(3); heart failure (2)
115921	Romania	M76	3	3	3	0	CD stone, cholangitis (5)
100792	Romania	M48	3	3	3	0	Acute CMV (4); hep B (1)
100338	Lithuania	M58	2	1	2	0	Hepatitis C (3); alc. hep (2)
103926	Taiwan	M61	3	4	3	0	Hepatocellular CA (5)
102733	Great Britain	M70	4	4	3	0	Pancreatic CA (5)
108584	Russia	F 67	1	1	2	1	Alcoholic hepatitis (2); uncertain 2
105059	Argentina	M78	2	3	3	0	Cardiogenic hepatopathy (5)
108182	Germany	M66	4	4	2	0	Pancreatic CA (5)
115901	Argentina	F 78	4	3	1	0	Colon CA, liver mets (5)
106725	Russia	F 58	2	1	2	2	Steatohepatitis 2; uncertain 2
108241	Romania	M52	2	1	2	1	Acute pancreatitis 3; uncertain 1
107710	India	F 74	3	3	3	1	Acute hepatitis E (4)
102861	Canada	M74	4	3	2	0	Pancreatitis, cholecystitis 5
115515	Romania	M81	3	2	3	0	Pancreatitis 3; cholecystitis 2
105348	Canada	M82	4	4	3	0	CD stones, cholecystitis 5
102253	Spain	M79	3	3	3	0	CD sludge, cholecystitis 5
101013	South Korea	M64	3	3	2	1	Chronic hepatitis B flare 4
105441	Czech Republic	M74	3	3	2	1	Cardiogenic hepatopathy 4
103861	Australia	M73	4	3	2	1	Acute CMV hepatitis 3;Augmentin 1
105428	South Africa	M79	4	4	3	0	Calculous cholecystitis 5
116413	Poland	M60	3	3	2	2	Worsened heart failure 3
107703	Russia	F 70	1	1	2	1	Hepatitis B 2; uncertain 2
111406	Russia	F 78	2	2	3	0	CD stone, cholecystitis 5
103877	Argentina	F 73	1	1	2	1	Uncertain 4
100098	Hungary	M64	0	0	2	1	Uncertain 4
100650	United States	M78	3	2	3	0	Pancreatic CA 5
107387	Russia	F 70	3	3	3	0	Calculous cholecystitis 5
105128	Philippines	F 78	1	1	2	1	CD stones 3; uncertain1
104495	United States	M89	4	4	3	0	CD stones 3; heart failure 2
101573	Chile	M62	0	1	1	1	Uncertain 4
105785	Argentina	M78	1	0	1	1	Covert alcoholic 2; uncertain 2
100402	Bulgaria	F 79	1	0	1	1	Uncertain 4
102409	India	M83	1	1	1	1	Uncertain 4
104083	India	F 87	0	0	2	2	Uncertain 3
113553	Bulgaria	M68	0	0	2	1	Uncertain 3; heart failure 1

And for the patients randomized to warfarin in the ROCKET study, we found:

Potential Hy's Cases Randomized to warfarin (40 of 7134 exposed; 0.56% or 1/178)							
subject	Country	sex age	CMP	INF	SEV	LIK R-ILI	probable cause
107035	Russia	M56	3	2	3	0	Cardiac arrest 5
112679	Poland	F 72	3	2	4	0	Pulmonary embolus, heart failure 5
113608	Brazil	M43	4	4	4	0	Severe cardiac failure 5
101773	Chile	F 62	4	3	3	1	Acute hepatitis B (4)
110960	South Korea	M61	3	2	2	1	Acute heart failure 4
108165	Canada	M81	1	2	3	1	Cardiogenic hepatopathy 4
106780	India	F 77	2	1	3	2	Diclofenac 2; heart failure 1
108569	United States	M76	4	4	3	1	CD stone, sludge 4
116639	Great Britain	M67	4	2	4	1	Cardiogenic hepatopathy 4
109730	Singapore	M72	3	2	2	1	Heart failure 3; CMV 1
116761	Argentina	M63	3	3	2	1	Acute hepatitis C (4)
101271	Thailand	M48	2	2	3	1	Worsened heart failure 3
111052	Brazil	M63	2	2	2	1	Hepatitis C (4)
110588	United States	F 66	3	3	3	1	Heart failure, shock 4
112126	Czech Republic	F 78	4	4	3	1	CD stones 4
104111	Czech Republic	F 76	4	4	3	1	CD stone 4
112771	United States	M89	3	3	2	0	Acute cholecystitis 5
109538	Czech Republic	M76	2	2	2	2	Gallbladder sludge 3
109103	United States	F 60	2	2	2	1	Acute pancreatitis 4
105006	Germany	F 75	2	2	3	1	CD stone 4
108475	China	F 78	2	2	4	1	Acute myocardial infarction 4
115267	China	F 84	2	2	3	1	Recurrent CD stone 4
106239	Australia	M78	2	1	2	2	Uncertain 3
109999	China	M76	1	1	2	1	Calculous cholecystitis 4
111453	United States	F 87	3	4	3	0	CD stone, cholangitis 5
101230	Taiwan	M72	2	2	1	2	Uncertain 3
102225	Philippines	M57	1	1	1	1	Uncertain 4; Gilbert syndrome
112147	Brazil	M69	3	3	3	0	Acute hepatitis A,B (4); lymphoma 1
106199	Ukraine	M75	1	1	1	1	Uncertain 4; Gilbert syndrome
103724	Philippines	M68	0	0	1	1	Uncertain 4; Gilbert syndrome
114789	Australia	M64	1	1	1	1	Uncertain 4
100044	United States	M84	2	2	2	1	Worsened heart failure 4
104949	South Korea	M79	2	1	2	1	Uncertain 4
111827	United States	F 60	2	2	2	2	Worsened heart failure 3
115879	Russia	M59	1	1	2	1	Alcoholic hepatitis 3; uncertain 1
103820	United States	M80	3	3	3	1	CD stones 4
108749	South Korea	M72	1	1	3	1	Alcoholic hepatitis 2; uncertain 2
110038	Poland	M72	2	2	2	1	Worsened heart failure 4
111778	Columbia	F 85	3	3	3	0	Acute heart failure 5
112797	Columbia	M71	3	3	3	0	Septic choledocholithiais 5

For each of the cases of special interest shown by the eDISH system in the right upper quadrant, inspection of the time course and review of the supplemental narrative information was done to attempt making a clinical diagnosis of what may have caused the liver dusfunction or injury that was observed. Not all of the cases had sufficient information to reach a firm conclusion about the

probable or most likely cause, which remained uncertain in a few of the cases, epecially those that were of mild severity and indicated mainly by slight elevations of peak ALT activities over 3xULN. Also, only a few of the cases showed sever dysfunction and evidence of acute liver failure, usually in the setting of severe cardiac injury with congestive failure and hypotension and with multi-organ failure (see warfarin cases 2, 3, 9, 21). In most cases the information that was provided allowed a clinical diagnosis of the probable (3), very likely (4), or almost certain (5) cause of the findings. No cases of probable serious DILI were found for either drug (it was not our practice to attribute the cause to the drug just because of uncertainty in these analyses).

We had not previously evaluated the quantity and quality of information used to make the differential diagnosis of the likelihood of what caused the abnormal findings, but made an initial attempt to do this, and 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 of the liver injury or dysfunction for each patient. We looked closely at the 79 cases shown by eDISH in the upper right (NE) quadrant, 40 of whom were on warfarin, 39 on rivaroxaban. Full tabulations of the abstracted data from narratives, clinical courses, and scores assessed for each of the 79 patients evaluated are shown in the Excel files of Appendix I for the ROCKET study, and truncated tabulations are shown below. Absent enough information, the probable diagnosis may be uncertain.

In considering these selected cases of potential "Hy's Law" applicability,we started with the eDISH extraction of cases of interest who showed {peak ALT >3xULN & peak TBL >2xULN}, then examined the time course of the four key variables ALT, AST, ALP, and TBL in each of them, and finally used the provided narrative summaries of clinical information to attempt making a diagnosis of the most likely cause of the liver problem in each case. Listed below are the estimated probable causes:

ADJUDICATED MOST LIKELY CAUSE OF LIVER DYSFUNCTION IN 79 POTENTIAL HY'S LAW" CASES

probable cause of observed liver dysfunction	rivaroxaban	warfarin
biliary tract disease, common ducts stones/sludge	10	11
cardiac failure, worse if with cardiogenic shock	5	14
uncertain diagnosis – inadequate information to diagnose	11	9
acute viral hepatitis – A, B, C, CMV	5	4
acute pancreatitis or discovery of carcinoma	6	1
acute alcoholic hepatitis	0	1
liver cancer – primary or metastatic	2	0
Total	39	40
rivaroxaban	**0**	**-**
warfarin	**-**	**0**

The patients from this sample with potentially serious liver injury came from a population sample with frequent obesity, diabetes mellitus, hypertension, past myocardial infarction or angina, pat ischemic strokes, fluctuating degrees of congestive heart failure, and atrial fibrillation. They averaged 71 years of age, had mean body mass index of about 29 (almost obese). Incidence of potentially serious liver injury or dysfunction was not rare, about 0.55% or

about 1 in 180 patients during the time of observation in these studies of chronic atrial fibrillation. There was no imbalance in the frequency of potentially serious liver injury, or of lesser injury manifested only by serum enzyme increases between the two groups on long-term anticoagulation. Although the concept of "background rate" may be a misnomer, the incidence of problems with a diagnosable cause was considerable. It was reassuring that subjects on rivaroxaban in the ROCKET study did not show as a group or as individuals any probable cases of serious liver injury that could be confidently attributed to either warfarin or rivaraoxaban. The high incidence of uncertain as the most likely diagnosis echoes the findings of the Acute Liver Failure Study Group that considers even more severe liver dysfunction in patients admitted to liver transplantation units, where even extensive and careful attempts to discover the probable cause are frustrated by insufficient available information to make a confident diagnosis. Until physicians learn to investigate, follow closely, and actively pursue the diagnosis of what caused liver injury in a patient under their care, we shall continue to be frustrated by inability to make causal diagnoses with accuracy.

Please scan the Excel files sent along with this Word document as Appendix I to view the more detailed listings of additional clinical information (body mass index [BMI],; peak values for ALTx, ASTx, ALPx, and TBLx; and "R" values (ratio of peak ALTx/ALPx to estimate the likelihood of hepatocellular (>5), cholestatic (<2), or mixed (2-5) liver injury. Also shown in the attached Excel tables are brief summaries of the clinical narrative information used to estimate likelihood of probable cause and severity in each case to see how the evidence was used to make the estimates.

It should be borne in mind by evaluators, the sponsor, investigators, and treating physicians that patients with atrial fibrillation represent 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 rivaroxaban. Nevertheless, it does not appear reasonable to recommend 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 is 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

This individual case review of the large ROCKET study provided confidence that no serious hepatoxicity could be attributed to rivaroxaban (or warfarin), which was in concurrence with the conclusion of the sponsor's expert hepatology panel and the findings of the shorter-term study in the RECORD analyses of 2009. It was also reassuring that there was no imbalance in the cases considered potentially "Hy's Law" by simple counts of serum chemistries (39 of 7131 exposed to rivaroxaban, 0.55% or 1/183, and 40/7134 exposed to warfarin, 0.56% or 1/178). The total of over 13,000 patients exposed to short-term (RECORD 6,183) or long-term (ROCKET 7,131)

treatment with rivaroxaban to reduce risks of DVT, PE, ischemic strokes, or peripheral emboli in susceptible patients was strong and compelling evidence for hepatic safety of rivaroxaban.

As a consequence, no additional warnings were suggested for the draft labeling now in consideration for possible approval, as communicated to the DHP labeling review team on 2 June:

I have been following labeling discussions by DHP closely, and refer to the latest draft versions circulated yesterday and today by Tyree Newman. Specifically with reference to section 6.1 (not 6.2) on Adverse reactions in clinical trials, (b) (4) *For section 8.8 (not 8.7) on Hepatic Impairment the principal concern is for bleeding if the drug is used in patients with previous liver disease, and the labeling appears to give sufficient warning to physicians, also reflected in Section 5.4 Hepatic Impairment. The labeling as it is being developed by DHP for those sections appears to be satisfactory with respect to liver-related problems.*

The more concerning issue is long-term exposure to rivaroxaban as an alternative to warfarin in prevention of strokes, under review in DCRP, and whether there might be greater problems as had been observed with ximelagatran (Exanta) that was not approved in 2004. We have conducted case-by-case critical review of patients in the ROCKET study and have not found numerical imbalance in cases showing serum enzyme rises or in those with consequent serum bilirubin increases in patients on rivaroxaban compared to those on warfarin. Further, probable cause of the abnormalities has not shown that the likelihood of probable, very likely, or definite attribution is different for either warfarin or rivaroxaban. We are awaiting some additional reports for smaller studies before reporting to DCRP, but will copy DHP with those findings and assessments.

Recommendations:

1) No additional labeling warnings or precautions beyond those already included in the current draft language are suggested.
2) Rivaroxaban appears relatively safe for long-term as well as short-term use as an anticoagulant agent for reduction of the incidence of DVT and PE in patients having knee or hip replacement procedure, as well as for reduction in ischemic strokes in patients with non-valvular atrial fibrillation.
3) Routine monitoring of serum indicators of liver injury during treatment has been found to be inefficient, ineffective, very burdensome, and is neither necessary nor recommended for this drug..

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Appendix I

Please see the Excel file “Hy’sR&Wcases.xls” sent along with this Word file “JRSrivaroxaban.doc” for detailed data on 39 cases for ROCKET subjects randomized to rivaroxaban and 40 cases for subjects randomized to warfarin who showed potential Hy’s Law findings of (peak ALT >3xULN & peak TBL >2xULN) during the period of their observation on study. These 79 cases were looked at in close detail, with eDISH plotting of their time courses of all four key liver test variables (ALT, AST, ALP, and TBL) during the period of their observation in the study. In addition, narratives providing additional clinical information on each of the cases were evaluated to make the best possible differential diagnosis of the most likely cause of the liver injury or dysfunction. In cases where the information provided was not adequate to make a diagnosis of probable cause, a diagnosis of “uncertain” was made. That diagnosis was not interpreted to infer possible drug-induced injury, but the best alternative possible diagnosis from the information available was assigned. The completeness of information provided, and how well it was used to inform the attending physicians was also estimated, and estimates of the severity of liver dysfunction and likelihood that it was caused by the study drug was estimated.

Unfortunately, the Excel tables that follow in the co-submitted file proved too large to be incorporated into this Word document, despite valiant efforts of several experts in Microsoft products. Therefore they are being submitted separately.

2009 (Day 737) showed ALT 1.9 xULN, rising to 12.9x on 30 November (Day 756). Investigation showed bile duct 11 mm and carcinoma of the head of the pancreas was shown 4 January (Day 791). Increasing jaundice was evident, and R was stopped 20 January 2010 (Day 807). A Whipple procedure was done (b) (6); liver tests normalized 9 March (Day 855).

007057	**108584**	**Russia**	**F**	**W**	**67**	**39.60**	**6.56**	**12.31**	**2.50**	**1.80**	**6.8**	**1**	**1**	**2**	**1**	alcoholic hepatitis 2, uncertain 2

Comment: A very obese Russian woman 67 with past hypertenion, transient ischemic attack,fairly severe heart failure and Class III and Af started R 18 June 2008. After over a year elevated serum aminotransferases (ALT 8.2 and AST 5.3 xULN) were noted on 3 September 2009, not confirmed on 22 September. No action was taken and tests remained normal until R was stopped 5 March 2010 (Day 626) because of "non-compliance." Recurrent elevations of aminotransferaes and total bilirubin were noted 7 April, a month later, normalizing 29 April. The family revealed that she occasionally drank alcohol.

054014	**105059**	**Argentina**	**M**	**W**	**78**	**33.61**	**11.08**	**12.25**	**4.83**	**0.78**	**15.7**	**2**	**3**	**3**	**0**	cardiogenic hepatopathy 5, Gilbert syndrome

Comment: An obese Argentinian man 78 with diabetes, hypertension, heart failure Class I, and Af started R on 29 January 2008. He showed repreated asymptomatic and mild bilirubin elevations (Gilbert syndrome) bu no serum enzyme increases until (b) (6) after he had been admitted to hospital for hematemesis and melena, found by endoscopy to have resulted from two prepyloric gastric ulcers. He was anemic and hypotensive, requiring tranfusions, and underwent antrectomy and duodenal resection. He did not do well, required mechanical ventilation, developed cardiogenic shock, cardiac arrest, and died (b) (6)

049062	**108182**	**Germany**	**M**	**W**	**66**	**30.60**	**10.00**	**12.01**	**2.03**	**3.54**	**3.4**	**4**	**4**	**2**	**0**	CA pancreas 5

Comment: An mildly obese German man 66 with history of diabetes, hypertension, mitral insufficiency, congestive heart failure Class II, and Af started R 5 June 2008. He showed two AST 6xULN elevations without ALT, ALP, or TBL increases after (b) (6) days that were not investigated or explained. After over a year on R he showed major aminotransferase elevations 19 Agust 2009 (b) (6) and investigation led to finding bile duct dilation (b) (6). R was stopped on 31 August, and further studies showed panceatic CA for which a Whipple procedure was done (b) (6). Liver tests were normalized postoperatively and he was still living when last seen 4 June 2010 (b) (6)

054012	**115901**	**Argentina**	**F**	**W**	**78**	**30.86**	**6.17**	**11.86**	**6.02**	**4.50**	**2.6**	**4**	**3**	**1**	**0**	CA colon. Liver metastases. 5

Comment: An obese Argentinian woman 78 with past hypertension,peripheral arterial disease, transient ischemic attack, mild congestive failure class I, and Af started R 26 March 2009.Over a year later on 18 May 2009 (Day 419) she was found to have ALT 12xULN and to be anemic (Hb 5.1 g/dL). Colonoscopy showed carcinoma and liver metastases were found. She had stopped R on 16 May, and when last seen 13 July had become jaundiced.

narrative truncated

007067	**106725**	**Russia**	**F**	**W**	**58**	**30.86**	**3.00**	**10.76**	**2.17**	**1.11**	**9.7**	**2**	**1**	**2**	**2**	steatohepatitis 2, uncertain 1

Comment: A slightly obese Russian woman 58 with diabetes, hypertension, angina, heart failure class II, and Af started R on 8 April 2008. She showed borderline ALT elevations repeatedly (possible steatohepatitis), but on 12 November (Day 219) ALT 10.7, AST 3, and TB: 2.2 xULN following her report of abdominal pain and nausea 1 November. No action was taken, but repeat testing over the next 8 days showed retun of the values to normal. Abdominal ultrasound testing showed enlarged fatty liver and R was stopped 14 November. Left renal stones were noted, and serum tests for viral hepatitis were reported to be negative.

040005	**108241**	**Romania**	**M**	**W**	**52**	**35.26**	**5.15**	**9.68**	**2.49**	**5.44**	**1.8**	**2**	**1**	**2**	**1**	acute pancreatitis 3, uncertain 1

Comment: An obese Romanian man 52 with prior hypertension, transient ischemic attack, congestive failure class II, and Af was started on R 23 May 2008, and showed no liver test abnormalities for over 22 months, but on 16 March 2010 (Day 663) he complained of abdominal pain and "meteroism' This was initially attributed to biliary colic, but ultrasonogram the next day showed a relaxed gallbladder with no stones. The ALT rose to 9.7x and AST 5.2x, but ALP to 5.4x and TBL 2.5x. Marked GGT elevation was also noted, and serum amylasewas 5xULN. He had claimed light alcohol use in the past, and did not admit to resuming. Tests for viral hepatitis makers were negative for acute disease.

091024	**107710**	**India**	**F**	**A**	**74**	**22.43**	**6.82**	**8.06**	**3.92**	**0.88**	**9.2**	**3**	**3**	**3**	**1**	acute hepatitis E - 4

Comment: An Indian woman 74 with past hypertension, transient ischemic attack, no heart failure, and Af started R on 2 May 2008 and continued for over a year with normal liver tests excpt for one small, asymptomatic, transient ALT 2.3x on August 19 (Day 110)that was not investigated or explained. On 22 October 2009 (Day 539), 18 months after starting R, her ALT and AST were elevated to 8.1x and 6.8x with TBL3.9xULN. She compolained of abdominal pain and weakness, and later testing showed heptitis E IgM anibody indicating acute infection. The R was stopped 30 October 2009, and she recovered

without treatment. She later was reported to have died of unkown cause [redacted] (b) (6).

011504	**102861**	**Canada**	**M**	**W**	**74**	**23.76**	**17.92**	**8.03**	**2.52**	**2.22**	**3.6**	**4**	**3**	**2**	**0**	pancreatitis 5; acute cholecystitis, Q225

Comment: A Canadian man 74 with history of diabetes, hypertension, mild mitral insufficiency by no heart failure started on R 29 October 2007 and continued on it for 20 months without abnormal liver tests. On 28 June 2008 he complained of epigastric pain and tests howed elevated serum enzymes and bilirubin, ultrasound a distended gallbladder with tiny stones and enlraged pancreas by tomography.His last dose of R had been on 6 June. Sphincterotomy was done, with drainage of purulent bile, and he recovered promptly.

040007	**115515**	**Romania**	**M**	**W**	**81**	**30.47**	**9.24**	**7.43**	**4.05**	**1.50**	**5.0**	**3**	**2**	**3**	**0**	pancreatitis 3; cholecystitis 2

Comment: An obese Romanian man 81 with prior hypertension, ischemic stroke, and Af started R on 9 March 2009. He showed a transient, isolated, asymptomatic AST elevation to 5.4xULN on April (Day 53) but no further abnormal liver tests until 31 March 2010 when he complained of abdominal pain and nausea, showed elevated AST, ALT, and TBL to 9.2x, 6.9x, and 4.1xULN on 2 April, with elevated serum amylase 3.3xULN. Gallbladder sludge but no stones were seen by ultrasound, and tests for viral hepatitis were negative. He reported perviou light alcohol use.He recovered on conservative treatment and R was continued until 15 June 2010 (Day 454).

011033	**105348**	**Canada**	**M**	**W**	**82**	**25.10**	**11.27**	**7.07**	**6.22**	**4.75**	**1.5**	**4**	**4**	**3**	**0**	acute cholecystitis , cd stones 5

Comment: A Canadian man 81 with previous hypertension, stroke, glaucoma, and Af started R on 7 February 2008 and had. no liver test abnormalities until 29 May 2009 [redacted] (b) (6) *when acute cholecystitis was diagnosed. Cholecystectomy was done* [redacted] (b) (6) *and a stent was inserted because all the stones could not be removed. An ERCP was done* [redacted] (b) (6) *and the stent removed. R had been interrupted during time of procedures, but was resumed for another year until 23 June 2010.*

034021	**102253**	**Spain**	**M**	**W**	**79**	**26.93**	**10.64**	**6.98**	**2.39**	**1.87**	**3.7**	**3**	**3**	**3**	**0**	acute cholecystitis, sludge 5

Comment: A slightly overweight Spanish man 79 with past hypertension and AF srarted R on 18 October 2007, continued on it for over 18 months without liver test abnormalities. He developed right upper abdominal pain 7 May 2009 with elevated serum enzymes and bilirubin and was diagnosed with acute cholecystitis with biliary sludge. He had antibiotic treatment and R was interrupted for 5 days, then resumed as the acute findings subsided. The R was stopped 9 June 2009.

082013	**101013**	**South Korea**	**M**	**A**	**64**	**28.26**	**4.71**	**6.98**	**2.28**	**0.90**	**7.8**	3	3	2	**1**	chronic hepatitis B flare 4

Comment: An overweight South Korean man 64 with history of hypertension, ischemic stroke, chronic hepatitis B, and Af started R on 30 July 2007 and continued on it for over 9 months without serious liver test abnormalities except for slight asymptomatic ALT elevations (chronic hepatitis B?) in the range of 1.5 to 2xULN. His ALT rose to 3xULN on 7 May 2008, and then to 7xULN on 26 May (Day 302), and R was stopped 3 June. This was followed by slowly rising TBL to 2.3xULN on 30 July 2008. The abnormalities subsided, and he was reported to have had a stroke [redacted] (b) (6) *later.*

042009	**115441**	**Czech Republic**	**M**	**W**	**74**	**22.05**	**6.59**	**6.20**	**2.83**	**2.43**	**2.6**	**3**	**3**	**2**	**1**	cardiogenic hepatopathy 4

Comment: A Czech man 74 with past hypertension, transient ischemic attack, angina, myocardial infarction, aortic and mitral regurgitation, heart failure class II,, peripheral arterial disease, and Af started R on 11 March 2009. Chest pain occurred on [redacted] (b) (6) *and diagnosis of recurrent myocardial infarction with reduced ejection fraction was made.R was stopped on 13 October* [redacted] (b) (6) *He recovered but was readmitted for hypotension and heart failure* [redacted] (b) (6) *and later had ventricular fibrillation, treated successfully but death in heart failure occurred* [redacted] (b) (6)

061032	**103861**	**Australia**	**M**	**W**	**73**	**29.86**	**5.29**	**5.63**	**2.15**	**3.08**	**1.8**	4	3	2	**1**	acute CMV infection 3; Augmentin toxicity 1

Comment: A slightly obese Australian man 73,with past hypertension, myocardialinfarction, bypass graft, heart failure class II, and Af started R on 4 December 2007. Serum total bilirubin wsa repeatedly elevated slightly (Gilbert syndrome) but more so on 2 April (Day 121) after worsened heart failure.He received Augmentin Forte for six weeks from 11 April to 21 May,and a week later showed rises in ALT and AST to 5.6x and 5.3xULN, with TBL 2.1xULN. Serological tests showed CMV IgM and IgG in blood taken 27 May (Day 176), and R was stopped 29 May 2008

027006	**105428**	**South Africa**	**M**	**W**	**79**	**31.84**	**4.55**	**5.45**	**4.00**	**5.32**	**1.0**	**4**	**4**	**3**	**0**	acute calculous cholecysttis 5

Comment: An obese South African man 79 with past hypertension, diabetes, angina and bypass, pacemaker, and Af started R on 7 February 2008. On 2 June [redacted] (b) (6) *) he showed ALT and ALP elevations to 4.1 and 3.1xULN, and then on 23 June* [redacted] (b) (6) *to 5.5x and 5.3xULN (cholestatic ratio). Ultrasound revealed gallstones and shrunken gallbladder, after which cholecytectomy was done* [redacted] (b) (6) *Abnormalities subsided despite continuing R until 23 July 2008.*

048027	**116413**	**Poland**	**M**	**W**	**60**	**37.75**	**7.11**	**5.02**	**2.25**	**1.66**	**3.0**	**3**	**3**	**2**	**2**	worsened heart failure 3;

Comment: A very obese Polish man 60 with history of hypertension, ischemic stroke, heart filure Classs II, and Af started R on 7 May 2009. Worse heart failure occurred in late August with elevated AST 4.8x and ALT 3.7xULN without bilirubin rise until 22 September (Day 139) when it rose to 2.25xULN. Biliary tract and viral tests were negative.

															2	
007026	107703	Russia	F	W	70	27.68	4.82	4.97	2.75	0.78	6.4	1	1	2	1	hepatitis B 2; uncertain 2

Comment: A somewhat overweight Russian woman 70 with past hypertension, transient ischemic attack, goiter, and Af was started on R 13 May 2008 and showed an asymptomatic unexplained rise in ALT to 2.0xULN on 10 June (Day 29) but then no further liver test abnormalities until 2 June 2010 (Day 751), about 2 years later, when ALT was 5x and AST 4.8xULN . and TBL 2.7xULN. Serological studies showed HBsAg, but further testing was refused, and R was stopped 1 June 2010.

007031	111406	Russia	F	W	78	36.16	4.69	4.69	2.21	1.33	3.5	2	2	3	0	cholecystitis, cd stone 5

Comment: A very obese Russian woman 78 with diabetes, hypertension, ischemic stroke, serious heart failure class III, and Af started R on 24 September 2008. She showed minor ALT elevations in February-April 2009 but no abnormalities until 9 February 2010 (b) (6) after mild right uppr abdominal pain. Bile duct dilatation and calculous cholecystitis was seen by ultrasound, and cholecystectomy was done (b) (6) R had been stopped on 10 March.

045039	103877	Argentina	F	W	73	28.89	9.12	4.56	2.06	2.97	1.5	1	1	2	1	uncertain 4

Comment: An overweight Argentinian woman 73 with diabetes, hypertension,transient ischemic attack, congestive heart failure class II, and Af started R on 12 December 2007. Isolated ALT elevation to 2.2x on 8 May (Day 149) was mild, asymptomatic and not explained. After 11 months on R ALT rose to 4.6xULN, AST 9.1xULN and TBL 2.1x on 29 October (Day 323), a month after R was stopped because the subject "withdrew consent" for unstated reason.

036016	102098	Hungary	M	W	64	28.70	8.09	4.51	2.33	0.64	7.0	0	0	2	1	uncertain 4

narrative truncated

Comment: An overweight Hungarian man 64 with diabetes, hypertension,myocardial infarction, congestive heart failure Class II, and Af started R on 1 October 2007. Transient asymptomatic ALT 3.1x and AST 2.3xULN wre noted 26 November (b) (6) but not investigated or explained, and R was continued for more than two years with only very minimal elevations of ALT to 1.7x and TBL to 1.2ULN on1 August 2008 (b) (6)). The subject had a transient ischemic attack (b) (6) and AST 8.1 and ALT 4.5xULN were noted and TBL rose to 2.3xULN on 18 March, after which R was stopped the next day (b) (6)). The cause of the abnormalities was not investigated.

001051	100650	United States	M	W	78	34.28	5.03	4.46	3.17	3.62	1.2	3	2	3	0	pancreatic carcinoma 5

Comment: An obese U.S. man 78 with diabetes, gout,hypertension, transient ischemic attack, prostatic hypertrophy and Af started R on 26 June 2007. Slight ALT increaes with rise in bilirubin were noted in November-January, rising to 3.03xULN 5 February 2008 (b) (6) Prior to that he had some bruising and minor bleeding. His R stopped 11 January (b) (6) after which he had an elective cholecystectomy (b) (6) , but liver biopsy at operation disclosed carcinoma that had metastasized from the pancreas. The bilirubin rise to 3.03xULN was three weeks after R stopped. He died (b) (6).

007012	107387	Russia	F	W	70	28.25	2.85	4.25	7.21	0.69	6.2	3	3	3	0	acute calculous cholecystitis 5

Comment: An overweight Russian woman 70 with past diabetes, hypertension, myocardial infarction, heart failure Class II, and Af started R on 23 April 2008. (b) (6) she complained of abdominal pain, nausea, and vomiting, leading to hospitalization for acute calculous cholecystitis. Serum ALT 4.3x, AST 2.9x,ALP 0.7x and TBL 7.2xULN were noted, and cholecystectomy was done (b) (6) later. She resumed taking R for 20 months more without serious liver injury although a transient ALT elevation to 2.9xULN occurred on 22 April 2009 (b) (6)

063004	105128	Philippines	F	A	78	20.67	2.68	4.22	2.08	1.01	4.2	1	1	2	1	CD stones 3, hepatitis D 1

Comment: A thin Philippina woman 78 with history of hypertension, stroke, congestive heart failure class II, and Af started R on 1 February 2008. After a year she showed elevated ALT 4.2 and SAT 2.7xULN but normal TBL and ALP. No action was taken and the abnormalities gradually subsided but recurred 16 July 2009 (Day 532) and ultrasound showd gallbladder sludge and stones. The abnormalities again subsided without surgical action and testing showed her positive for hepatitis D but not B (!).She continued on R until 31 May 2010 (Day 831).

001492	104495	United States	M	W	89	25.06	6.05	4.06	4.58	8.67	0.5	4	4	3	0	CD stones 3,heart failure 2

Comment: A U.S. man 89 with past hypertension, peripheral arterial disease, mild congestive failure class I and Af started R on 9 Januray 2008. He had hemorrhoidal bleeding and was transfused with two units of fresh frozen plasma and one of packed red cells (b) (6) he developed shortness of breath and acute heart failure and on 1 April showed ALT 4.1x, AST 4.4x, and TBL 3.8x, ALP 8.7xULN and tomography showed common duct stones. The

stones were removed surgically, after stopping R [redacted]

056004	101573	Chile	M	W	62	27.10	2.25	3.79	2.83	0.71	0.0	0	1	1	1	uncertain 4

Comment: An overweight Chilean man 62 with history of diabetes, hypertension, and Af started R on 14 September 2007. He showed modestly elevated bilirubin concentrations repeateedly without symptoms (probable Gilbert syndrome). A transient ALT elevation to 3.8xULN on 12 September 2008 was not confirmed and not studied. Another ALT rise to 3.3xULN on 2 December 2009 was confirmed at 3.5x on 16 December, but again was ignored and R was continued until 25 June 2010 (Day 1016). Information about liver effects was almost nil.

054028	105785	Argentina	M	W	78	39.45	6.11	3.69	2.18	1.22	3.0	1	0	1	1	uncertain 2; secret drinker 2

Comment: A very obese Argentinian man 78 with pastdiabetes, hypertension, mitral insufficienct, congeative failure Class II, and Af started R on20 February 2008. He had trauma to the left thigh [redacted] *with a rise in serum TBL to 2.2 on 29 October* [redacted] *with rise in ALT, attributed to pigment from the thigh hematoma. On 8 May 2009* [redacted] *) his AST was found to be 6.1x and ALT 3.7xULN without elevation of ALP or TBL, after complaints of gastroenteritis, melena, and dehydration for two days, and R was stopped 11 May 2009* [redacted]

359001	100402	Bulgaria	F	W	79	18.83	6.74	3.49	3.29	2.77	1.3	1	0	1	1	uncertain 4

Comment: A very thin Bulgarian woman 79 with history of hypertension, myocardial infarction, ischemic stroke, congestive failure Class II, and Af started R on 8 June 2007. On 5 August (Day 307) she had abdominl pain, vomiting, and was admitted with adiagnosis of "gastritis," but was shown by ultrasound to be due to common duct stone with serum AST 4.1x, ALT 3.5x, ALP 2.4x, TBL 3.3xULN. She was treated conservatively and the abnormalities subsided despite resumtion of R treatment. On 9 April 2008, similar symptoms led to gastroscopy that showed acute exudative gastritis; her AST was 6.7, ALT 2.7x, and TBL 1.9xULN. These findings were not investigated, and she remained on R until 3 June 2010 (Day 1092).

380019	102409	India	M	W	83	25.06	3.08	3.43	2.83	0.65	5.3	1	1	1	1	uncertain 4

Comment: An Indian man 83 with hypertension, angina, congestive failure class II, and Af started R on 16 October 2007. He showed asymptomatic, repeated but small TBL elevations for a year (Gilbert syndrome), then on 8 January 2009 his ALT rose to 3.4x, AST 3.1xULN, not explained. [redacted] *he reported exertional dyspnea and required hospitalization for treatment of worsened heart failure. She remained on R until 10 June 2010* [redacted]

091016	104083	India	F	A	87	26.31	2.47	3.25	2.08	0.83	3.9	0	0	2	2	uncertain 3

Comment: A slightly overweight Indian woman 87with history of hypertension, stroke, Af was started on R 19 December 2007. On 23 January (Day 36) she showed rise in ALT to 3.3x, AST 2.5x, TBL 2.1xULN without reporte symptoms, and negative physical examinationbut no studies were done.The abnormalities resolved without treatment and she continued R until 2 July 2008 (Day 197) when she refused to participate any longer..

359015	113553	Bulgaria	M	W	68	32.28	2.39	3.03	3.00	0.46	6.6	0	0	1	1	uncertain 3; heart failure 1

Comment: An obese Bulgarian man 68 with diabetes, hypertension, congestive failure class I, and Af was started on R on 30 December 2008. He showed repeated very slight TBL elevations (Gilbert syndrome) for a year. On 2 Decmber (Day 338) his ALT was 2.3xULN. Repeat tests showed slow climb of ALT to 3.03x, AST to 2.4xULN, after which the slight abnormalities subsided and he stayed on R until 2 June 2010 (Day 675). No investigations were done.

39 cases

Site	Subj	Country	Sex	race	Age	BMI	pASTx	pALTx	pTBLx	pALPx	R	CMP	INF	SEV	LIK	probable cause

WARFARIN **WAR**

Site	Subj	Country	Sex	race	Age	BMI	pASTx	pALTx	pTBLx	pALPx	"R"	CMP	INF	SEV	LIK	probable cause
		40 cases														
048008	112679	Poland	F	W	72	40.25	350.78	100.90	4.68	0.70	144.1	3	2	4	0	heart failure 5; pulmonary embolus,
Comment: A morbidly obese Polish woman 72 with diabetes, hypertension, moderately severe heart failure class III, and Af started W on 12 November 2008, and showed only two very slight elevations in TBL (possible Gilbert syndrome) in over a year on W. (b) (6)) she had a pulmonary embolus with subsequent acute heart falure and her AST rose sharply to 351x, ALT 101xULN on 19 December. The W was stopped (b) (6), and she died in heart and multiorgan failure (b) (6)																
055074	113608	Brazil	M	W	43	29.38	33.00	69.02	11.90	1.14	60.5	4	4	4	0	cardiac failure 5
Comment: An almost-obese Brazilian man 43 with diabetes, hypertension, coronary stent congestive heart failure class II, and Af started W 23 December 2008 and tolerated it wlel for a year, with no abnormal liver tests. (b) (6) (b) (6) he developed worsened heart failure for which he was hospitalized (b) (6) with cardiorespiratory arrest from which he was resuscitated. (b) (6) he showed renal failure, attributed to sepsis, and W was stopped the next day. (b) (6) he showed ALT 69x, AST 33x, and TBL 11.9xULN and died (b) (6)															*narrative truncated HEAC+*	
056019	101773	Chile	F	I	62	56.77	54.41	53.23	17.59	4.12	12.9	4	3	3	1	acute hepatitis B (4)
Comment: A morbidly obese Chilean woman 62 with history of chronic obstructive pulmonary disease, hypertension, heart failure class III, and AF started W on 24 September 2007 Petechiae of the lower legs were noted 17 October, and a week later ALT and AST rose to 20.5x and 17.6x, TBL 1.2x and ALP 1.7xULN. W was stopped on 25 October (b) (6) The abnormalities peaked (b) (6) at ALT50.7x, AST 54.4x, TBL 13.1x, and ALP 4.1xULN and she was hospitalized with jaundice (b) (6)). Tests of sera revealed heptitis B IgM and HBsAg; the acute events subsided after she was discharged (b) (6) she was followed with no further liver test abnormalitis until 27 February 2008.																
082009	110960	South Korea	M	A	61	23.31	78.08	42.61	2.58	1.40	30.4	3	2	2	1	acute heart failure 4
Comment: A South Korean man 61 with history of diabetes, hypertension, ischemic stroke, myocardial infarction, and Af started W on 16 September 2008. He showed slight TBL elevations without symptoms on several occasions during the first year on W but no serum enzyme abnormalities (probable Gilbert syndrome). Hematuria occurred (b) (6) and a left ureteral stone was found by computed tomography. His W was stopped and shockwave lithotripsy was done the next day, complicated by pneumonia. (b) (6)) chest xray showed pulmonary edema, cardiomegaly, and pleural effusion, followed by worse dyspnea (b) (6) and very sharp rise in AST to 78.1, ALT to 38.1xULN (b) (6) . He was treated for heart failure and the serum aminotransferases quickly declined, but he did not wake and was transferred in vegetative state (b) (6), then died (b) (6) Cause of death was recorded as dysrhythmic cardiac arrest.															*narrative truncated HEAC+*	
011578	108165	Canada	M	W	81	29.16	39.07	26.35	3.06	3.34	7.9	1	2	3	1	cardiogenic hepatopathy 4
Comment: An overweight Canadian man 81 with history of diabetes, hypertension, aortic stenosis, mitral regurgitation, mild heart failure class I, and Af started W on 11 June 2008. His liver tests remained normal for 22 months despite a myocardial infarction (b) (6) and subsequent coronary bypass graft (b) (6) recurrent heart failure occurred and W was stopped, but AST rose to 39.1x, ALT 26.4x, TBL 3.1x, ALP 3.3x on (b) (6) when myocardial infarction and ischemic hepatitis were diagnosed, with death that day															*narrative truncated HEAC+*	
091022	106780	India	F	A	77	23.63	18.29	24.94	3.82	1.38	18.1	2	1	3	1	diclofenac 2; uncertain 1; heart failure 1
Comment: An Indian woman 77 with hypertension and Af started W on 28 March 2008. She complained of arthralgia on 21 September (b) (6)) and was treated with diclofenac for three weeks. On 11 November slightly elevated ALT 1.8xULN was noted, increasing to 4.3xULN on 5 December (b) (6)) and W was stopped 4 days later because it was suspected as a cause.Her ALT continued to rise to 29.4xULN on 22 January and AST to18.x TBL 3.8xULN on 27 January (b) (6)). Serological testing was negative for viral hepatitis A, B, C, D, and E, and abdominal sonography was not diagnostic. The liver test abnormalities subsided but did not normalize and worsened again when she developed bronchopneumonia 21 May 2009 and severe heart failure, leading to her death (b) (6)															HEAC+	
001826	108569	United States	M	W	76	37.76	24.06	21.77	2.17	1.73	12.6	4	4	3	1	cd stone, sludge 4
Comment: A very obese U.S. man 76 with diabetees, hypertension,acarotid and peripheral arterial disease, angina, coronary																

bypass graft, previous cholecystectomy and choledocholithiasis, benign prostatic hypertrophy, renal calculi, memory loss, and AF started W on 16 June 2008. Unexplained ALT elevation to 2.3xULN was noted 23 April 2009 (b) (6), and on 10 July (b) (6) showed AST 24.1x and ALT21.8x, TBL 2.2xULN; sonography showed dilated common ile duct, with sludge and stones, and sphincterotomy was done (b) (6) but cholangitis developed , treated with antibiotics. W was restarted 31 July and continued without further liver test abnormalities until 31 May 2010 (b) (6)

044023	**116639**	**Great Britain**	**M**	**W**	**67**	**22.88**	**0.64**	**18.58**	**3.06**	**1.06**	**17.5**	**4**	**2**	**4**	**1**	cardiogenic hepatoathy 4

Comment: A British man 67 with history of ischemic stroke, myocardial infarction, cardiomegaly,Churg-Strauss syndrome (allergic vasculitis), pulmonary congestion, and Af started W on 23 April 2009. After recurrent cardiac ischemia and new cerebral ischmic attack W was stopped on 2 February 2010 (b) (6) Another myocardial infarction with cardiac arrest occurred (b) (6) and ALT was 14.7x, TBL 1.4xULN on 15 March (b) (6)), rising to ALT 18.6x, TBL 3.1xULN (b) (6) when he died. The death certificate recoed acute hepatic failure; no autopsy was done.

narrative truncated
HEAC+

065001	**109730**	**Singapore**	**M**	**A**	**72**	**25.75**	**6.00**	**15.80**	**2.25**	**2.08**	**7.6**	**3**	**2**	**2**	**1**	heart failure 3, CMV 1

Comment: A slightly overweight Singapore man 72 with hypertension, ischemic stroke, obstructive lung disease, angina, coronary stent, congestive failure Class II, and AF startedW on 14 July 2008). On 30 July (b) (6) ALT elevation to 3.1x, AST 2.2x, TBL1.2xULN were noted, rising to ALT 8.2x, AST 6.0x, TBL 1.8x ALP 1.7xULN on 1 August, and ALT 15.8x, TBL 2.3xULN on 5 August (b) (6) Serology reported positive CMV (?acute or chronic) and past EBV, and W was stopped 4 August (b) (6) (b) (6) he was admitted to hospital for acute congestive heart failure. It was treated but recurred (b) (6), although his elevated liver tests had normalized and remained so until his death from sepsis (b) (6) days after the last W dose).

054012	**116761**	**Argentina**	**M**	**W**	**63**	**32.10**	**13.53**	**13.92**	**2.75**	**1.24**	**11.2**	**3**	**3**	**2**	**1**	acute hepatitis C (4)

Comment: An obese Argentinian man 63 with history of diabetes, hypertension, ischemic stroke, congestive heart failure, and Af started W on 5 May 2009. Heart failure worsened again on Day 157, resolved, but recurred on Day 219 with slight bilirubin elevation transiently. Serum aminotransferases became elevated on Day 325 along with hyperglycemia following glibencamide cessation and increase in glimepiride dose 9 days before, and W was stopped, but jaundice was noted on Day 351 when aminotransferase levels also peaked and glimepiride was also stopped. No viral hepatitis cause was found, and acute mild hepatitis C was discovered, with confirmation by HCV RNA 4430 IU/L.

066006	**101271**	**Thailand**	**M**	**A**	**48**	**26.73**	**18.71**	**11.66**	**25.96**	**2.00**	**5.8**	**2**	**2**	**3**	**1**	worsened heart failure 4

Comment: A slightly overweight Thai man 48 with history of diabetes, hypertension, fatty liver, ilent gallbladder stones, obstructive lung disease, congestive failure II, myocardial infarction, and Af started W on 21 August 2007. Repeated but modest and asymptomatic bilirubin elevations indicated probable Gilbert syndrome. Acutely worsened heart failure was noted on (b) (6) (21 November), with sharp rise in serum bilirubin concentration and aminotransferase activities not improved by stopping warfarin, but returning to normal after the heart failkure was treated successfully in late November, although the bilirubin remained elevated for many weeks during which recurrent heart failure occurred that led to his death (b) (6) after warfarin was stopped.

055041	**111052**	**Brazil**	**M**	**W**	**63**	**27.94**	**18.06**	**11.09**	**2.85**	**1.62**	**6.8**	**2**	**2**	**2**	**1**	hepatitis C( )4

Comment: An overweight Brazilian man 63 with history of diabetes, light alchol use, schemic stroke, pacemaker, and Af started W on 11 September 2008. He reported a skeletal injury on (b) (6), took analgesics for pain, and then an episode of acute alcoholic intoxication in (b) (6) a toe injury with infection and susequent amputation (b) (6). Study warfarin was stopped 31 May, and hepatitis C was diagnosed (b) (6) after W was stopped.

narrative truncated

002529	**110588**	**United States**	**F**	**W**	**66**	**34.08**	**59.05**	**10.78**	**3.53**	**2.99**	**3.6**	**3**	**3**	**3**	**1**	congestive heart failure, shock 4

Comment: An obese white U.S. woman 66 with history of diabetes, obstructive lung disease, hypertension, coronary bypass surgery, aortic and mitral regurgitation, congestive failure II, and Af started W on 20 August 2008. On 18 October she had severe congestive failure with hypotension and very sharp AST elevation to 60x , ALT 10.8x ULN and mild jaundice TBL (3.5 x ULN), all responding to treatment of her heart failure. Warfarin was stopped 3 November (Day 76).

042029	**112126**	**Czech Republic**	**F**	**W**	**78**	**32.79**	**9.57**	**10.31**	**3.85**	**6.17**	**1.7**	**4**	**4**	**3**	**1**	common duct stones. 4

Comment: An oese Czech woman 78 with history of diabetes, hypertension, fatty liver, congestive failure II, angina, stones in gallbladder, osteoporosis, peripheral neuropathy, and Af started W on 21 October 2008. After a bout of worsened heart failure and aminotransferse elevations (b) (6), she developed bilirubin elevation with abdominal pain and was found

narrative truncated

to have dilated common bile duct and stones were removed by ERCP. Warfarin wsa interrupted but rsumed and continued until 2 Jun 2010 (b) (6) without recurrent liver injury.

042026	**104111**	**Czech Republic**	**F**	**W**	**76**	**28.58**	**8.68**	**7.81**	**5.50**	**2.84**	**2.8**	4	4	3	0	common duct stone 5

Comment: An overweight Czech woman 76 with history of bone tuberculosis, left mastectomy, hysterectomy, depression, colon polyps, osteoporosis, past hepatitis A, pneumonia, aotric insufficiency, chronic heart failure, pericardial effusion, cerebral arteriosclerosis, transient ischemic attack, gastric ulcer, and Af started W on 13 December 2007. (b) (6) her TBL was 6.6 mg/dL, AST and ALT elevated to 8.7 and 7.8 xULNand ALP 2.8 xULN. She was admitted (b) (6) after seversal days of abdominal pain, nausea and vomiting, and was found to have cholecystitis that was treated with Augmentin and ERCL removal of a common duct stone (b) (6). Warfarin was restarted on 4 November (b) (6) and continued until 9 November 2009 (b) (6) without further liver test abnormalities.

001553	**112771**	**United States**	**M**	**W**	**89**	**27.52**	**11.06**	**7.71**	**3.45**	**0.64**	**12.0**	**3**	**3**	**2**	**0**	acute cholecystitis 5

Comment: An overweight U.S.man 89 with history of diabetes, hypertension bronchitis, constipation, Gilbert syndrome, peripheral arterial disease, pacemaker, and Af started W on 3 December 2008. He showed recurrent slight bilirubin elevations consistent with his Gilbert syndrome during the ensuing year, but had an attack of acute cholecystitis on (b) (6) (16 November) with rise in bilirubin but not serum enzymes activities. (b) (6)) laproscopic cholecystectomy was done after which warfarin was resumed from 31 January to 7 June (b) (6) without further liver injury test abnormalities being observed.

O42009	**109538**	**Czech Republic**	**M**	**W**	**76**	**25.21**	**9.39**	**7.49**	**2.75**	**1.98**	**3.8**	2	2	2	2	gallbladder sludge 3

Comment: A Czech man 76 with history of myocardial infarction, angina,mitral regurgittion, pacemaker, congestive failure class II, ischemic stroke, and Af started W on 9 July 2008. Slight recurrent bilirubin elevations without symptoms or rises were noted over the next 7 months, but AST and ALT elevations to 9.3 and 7.5 xULN were found on 18 February 2009 (Day 228). Investigation by ultrasound disclosed gallbladder sludge. His warfarin was stopped and ursodeoxycholic treatment acid led to resolution of the abnormalities.

001342	**109103**	**United States**	**F**	**W**	**60**	**42.08**	**8.97**	**6.75**	**4.69**	**1.63**	**4.1**	2	2	2	1	acute pancreatitis 4

Comment: A morbidly obese U.S.woman 60 with history of hypertension, sleep apnea, uterine cancer, ischemic stroke, gastroesophageal reflux, sciatica, tinnitus, vertigo, and Af started W on 11 July 2008. Abdominal pain, nausea, vomiting (b) (6) led to hospitalization and diagnosis of acute cholecystitis and ancreatitis with common duct compression but no stones, and warfarin was stopped. The pancreatitis subsided with intravenous fluids, suppression of gastric acid, and she was followed for another month.

049062	**105006**	**Germany**	**F**	**W**	**75**	**30.12**	**5.83**	**5.83**	**20.35**	**2.92**	**2.0**	2	2	3	1	common duct stone 4

Comment: An obese German woman 75 with history of diabete, hypertension, hypothyroidism, gallbladder stones, aortic and mitral regurgitation,and Af started W on 7 February 2008. Slight elevation of ALT was noted on 13 October and again on 11 November, and warfarin was stopped 18 November (Day 286). On 27 November jaundice was noted and she was found to have a common duct stone that caused jaundice to 20.3 xULN on (b) (6), after which the stone was removed endoscopically, with resolution.

086024	**108475**	**China**	**F**	**A**	**78**	**26.17**	**40.66**	**5.76**	**3.25**	**1.80**	**3.2**	2	2	4	1	acute myocardial infarction 4

Comment: A slightly overweight Cinese woman 78 with history of diabetes, hypertension, myocardial infarction, class III heart failure, and Af was started W on 13 June 2008. Bilirubin elevation without enzyme rises were noted over the next several months but warfarin was continued and her failure was treated. (b) (6) she went into worse heart failure with hypoglycemic coma and was admitted with AST 40.7 xULN. Acute myocardial infarction was diagnosed with CPK very elevated, creatinine increased, heart failure. She was treated effectively, the liver test abnormalities fell to normal and warfain was resumed from21 April to 27 May without recurrent rises.

086031	**115267**	**China**	**F**	**A**	**84**	**20.00**	**3.97**	**5.70**	**7.34**	**0.96**	**5.9**	2	2	3	1	recurrent CD stone 4

Comment: A thin Chinese woman 84 with history of hypertension, ischemic stroke, obstructive pulmonary diease, previous cholecystectomy and common duct stone, and Af started W on 6 March 2009. (b) (6) she was admitted to hospital with fever, leukocytosis, jaundice, abdominal pain, and vomiting. She was found to have pneumonia and another common duct stone. Treatment with antibiotics led to resolution and the stone passed spontaneously. The abnormalities returned to near normal on 3 November and warfarin was stopped 12 November 2009.

narrative truncated

061042	**106239**	**Australia**	**M**	**W**	**78**	**24.93**	**3.14**	**5.26**	**2.75**	**1.57**	**3.4**	2	1	2	2	uncertain 3

Comment: An Australian man 78 with history of hypertension, mitral regurgitation, myocardial infarction, bypass graft, valve surgery, and Af started W on 12 March 2008. He had a transient episode of dyspnea on 10 June (Day 91), and syncope with epistaxis and minor bleeding in mid-August. His ALT and AST were elevated on 26 August (Day 168) to ALT 5.3 and AST to 3.1 xULN that but were not explained and were back to normal 6 days later on 1 September (Day 174) despite his continuing warfarin..He continued on warfarin until 30 December (Day 294), 13 days after another transient spike of ALT to 4.4 and TBL to 2.7 xULN on 17 December (Day 281). The mild enzyme elevations were attributed to to warfarin by the investigator, but very little attempt was made to establish the probable cause of the mild, transient test abnormalities.

086007	**109999**	**China**	**M**	**A**	**76**	**22.20**	**6.22**	**4.93**	**5.67**	**1.79**	**2.8**	1	1	2	1	calculous cholecystitis 4

Comment: A slim (BM! 22.2) Chinese man 66 with past hypertension, ischemic stroke, and Af started W on 6 August 2008. On 29 October (b) (6) AST 4.6 and ALT 4.0 xULN were noted , without symptoms or bilirubin increase. The tests were checked again 6 days later on 4 November (b) (6) and were within normal range. He remianed on warfarin for 7 months until (b) (6) when he presented with fever and jaundice, ALT 5.9, AST 6.2, TBL 5.7 xULN. Workup in hospital showed cholecystitis and gallbladder stones, and warfarin was stopped. He was treated with antibiotics and was refrerred to another hospital for gallstone removal, but no followup information was obtained (b) (6) later he was reported to have had a fatl myocardial infarction.

001362	**111453**	**United States**	**F**	**W**	**87**	**29.24**	**4.74**	**4.82**	**3.58**	**3.58**	**1.3**	3	4	3	0	cholangiolitic choledocholithiasis 5

Comment: A moderately obese American woman 87 with diabetes, obsrrtuctive pulmonary disease, angina, coronary stent, patent foramen ovale, congestive failure II, gout, hysterectomy, colostomy, hypothyroidism, choledocholithiasis, spinal stenosis, gastroesophageal reflux, and Af started W on 25 September 2009. (b) (6) she presented to an emergency room with right flank pain, fever, and jaundice, with ALT 4.8, AST 4.7, ALP 3.6, and TBL 1.7 xULN diagnosed as cholangitis and common duct stone. An ERCP was done the next day to remove 2 large common duct stones, with sphincterotomy and antiobiotic follow-up. She was restarted and continued on warfarin until 8 Jun 2010 (b) (6) withou further serious liver test abnormalities.

886009	**101230**	**Taiwan**	**M**	**A**	**72**	**26.72**	**2.08**	**4.49**	**2.75**	**0.55**	**8.2**	2	2	1	2	uncertain 3; Gilbert syndrome

Comment: A slightly overweight Taiwanese man 72 with hypertension, mild congestive failure I, emhysema, osteoporosis, gout, hernia, prostatic hypertrophy, and Af started W on 20 August 2007. Serum ALT was slightly high before he started warfarin at 1.7 x ULN and rose to 4.5 with ASST 2.1 xuLN on 15 October (Day 57). Retseat tests a week and three weeks later showed reurn to near-normal range. He also showed repeated mild elevations of TBL, probably Gilbert syndrome, but never deloped any significant liver abnormalities ov er a long course of warfarin until 27 April 2009 (Day 617) or after-ward until7 December 2009 (Day 841)

063006	**102225**	**Philppines**	**M**	**A**	**57**	**23.92**	**1.11**	**4.42**	**2.25**	**0.89**	**5.0**	1	1	1	1	uncertain 4; Gilbert syndrome

Comment: A Philippino man 57 with hypertension, angina, ischemic heart disease, mild congestive failure class I, and Af started W on 9 October 2007. On 1 September 2008 he reported dyspnea and on 10 September ALT was 4.4 xuULN, but not investigated and warfarin was continued. Recheck on 7 October 2008 (Day 365) showed a normal value and he stayed on warfarin until 14 June 20110 (Day 980) without further ALT rise, although many mild elevations of TBL were noted (were probably Gilbert syndrome).

055005	**112147**	**Brazil**	**M**	**W**	**69**	**28.39**	**4.11**	**4.40**	**11.00**	**1.23**	**3.6**	3	3	3	0	acute hepatitis A and B 3; lymphoma 2

Comment: An overweight Brazilian man 69 with history of hypertension, ischemic stroke, mitral and aortic regurgitation, mild congestive failure class I, and Af started W 29 October 2008. He had a brief episode of worsened heart failure on 3 June (Day 218), with changes in liver tests, and continued warfarin. Jaundice was noted on 17 October (Day 354) after findings of elevated ALT 4.4 and AST 4.1 xULN on 5 October (Day 342) with little change in ALP. Investigation disclosed lymphoma involving the head of the pancreas, and warfarin was stopped 19 October. The TBL rose further to 11 xULN as the aminotransferases declined, and he had a laparotomy for diagnostic evaluation. Liver biopsy showed cholestasis, but later serological testing show IgM antibodies against heaptitis A and B. Liver test abnormalities subsided, the lymphoma was treated with chemotherapy, and he was followed until 10 June 2010 without further liver test abnormalities.

380002	**106199**	**Ukraine**	**M**	**W**	**75**	**26.99**	**0.75**	**4.34**	**3.33**	**0.78**	**5.6**	1	1	1	1	uncertain 4; Gilbert syndrome

Comment: A slightly overweight Ukranian man 78 with history of angina, transient ischemic attack, congestive heart failure Gilbert syndrome 3

class II, and Af started W on13 March 2008. He showed repeated high TBL values without symptoms or serum enzyme activity elevation (probable Gilbert syndrome) for over two years on warfarin. Which was stopped 1 June 2010 (Day 811). A transient, isolated peak of ALT to 4.3 xULN four weeks later was not investigated or explained.

063007	**103724**	**Philppines**	**M**	**A**	**68**	**28.29**	**2.42**	**4.26**	**2.08**	**1.43**	**3.0**	0	0	1	1	uncertain 4; Gilbert syndrome

Comment: An overweight Philippino man 68 (no history) started W on 3 December 2007. He showed minor TBL elevations between 15. and 2.1 xULN repeatedly, with elevations in serum enzyme activities. An unexplained elevation of ALT to 4.3 and AST to 2.4 xULN was noted on 27 August (Day 26), and warfarin was stoppe. The cause was not investigated.

no narrative

043011	**114789**	**Australia**	**M**	**W**	**64**	**24.93**	**3.44**	**4.21**	**3.25**	**0.73**	**5.8**	1	1	1	1	uncertain 4

Comment: An Australian man 64 with history of hypertension, ischemic stroke,, urinary infection, high bilirubins, and AF started W on 12 February 2009.Although the TBL was slightly elevated before starteding the drug, it jumped to 3.3 xULN three weeks later, then subsided but showed repeated mild elevations (consisttent with Gilbert syndrome). Mild ALT elevations to 2.4 xULN were noted 4 August, rising to 4.2 xULN 15 October (Day 236). Viral hepatitis tests were negative, but he reported light alcohol use, and ultrasound was said to show steatohepatitis. No diagnosis was made, but warfarin was stopped 15 October 2009 (Day 246).

001111	**100044**	**United States**	**M**	**W**	**84**	**25.61**	**4.06**	**4.18**	**2.40**	**1.10**	**3.8**	2	2	2	1	worsened heart failure 4

Comment: A U.S. man 74 with history pf hypertension, mitral regurgitation, myocardial infarction, congestive heart failure class III, bypass surgery, pacemaker, and Af started W on 21 February 2007. He had some episodes of slightly worsened heart failure in May and November, with minor ALT elevations, but on 23 May 2008 (b) (6) worse cardiac failue with renal insufficiency occurred and ALT rose to 4.2, AST 4.1, and TBL 2.4 xULN , all resolveing quickly with treatment of the heart failure. His warfarin had been stopped 16 May 2008 (b) (6) He later died (b) (6) after apsiration pneumonia from which he did not recover.

082009	**104949**	**South Korea**	**M**	**A**	**79**	**26.13**	**3.86**	**4.03**	**4.17**	**1.80**	**2.2**	2	1	2	1	uncertain 4

Comment: A slightly overweight South Korean man 79 with history of hypertension, hypertrophic cadiomyopathy, moderate alcohol consumption, and AF started W on 29 January 2008. Over two years later on 1 June 2010 (Day 855) his ALT was elevated to 3.6, AST 2.6, TBL 4.1, ALP 1.5 xULN with mild abdominal discomfort and prurius. Tests for viral hepatitis were negative, but no further warfarin was taken. Gallbladder stones were seen by ultrasound but no explanation was found for the liver test abnormalities, which resolved promptly.

001555	**111827**	**United States**	**F**	**W**	**60**	**27.58**	**6.24**	**3.85**	**2.58**	**4.12**	**0.9**	2	2	2	2	worsened heart failure 3

Comment: A somewhat overweight U.S. man 76 with history of diabetes, hypertension, obstructive pulmonary disease, coronary artery bypass, valvular disease, serious congestive failure class III, and AF started W on 24 October 2008. He had an episode of renal failure on Day 6, thought due to excessive diruesis. On 15 January 2009 (Day 84) he was found to 2.6 xULN attributed to the drug by the investigator and warfarin was stopped 4 days later, but RUQ ultrasound indicated cardiogenic hepatic congestion. Past hepatitis E and CMV but not acute viral hepatitis markweers were found, but slightly high alpha-1-antitrypsin anf ANA markers wer seen before drug wa started.

007070	**115879**	**Russia**	**M**	**W**	**59**	**25.06**	**4.44**	**3.56**	**3.00**	**1.15**	**3.1**	1	1	2	1	alcoholic hepatitis 3; uncertain

Comment: A Russian man 59 with history of hypertension, transient ischemic attack, cholecystitis, and AF started W on 1 April 2009. Slight bilirubin elevations were noted (1.3-1.9 xULN), probably due to Gilbert syndrome. He admitted to an episode of alcohol abuse on 2 March 2010 and the next day showed AST 4.4, ALT 3.6, ALP 1.2, and TBL 2.7 xULN that were not immediately investigated, and warfain was continued and the abnormalities subsided. Another isolated bilirubin increase to 3 xULN was noted on 28 April 2010 (Day 393), also not explained.Warfarin was continued until 22 June 2010 (Day 458) but no further laboratory testing was done

001381	**103820**	**United States**	**M**	**O**	**80**	**25.95**	**6.19**	**3.54**	**9.92**	**1.98**	**1.8**	3	3	3	1	common duct stones 4

Comment: A slightly overweight U.S.non-Caucasian man 80 with history of hypertension, obstructive pulmonary disease, asthma, hypothyroidism, prostatic hypertrophy, chronic renal disease, peptic ulcer, myocardial infarction, bypass graft, serious congestive heart failre class III, and Af started W on 30 November 2007. (b) (6) he was found to have acute cholecystitis with TBL 9.9, AST 2.5, ALT 2.1, ALP 1.2 xULN, and was admitted to hospital. Common duct stone was found, and cholecystectomy was done (b) (6), after which warfarin was restarted following a one-week interruption. He continued on warfain for over 10 months without recirrent of liver test abnormalities, but abdominal pain and jaundice

recurred (b) (6) *and warfarin was stopped. He was found to have sludge and small sones in his common duct, removed ay ERCP, after which the abnormalities resolved promptly.*

082006	**108749**	**South Korea**	**M**	**A**	**72**	**25.51**	**11.37**	**3.53**	**4.00**	**1.17**	**3.0**	1	1	3	1	alcoholic hepatitis 2; uncertain 2

Comment: A slightly overweight South Korean man 72 with past hypertension, transient ischemic attack, high cholesterol, prostatic hypertrophy, and AF started W on 11 June 2008. Elevated ALT 2.2 xULN was noted on 10 September (Day 92) and TBL 2.6 xULN 10 days later. He admitted to consuming excess alcohol prior to these events and had sustained some bruising. He showed mild increases in ALT and TBL intermittently but continued warfarin. On 26 April 2010 (Day 685) T BL was 4.4 and AST 4.0 xULN but these findings were not investigated or reported. Warfarin was stopped 6 June 2010 after he had been taking it for almost two years. *narrative truncated*

048036	**110038**	**Poland**	**M**	**W**	**72**	**25.01**	**1.13**	**3.23**	**2.12**	**0.57**	**5.7**	2	2	2	1	worsened heart failure 4

Comment: A Polish man 72 with history of diabetes, hypertension, ischemic stroke, myocardial infarction, bypass graft, serious congestive heart failure class III, and Af started W on 29 July 2008. On 21 October (Day 85) he presented with increased dyspnea, worse heart failure, bradycardia and ALT 2.6, TBL 2.1 xULN. The heart failure was treated and liver test abnormalities resolved and remained normal for over a year until warfarin was stopped 17 Februarty 2010 (b) (6)

057014	**111778**	**Columbia**	**F**	**B**	**85**	**27.98**	**4.47**	**3.19**	**2.17**	**0.81**	**3.9**	3	3	3	0	acute heart failure 5

Comment: A short (4'5") overweight black Columbian woman 85 with history of hypertension, transient ischemic attack, depression, renal insufficiency, myocardial infarction, serious congestive heart failure class III, and Af started W on 8 October 2008. She continued on warfarin for 20 months with only two minor ALT elevations to 1.4, 1.5 xULN until (b) (6) *when she had worse heart failure after bronchopneumonia and showed AST 4.5, ALT3.2, TBL 2.2 xULN* (b) (6) *She was treated intensively but died in heart failure* (b) (6)

057014	**112797**	**Columbia**	**M**	**W**	**71**	**31.16**	**9.65**	**3.17**	**7.83**	**0.82**	**3.9**	3	3	3	0	septic choledocholithiasis 5

Comment: An obese Columbian man 71 with past hypertension, ischemic stroke, congestive heart failure class II, and Af started W on 13 November 2008. (b) (6) *he showed jaundice, fever, dark urine and was admitted for study and diagnosis.. Warfarin was stopped 16 April, and he was found to have acute suppurative cholangitis, and stones in the common duct. Despite antibiotics and ERCP he developed sepsis and died* (b) (6)

40 cases

Site	Subj	Country	Sex	race	Age	BMI	pASTx	pALTx	pTBLx	pALPx	R	CMP	INF	SEV	LIK	probable cause

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/s/

JOHN R SENIOR
06/16/2011

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications

****Pre-decisional Agency Information****

Memorandum

Date: 6/8/2011

To: Tyree Newman, Regulatory Project Manager
Division of Hematology Products

From: James Dvorsky, Regulatory Reviewer
Division of Drug Marketing, Advertising, and Communications

Subject: Comments on draft labeling (Package Insert) for NDA 22406, Xarelto (rivaroxaban) film-coated oral tablets

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In response to your labeling consult request on February 11, 2011, we have reviewed the draft Package Insert for Xarelto and offer the following comments. Note that these comments are based upon the 6-1-11 label version.

Package Insert Labeling:

Section	Statement	Comment
Highlights – Warnings and Precautions	(b) (4)	As currently written, this statement gives instructions (b) (4) and does not present important risk information as the Warnings and Precautions are intended. DDMAC recommends either excluding this Highlight as the risk is outlined in the Black Box, or specifically state that caution should be used when removing catheters and specific dosing instructions should be followed.
2.1 Use with P-gp and strong CYP3A4 inducers 7.2, 7.3, 7.4 & 8.7		This statement is misleading as it can be interpreted in different ways (two drugs: one P-pg inducer plus one CYP3A4 inducer or just one drug possessing both induction properties). Section 7.1 uses the terminology "**combined** P-pg and CYP3A4 inhibitor" clarifying that this refers to one drug having both induction characteristics. DDMAC

		recommends revising the relevant sections to clarify the "combined" trait.
4 Contraindications	(b) (4)	DDMAC recommends removing the reasoning behind the contraindication and only present the contraindication itself, pregnancy.
7.1 Drugs that Inhibit Cytochrome…		According to the data presented above, erythromycin would also fall into this category. DDMAC suggests adding "erythromycin" to this listing.
8.6 Geriatric Use		DDMAC recommends removing the second half of this sentence as it is making an efficacy claim about a subpopulation within the trial.
14 Clinical Studies	Description of the 4 studies	DDMAC recommends describing the primary endpoints for each study. The presentation is misleading the data is presented but no indication is given as to what the study was designed to show or prove. According to the studies: Two trials (RECORD 2 and 3) were designed as superiority trials and two trials (RECORD 1 and 4) were designed as non-inferiority trials. The primary efficacy endpoint was a composite endpoint of • Any deep vein thrombosis (DVT) (proximal and/or distal) • Non-fatal pulmonary embolism (PE) • Death from all causes. The pre-specified secondary efficacy endpoints were: • Major VTE (proximal DVT, non-fatal PE, VTE-related death) as main secondary endpoint.
14 Clinical Studies	(b) (4)	This endpoint was listed as a secondary endpoint in all 4 trials.

		(b) (4) [redacted] Therefore, DDMAC recommends removing this endpoint from the PI.

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/s/

JAMES S DVORSKY
06/08/2011

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Pediatric and Maternal Health Staff
Office of New Drugs
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Maternal Health Team Review

Date: June 7, 2011 **Date Consulted:** February 11, 2011

From: Upasana Bhatnagar, MD
Medical Officer, Maternal Health Team
Pediatric and Maternal Health Staff

Through: Karen B. Feibus, MD
Medical Team Leader, Maternal Health Team
Pediatric and Maternal Health Staff

Through: Lisa Mathis, M.D.
Associate Director, Office of New Drugs
Pediatric and Maternal Health Staff

To: Division of Hematology Products (DHP)

Drug: **Xarelto (Rivaroxaban)- NDA-022406 (SND70)**

Subject: Pregnancy and Nursing Mothers Labeling Review

Materials Reviewed:

Pregnancy and Nursing Mothers subsections of Sponsor's proposed labeling,

Consult Question:

Please review the Sponsor's proposed labeling for the Pregnancy and Nursing Mothers subsections.

In animal studies, Xarelto crosses the placenta and there are no studies of Xarelto use in pregnant women. The animal studies indicate an increased risk of fetal wastage/post implantation loss and maternal hemorrhagic complications. An initial pharmacology/ toxicology review was done by Dr. Yash Chopra dated May 12, 2009. However, the division is currently finalizing its analysis.

Anticoagulation during pregnancy

Pregnancy is a hypercoagulable state due to changes that occur in the coagulation system. Pregnant women have a fivefold increased risk of venous thromboembolism in comparison to non-pregnant women. The absolute risk of symptomatic venous thrombosis during pregnancy is between 0.3 and 0.5 per 1,000 women.[2] Pulmonary embolism during pregnancy is a leading cause of maternal mortality. Because of the high prevalence and associated mortality from hypercoagulability, anticoagulant therapy is frequently used during pregnancy and post-partum period for various indications. The goal of anticoagulation in pregnancy is to prevent both maternal thrombosis and adverse pregnancy outcomes. Women with thrombophilia have an increased risk of pregnancy complications such as preeclampsia, fetal growth restriction, placental abruption, and fetal loss.[3]

According to the Eighth American College of Chest Physicians Conference,[4] indications for treatment of patients with either prophylactic or adjusted doses of anticoagulants in pregnancy include the following:

- acute venous thromboembolism
- prior history of venous thromboembolism
- antithrombin deficiency or other thrombophilias
- recurrent pregnancy loss.

During pregnancy, these conditions are currently managed with parenteral unfractionated or fractionated heparin products, which do not cross the placenta. Occasionally, patients at particularly high risk for thrombosis (e.g. those with mechanical heart valves) are managed with coumadin. Coumadin is the only oral anticoagulant currently approved for use in the United States, and it is a known human teratogen that causes a characteristic embryopathy in about 5% of fetuses exposed during the first trimester of pregnancy.[5] An oral medication with an acceptable maternal and fetal safety profile would be a convenient option for pregnant patients needing anticoagulation. In addition, Xarelto could be used for patients with heparin-induced thrombocytopenia.

In clinical practice, pregnant patients who require anticoagulation are often maintained on longer acting agents until a transition is required due to clinical circumstances or advancing gestational age. During the peripartum period, patients are transitioned to unfractioned

[2] ACOG Practice Bulletin, Thromboembolism in Pregnancy, Number 19, August 2000.
[3] ACOG Practice Bulletin. Inherited Thrombophilias in Pregnancy. Number 113. July 2010.
[4] Bates SM, Greer IA, et al. Venous Thromboembolism, Thrombophilia, Antithrombotic Therapy, and Pregnancy:American College of Chest Physicians Evidence Based Practice Guidelines (8th Edition). *Chest.* 2008;133;844S-886S
[5] Gabbe S, Niebyl JR, Simpson JL eds. Obstetrics Normal & Problem Pregnancies. 3rd ed, New York,1996: 255.

heparin, which has a short half life and can be discontinued a few hours prior to surgery or delivery.[6] The anticoagulant effects of both heparin products and coumadin can be reversed – heparin with protamine sulfate and coumadin with vitamin K. If obstetrical hemorrhage occurs in the presence of an anticoagulant, supportive care often involves the administration of blood products, such as cryoprecipitate and/or fresh frozen plasma, to provide exogenous sources of coagulation factors

Pregnancy labeling

The Maternal Health Team (MHT) has been working to develop a more consistent and clinically useful approach to the Pregnancy and Nursing Mothers subsections of labeling. The Pregnancy and Nursing Mothers section of labeling should describe available animal and human data in a manner that allows clinicians, who are prescribing medication for pregnant patients and female patients of reproductive potential, to balance the benefits of treating the patient with the potential risks to the mother, fetus, and/or infant. PMHS-Maternal Health labeling recommendations not only comply with current regulations but also incorporate "the spirit" of the Proposed Pregnancy and Lactation Labeling Rule (published on May 29, 2008). Usually the first paragraph in the pregnancy subsection of labeling summarizes available data from published literature, the required regulatory language for the designated pregnancy category, and, when available, outcomes of studies conducted in pregnant women and studies conducted in animals. The paragraphs that follow provide more detailed descriptions of the available human and animal data and appropriate clinical information that may affect patient management.

This review provides the Maternal Health Team's (MHT) recommended revisions to the pregnancy and nursing mothers sections of the Sponsor's proposed labeling. Additionally, the MHT recommendations include creation of section 8.6 Females of Reproductive Potential.

REVIEWED MATERIALS

Sponsors Proposed Pregnancy and Nursing Mothers Labeling

[6] James AH, Abel DE, Brancazio LR. Anticoagulants in Pregnancy. Obstetrical and Gynecological Survey. 2005.61;59-69.

REVIEW OF LITERATURE AND PRACTICE GUIDELINES

A literature search was performed in PubMed for the following:

- Pregnancy and rivaroxaban
- Lactation and rivaroxaban

No studies of Xarelto use in pregnancy or lactation were found with these queries.
The Reprotox and LactMed databases were also queried for Xarelto (rivaroxaban) and no results were obtained.

A further search was performed in PubMed

- factor Xa and pregnancy
- factor Xa fluctuations and pregnancy
- vaginal bleeding and pregnancy

Factor Xa and Pregnancy

Factor Xa (FXa) plays key roles in the coagulation pathway. In the initiation phase, FXa in conjunction with Factor Va converts prothrombin to thrombin by forming the Prothrombinase complex.[7] Subsequently, in the amplification phase, the thrombin formed potentiates platelet activation and activates other coagulation proteins. Furthermore, in the

[7] Toschi, V, Lettino M. Inhibitors of propagation of coagulation: factors V and X. "accepted article" British Journal of Clinical Pharmacology. May 4, 2011.

propagation step, both activated platelets and coagulation factors promote a burst of thrombin generation and further coagulation. Drugs that directly inhibit FXa, such as Xarelto, are small molecules and can enter a thrombus and inhibit both circulating and thrombus-bound, functionally active, factor Xa and thereby diminish thrombin mediated coagulation.

Even in healthy pregnant patients, many changes are seen in the blood coagulation pathway resulting in a hypercoagulable state. Factor XII, X, and IX increase throughout pregnancy, whereas factor XI decreases in pregnancy. Factor V increases in concentration during early gestation and then decreases to a stable level.[8] These prothrombotic changes are somewhat counterbalanced by increases in the activity of the fibrinolytic system.

Several studies have analyzed FXa levels in pregnant patients using anticoagulant therapy. Although they are small studies, they demonstrate that notable variation exists in measured FXa levels throughout pregnancy. In a retrospective review of 77 patients receiving prophylactic low molecular weight heparin, factor Xa levels were drawn four hours post injection at various stages of gestation. The study found that 26% of patients had subprophylactic factor Xa levels, 15% were supraprophylactic, and 59% of patients were in the therapeutic range. In their analysis, the authors did not find a correlation between anti-factor Xa levels and maternal age, gestational age, weight, or BMI.

Reviewer comments: *If Xarelto was used in pregnant patients, the therapeutic window must be established and physiologic changes of pregnancy, such as changes in the coagulation pathway (especially fluctuation of Xa levels), should be considered when establishing the dose.*

Bleeding and Pregnancy

Vaginal bleeding occurs in about 20 to 30% of confirmed pregnancies during the first 20 wks, and about half of these pregnancies end in spontaneous abortion.[9] In a study by Yang et al, 2802 pregnancies were prospectively enrolled in the Pregnancy, Infection and Nutrition (PIN) Study database and patients from 24-29 weeks gestation were interviewed about vaginal bleeding. A total of 24.4% (683 out of 2,802) of women reported vaginal bleeding during pregnancy.

In a meta-analysis of 21 studies, from 1950 to 1992, Ananth et al. studied vaginal bleeding during pregnancy. They excluded known etiologies of vaginal bleeding such as placenta previa, abruptio placenta, and premature rupture of membranes in their analysis. Vaginal bleeding was defined as bleeding in pregnancy prior to 28 weeks gestation. Their pooled estimate of vaginal bleeding frequency across all studies, both case controlled and cohort studies, was 12.2%.

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[8] Holmes VA, Wallace JMW. Hemostasis in normal pregnancy: a balancing act? Biochemical Society Transactions. 2005. 33;2.428-32.

[9] The Merck Manual of Diagnosis and Therapy- 18th Ed. (2006) Section18 – Gynecology and Obstetrics 259. Approach to the Pregnant Woman and Prenatal Care. http://online.statref.com/document.aspx?fxid=21&docid=880, accessed 5/16/2011.

Reviewer comments*: These studies indicate that vaginal bleeding frequently complicates pregnancy. Therefore, the use of an irreversible anticoagulation may not be appropriate in the obstetric population.*

FDA DOCUMENTS

Clinical Pharmacology Review

Two thirds of Xarelto is eliminated by metabolic degradation.[10] This portion of the drug is eliminated half through the kidneys and half through fecal route after metabolism in the GI tract and/or liver. The other one third is cleared renally as unchanged active substance. In healthy adults, the terminal half life of Xarelto is 5 to 9 hours whereas the therapeutic effect is seen up to 24 hours.[1] There were no clinically relevant exposures in studies correlating body weight or sex with pharmacokinetics. However, increased bleeding risk was noted in subjects at the extremes of body weight in phase 3 trials.

The predictive value of laboratory tests to monitor the therapeutic effect of Xarelto has not been adequately studied. Xarelto prolongs blood prothrombin time (PT) and activated partial prothrombin time. Although monitoring of these tests is not proposed with Xarelto, prolongation of the prothrombin time (PT) had a linear relationship with Xarelto plasma concentration. The factor Xa assay used in the clinical trials has a curvilinear relationship with Xarelto concentration so cannot be easily correlated with plasma concentration of Xarelto for dose adjustment.

Reviewer comments: *There are no studies in the pregnant population regarding the optimal dosing of Xarelto. When using Xarelto in pregnant patients, the effect of increased glomerular filtration rate that occurs during pregnancy upon the therapeutic levels of the drug should be considered. In a personal communication with Joseph Grillo, Pharm.D of clinical pharmacology, he indicated that although the PT has a linear relationship with Xarelto plasma concentration, data from the phase 3 trials indicate that this is not always a predictable relationship. Therefore, no laboratory test is well correlated with therapeutic effect of Xarelto. It may be difficult for healthcare providers to use this anticoagulant in the setting of pregnancy when physiologic changes may require dose adjustment.*

SPONSOR'S SUBMISSIONS

Safety Updates

The Sponsor's periodic safety update reports (PSUR) were reviewed from September 2008 to March 2011. Overall, 12 unintended exposures to Xarelto occurred in women of

[10] Clinical pharmacology review, Joseph Grillo 4/6/09

childbearing age, six were among patients enrolled in clinical trials. Of the nine known outcomes, two "healthy" babies were delivered, one preterm delivery occurred, one missed abortion, and five elective terminations were noted. There was one reported exposure to a neonate who was human milk fed for three weeks. No adverse events were attributed to Xarelto use in this neonate.

Reviewer comments: *Although, little can be extrapolated from this limited experience with Xarelto in pregnancy and lactation, these reports underscore the potential for unintended exposures of females of reproductive potential through both the labeled and off-label use of Xarelto.*

DISCUSSION

Xarelto (rivaroxaban) is a first in class oral anticoagulant that directly inhibits factor Xa in the coagulation pathway. Xarelto binds both circulating and functionally active factor Xa and inhibits thrombin mediated coagulation. The Sponsor's current submission is for the use of Xarelto for the indication of deep venous thrombosis and pulmonary embolism prophylaxis after knee and hip replacement procedures.

Pregnancy exposures may occur whether planned or inadvertent. This is evidenced by the pregnancy exposures that have already reported in the clinical trials and through spontaneous reports. Furthermore, once marketed, this drug may be used to treat disorders that occur more frequently in females of reproductive potential. Therefore, if healthcare providers plan to use Xarelto in females of reproductive potential, they should discuss pregnancy planning with these patients. Similarly, women who are lactating should be counseled about potential benefits of Xarelto use and the potential risks to a nursing infant.

The Maternal Health Team recommends that Xarelto be labeled as Category C. At the time of this review, the pharmacology toxicology review is in progress. The preliminary results suggest that animal reproduction studies show no increased risk of structural malformations but an increased risk of post-implantation pregnancy loss in rabbits.

However, the MHT is concerned about the irreversible anticoagulation effects of Xarelto in the setting of obstetric hemorrhage. Currently, there is no antidote to reverse the action of Xarelto, and the therapeutic effects lasts up to 24 hours. Irreversible anticoagulation during pregnancy could result in devastating hemorrhagic complications for the pregnant patient. In early gestation, spontaneous abortion or fetal death may occur, necessitating a dilation and curettage procedure or induction of labor and delivery. Once the fetus is viable after 24 weeks gestation, emergent delivery may be needed due to unexpected maternal or fetal complications or because of conditions that increase bleeding risk such as placenta abruption or placenta previa. Therefore, in clinical practice, unexpected bleeding complications can occur throughout pregnancy and at delivery. Optimal strategies for treatment of life threatening hemorrhage requiring reversal of Xarelto have not been established. As with other anticoagulants, patients will have to be transitioned off Xarelto prior to planned

delivery and may require supportive therapy such as blood and blood products to reverse the anticoagulant effects of Xarelto in the event of a major bleeding episode.

Other factors that will influence proper dosing of Xarelto in pregnancy include determining and measuring the therapeutic range for Xarelto during pregnancy. Factor Xa levels fluctuate in normal pregnancy. Furthermore, Xarelto is eliminated through the kidneys, and the glomerular filtration rate is substantially increased in pregnancy. These physiologic changes may influence the metabolism of Xarelto during pregnancy and would then affect dosing during pregnancy. Therefore, healthcare providers may need an established standard laboratory test to titrate drug effect and adjust the dosing of Xarelto during pregnancy.

RECOMMENDATIONS

1. The Maternal Health team recommends labeling Xarelto (rivaroxaban) Category C in pregnancy. Because the concerns regarding Xarelto use in the setting of obstetric hemorrhage remain, additional language has been added to the Warnings and Precautions section of labeling. *(see 5.3)*

2. Recommendations for the pregnancy and lactation subsection labeling revisions are provided below. See Appendix A for the track changes version.

3. The MHT recommends adding Section 8.6 Females of Reproductive Potential for the labeling of Xarelto to inform healthcare provides to consider pregnancy planning in women who are using this medication as an anticoagulant.

PMHS – Maternal Health Labeling Recommendations

HIGHLIGHTS OF PRESCRIBING INFORMATION

----------WARNINGS AND PRECAUTIONS----------

- Pregnancy related hemorrhage: Use with caution in pregnant women due to the potential for obstetric hemorrhage and/or emergent delivery with an anticoagulant that is not readily reversible.

5. Warnings and Precautions

5.3 Pregnancy related hemorrhage

Xarelto should be used with caution in pregnant women. Xarelto dosing in pregnancy has not been studied. The anticoagulant effect of Xarelto can neither be monitored with standard laboratory testing nor readily reversed. Counsel pregnant women about the risks of hemorrhage and benefits of anticoagulation during pregnancy with Xarelto.

8 Use in Specific Populations

8.1 Pregnancy

Pregnancy Category C: There are no adequate or well-controlled studies of Xarelto in pregnant women, and dosing for pregnant women has not been established. Use Xarelto with caution in pregnant patients because of the potential for pregnancy related hemorrhage and/or emergent delivery with an anticoagulant that is not readily reversible. The anticoagulant effect of Xarelto cannot be reliably monitored with laboratory testing. Animal reproduction studies showed no increased risk of structural malformations but increased post-implantation pregnancy loss occurred in rabbits. Xarelto should be used during pregnancy only if the potential benefit justifies the potential risk to mother and fetus.

Animal reproduction studies have shown pronounced maternal hemorrhagic complications in rats and an increased incidence of post-implantation pregnancy loss in rabbits. Rivaroxaban crosses the placenta in animals. Rivaroxaban increased fetal toxicity (increased resorptions, decreased number of live fetuses, and decreased fetal body weight) when pregnant rabbits were given oral doses of >= 10 mg/kg rivaroxaban during the period of organogenesis. This dose is about 11 times the human exposure of unbound drug, based on AUC comparisons at the maximum recommended human dose of 10 mg/day. Fetal body weights decreased when pregnant rats were given oral doses of 120 mg/kg. This dose is about 40 times the human exposure of unbound drug.

8.2 Labor and Delivery

Safety and effectiveness of rivaroxaban during labor and delivery have not been studied in clinical trials; however, in animal studies maternal bleeding and maternal and fetal death occurred at the rivaroxaban dose of 40mg/kg (17 times maximum human exposure of the unbound drug at the human dose of 10 mg/kg).

8.3 Nursing Mothers

It is not known if rivaroxaban is excreted in human milk. Rivaroxaban and/or its metabolites are present in rat milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from rivaroxaban, a decision should

be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

8.6 Females of Reproductive Potential

Females of reproductive potential requiring anticoagulation should discuss pregnancy planning with their physician.

17 PATIENT COUNSELING INFORMATION

17.6 Females of Reproductive Potential

Advise patients who can become pregnant to discuss pregnancy planning with a healthcare professional.

2 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

UPASANA BHATNAGAR
06/08/2011

Karen B FEIBUS
06/08/2011
I agree with the information and recommendations provided in this review.

LISA L MATHIS
06/10/2011

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Office of New Drugs - Immediate Office
Pediatric and Maternal Health Staff
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M E M O R A N D U M

Date: May 26, 2011

From: Elizabeth L. Durmowicz, MD, Medical Officer
Pediatric and Maternal Health Staff

Through: Hari Cheryl Sachs, MD, Team Leader
Lisa Mathis, MD, OND Associate Director
Pediatric and Maternal Health Staff

To: Min Lu, MD, MPH, Medical Reviewer
Kathy Robie-Suh, MD, Team Leader
Division of Hematology Products (DHP)

Re: Pediatric Labeling

Submission Date: December 30, 2010

Sponsor: Johnson and Johnson Pharmaceutical Research & Development, LLC

Drug: rivaroxaban

Proposed Trade Name: Xarelto™

Application: NDA 22-406

Indication (proposed): Prophylaxis of deep vein thrombosis (DVT) and pulmonary embolism (PE) in patients undergoing hip or knee replacement surgery

Dosage form: 10 mg film-coated immediate release tablet

Route of administration: oral

Proposed Dosing (adults): 10 mg once daily administered orally for 35 days in patients undergoing hip replacement surgery and 14 days for patients undergoing knee replacement surgery.

Consult Question:
DHP requests review of proposed pediatric labeling.

Materials reviewed

- PMHS Rivaroxaban Consult Reviews, April 2009 and June 2010
- Sponsor's Proposed Labeling, December 28, 2010

Background
Xarelto™ (rivaroxaban), a selective Factor Xa inhibitor, is being studied in adults as an oral anticoagulant for the treatment of multiple thrombosis-mediated conditions. NDA 22-406 was originally submitted in July 2008 for prophylaxis of deep vein thrombosis (DVT) and pulmonary embolism (PE) in patients undergoing hip or knee replacement surgery. A Complete Response was issued in May 2009 secondary to potential hepatotoxicity, as well as data integrity and drug product issues. Labeling comments were not provided. A Class 2 Resubmission was received in December 2010.

Pediatric Development:
The Division and the Pediatric Review Committee agreed with a full waiver of PREA studies for this application since studies would be impossible or highly impractical because there are too few children with the disease/condition, i.e. pediatric patients undergoing hip or knee replacement surgery. However, the Sponsor is in the process of developing rivaroxaban for the treatment and secondary prophylaxis of VTE (b) (4) In April 2009, the Sponsor met with the Agency to discuss pediatric development, and in April 2010, nonclinical juvenile animal data and a protocol for a single-dose pilot study in pediatric patients were submitted. Although the Agency provided comment on the clinical protocol, no clinical hold issues were identified. Per clinicaltrials.gov, a multicenter study, including a US site, entitled "Single-dose Pilot Study of Oral Rivaroxaban in Pediatric Subjects with Venous Thromboembolism" is currently recruiting.

Reviewer Comment:
Per personnel correspondence with Min Lu, clinical reviewer (May 12, 2011), no additional information about pediatric development and no pediatric data have been submitted to the Agency. Input from the Pharmacology/Toxicology reviewer is needed to confirm that no safety signal has been identified in the available nonclinical data submitted in support of pediatric clinical trials. Search of PubMed did not identify a specific pediatric safety concern regarding rivaroxaban use in pediatric patients.

If a risk is associated with the use of a drug in a particular pediatric population, the risk should be described in labeling. However, no safety concerns appear to have been identified.

Proposed Labeling:

The Sponsor has proposed the following language to be included under Section 8.4, Pediatric Use:

(b) (4)

Reviewer Comment:
When substantial evidence does not exist to support a pediatric indication in any pediatric population, or the drug has not been studied in any pediatric population, the following statement (or a reasonable alternative) must be included in the Pediatric Use section of labeling (8.4): "Safety and effectiveness in pediatric patients have not been established." (See 21 CFR 201.57(c)(9)(iv)(F) http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm).

Although the labeling proposed by the Sponsor would be acceptable, the Division may wish to choose the more standard language:

"Safety and effectiveness in pediatric patients have not been established."

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/s/

ELIZABETH L DURMOWICZ
06/07/2011

HARI C SACHS
06/07/2011

LISA L MATHIS
06/10/2011

M E M O R A N D U M

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

COMPLIANCE REVIEW

DATE: May 24, 2011

TO: Tyree Newman, Regulatory Project Manager
Min Lu, M.D., Medical Officer
Division of Hematology Products

FROM: Susan D. Thompson, M.D., Medical Officer
Good Clinical Practice Branch II
Division of Scientific Investigations

THROUGH: Tejashri Purohit-Sheth, M.D.
Branch Chief
Good Clinical Practice Branch II
Division of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: 22-406

APPLICANT: Johnson & Johnson

DRUG: Xarelto (rivaroxaban)

NME: Yes

THERAPEUTIC CLASSIFICATION: Standard Review

INDICATIONS: 1. Prophylaxis of deep vein thrombosis and pulmonary embolism in patients undergoing hip or knee replacement surgery

CR LETTER DATE: May 27, 2009

(b) (4) AUDIT SUBMISSION DATE: April 19, 2010

(b) (4) INFORMATION REQUEST RESPONSE DATE: September 26, 2010

CR SUBMISSION DATE: December 23, 2010

I. BACKGROUND: Rivaroxaban is a highly selective direct factor Xa (FXa) inhibitor for oral administration. Inhibition of FXa produces antithrombotic effects by decreasing the amplified generation of thrombin, thus diminishing thrombin-mediated activation of both coagulation and platelets, without affecting existing thrombin levels. The sponsor states that the remaining thrombin should be sufficient to ensure primary hemostasis, resulting in a favorable efficacy to safety (bleeding) margin for rivaroxaban. The sponsor submits this NDA to support the use of rivaroxaban for the indication of prophylaxis of deep vein thrombosis (DVT) and pulmonary embolism (PE) in patients undergoing hip or knee replacement surgery.

Patients undergoing major orthopedic surgery, including total hip replacement (THR) and total knee replacement (TKR) surgeries, are a group that is at a particularly high risk for venous thromboembolism (VTE), which includes DVT and PE. Without prophylaxis, the incidence of objectively confirmed total DVT based on older studies is approximately 40 to 60% following THR or TKR, with a 10-30% incidence of proximal DVT. The most appropriate strategy to reduce the incidence of VTE is prophylaxis for all patients undergoing THR or TKR. Current therapeutic agents available for anticoagulant prophylaxis include low molecular weight heparins (LMWHs), fondaparinux, and adjusted-dose vitamin K antagonists such as warfarin. The duration of therapy is at least 10 days for both THR and TKR; for patients undergoing THR, extended prophylaxis to up to 35 days after surgery is recommended. LMWHs and fondaparinux are administered subcutaneously, which may be associated with pain and bruising as well as poor compliance. Warfarin is the only available oral anticoagulant for VTE prophylaxis after major orthopedic surgery in the U.S. However, warfarin has a narrow therapeutic window, exhibits variable dose response, has many dietary and medicinal interactions, requires dose adjustment, and has a slow onset of action. Rivaroxaban offers an alternative oral prophylactic therapy for VTE.

IND 64,892 for rivaroxaban was submitted on May 29, 2002 for the treatment and secondary prophylaxis of VTE by Bayer. All of the clinical trials submitted with the current NDA were conducted by Bayer. Approximately one month prior to the submission of this NDA, Bayer sold the rights of reference for use of the investigations to Johnson and Johnson. Johnson and Johnson submitted NDA 22-406 as the applicant on July 28, 2008. Of note, both Bayer and Johnson and Johnson submitted letters to the review division that the IND is now transferred to Johnson and Johnson.

The pivotal protocols in support of NDA 22-406 were:

RECORD 1 Study: Regulation of Coagulation in Orthopedic Surgery to prevent DVT and PE; controlled, double-blind, randomized study of BAY 59-7939 in the extended prevention of VTE in patients undergoing elective total hip replacement (Protocol 11354)

RECORD 2 Study: Regulation of Coagulation in Orthopedic Surgery to prevent DVT and PE; controlled, double-blind, randomized study of BAY- 59-7939 in the extended prevention of VTE in patients undergoing elective total hip replacement (Protocol 11357)

RECORD 3 Study: Regulation of Coagulation in Orthopedic Surgery to prevent DVT and PE; a controlled, double-blind, randomized study of BAY 59-7939 in the prevention of VTE in patients undergoing elective total knee replacement (Protocol 11356)

RECORD 4 Study: Regulation of Coagulation in Orthopedic Surgery to prevent DVT and PE; a controlled, double-blind, randomized study of BAY 59-7939 (rivaroxaban) in the prevention of VTE in subjects undergoing elective total knee replacement (Protocol 11355)

FDA Inspections

During the conduct of the clinical studies for this NDA, complaints were received regarding two investigators enrolling subjects, Dr. Arturo Corces in RECORD 2 and Dr. David Loucks in RECORD 4. (b) (4)

(b) (4)

On July 28, 2008, Johnson & Johnson submitted the data from the RECORD 1, 2, 3, and 4 studies to the FDA to support the approval of rivaroxaban for the indication of prophylaxis of deep vein thrombosis and pulmonary embolism in patients undergoing hip or knee replacement surgery (NDA 22-406). After receipt of the NDA, eight FDA data validation inspections of investigators who enrolled subjects in the four RECORD studies were conducted. The results of these clinical investigator inspections resulted in the identification of multiple regulatory violations from many of these sites, raising concerns with the overall integrity of the data submitted for approval of the NDA. Details of the first cycle of clinical investigator, sponsor, and applicant inspections, as well as RECORD 1-4 investigators identified as problematic prior to submission of the NDA, are summarized in the following table:

Table 1: NDA 22-406 Pre-NDA and First Cycle Clinical Investigator Data Validation Audits

Name of CI or Sponsor Location	Protocol # and # of Subjects	Major Findings	Inspection Date	Interim Classification	DSI Classification
Andrzej Gorecki Szpital Kliniczny Dzieciatka Jezus – Centrum Leczenia Obrazen Klinika Ortopedii I Traumatologii Narzadu Ruchu Ul. Lindleya 4 02-005 Warszawa , Poland	Protocol #11354, RECORD 1 Site # Poland 18006 # of subjects (Total #: 71): Xarelto: 36 Enoxaparin: 35	None	(b) (4)	NAI	NAI
Tadeusz Gazkzik Slaska Adademia Medyczna Katedra I Oddzial Kliniczny Ortopedii'Wojewodzki Szpital Specjalistyczny Nr 5 Im. Sw. Barbaby Pl. Medykow 1 41-200 Sosnowiec, Poland	Protocol #11354, RECORD 1 Site # Poland 18012 # of subjects (Total #: 76): Xarelto: 38 Enoxaparin: 38	None		NAI	NAI
[redacted]					(b) (4)
Qingming Yang Rui Jin Hospital, Shanghai Second Medical University Orthorpaedic Department Shanghai Ryuijin Hospital No. 197 Ruijin Second Road Shanghai, China 200025	Protocol # 11357, RECORD 2 Site # China 54005 # of subjects (Total# 34): Xarelto: 17 Enoxaparin: 17	AEs not reported, including abnormal liver function tests and bleeding; protocol violations, recordkeeping deficiencies		OAI	OAI (untitled)
Cesar Diaz Valverde Hospital Edgardo Rebagliati Martins Av. Edgardo Rebagliati Martins S/N Jesus Maria Lima Lima, 11 Peru	Protocol # 11357, RECORD 2 Site # Peru 64005 # of subjects (Total#: 41): Xarelto: 20 Enoxaparin: 21	AEs (relatively minor) not reported; protocol and recordkeeping deficiencies		VAI	VAI

Table 1: NDA 22-406 Pre-NDA and First Cycle Clinical Investigator Data Validation Audits

Name of CI or Sponsor Location	Protocol # and # of Subjects	Major Findings	Inspection Date	Interim Classification	DSI Classification
Binfang Zeng Affiliated Sixth People's Hospital Orthorpaedic Department No. 600 Yishan Road, Xuhui District Shanghai, China 200233	Protocol # 11356, RECORD 3 Site # China 54014 # of subjects (Total# 26): Xarelto: 13 Enoxaparin: 13	AEs not reported, including 2 SAEs; protocol violations	(b) (4)	OAI	VAI
Jacek Kruczynski Szpital Uniwersytecki im. Antoniego Jurasze Klinika Ortopedii i Traumatogii Narzadu Ruchu Ul. M. Sklodowskiej-Curie 9 85-094, Bydgoszcz Poland	Protocol # 11356, RECORD 3 Site # Poland 18003 # of subjects (Total# 36): Xarelto: 18 Enoxaparin: 18	Protocol violations		VAI	VAI
(b) (4)					
Ricardo Esquivel Naulcapan, Mexico	Protocol # 11355, RECORD 4 Site # 32006 # of subjects (Total# 42): Xarelto: 22 Enoxaparin: 20	Drug disposition, record deficiencies, missing records		NA	Data not usable
R. Michael Murray Capstone Clinical Research 2018 Brookwood Medical Center Suite 314 Birmingham, AL 35209	Protocol # 11355, RECORD 4 Site # 14005 # of subjects (Total # 152) Xarelto: 76 Enoxaprin: 76	Post-operative randomization in violation of protocol, possible unblinding		OAI	OAI-WL
David Fox Unlimited Research, LP 12709 Toepperwein Road	Protocol #11355, Record 4 Site #14022 # of subjects	Informed consent deficiencies and protocol violations		VAI	VAI

Table 1: NDA 22-406 Pre-NDA and First Cycle Clinical Investigator Data Validation Audits

Name of CI or Sponsor Location	Protocol # and # of Subjects	Major Findings	Inspection Date	Interim Classification	DSI Classification
Suite 101 San Antonio, TX 78233	(Total # 64) Xarelto: 32 Enoxaparin: 32		(b) (4)		
Bayer Pharmaceutical 340 Change Bridge Rd. Pine Brook, NJ 07058	Protocol # 11354, RECORD 1 Protocol # 11357, RECORD 2 Protocol # 11356, RECORD 3 Protocol #11355, Record 4	Monitoring deficiencies, protocol violations, failure to ensure that FDA was informed of all AEs		VAI	VAI
Johnson & Johnson 920 U.S. Highway 202 Raritan, NJ 08869-0602	Protocol # 11354, RECORD 1 Protocol # 11357, RECORD 2 Protocol # 11356, RECORD 3 Protocol #11355, Record 4	No significant issues noted; however, inspection limited in scope		NAI	VAI

Key to Classifications
NAI = No deviation from regulations.
VAI = Deviation(s) from regulations.
OAI = Significant deviations from regulations. Data unreliable.

As can be seen in Table 1, there were a variety of major findings, including protocol violations, deficiencies in drug dispensation records, AE reporting, and informed consent. A major issue identified during inspections of RECORD 4 study sites was post-operative randomization of subjects, instead of randomization of subjects prior to surgery as specified in the protocol. In order to characterize more fully how frequently post-operative randomization in violation of the protocol occurred, an assignment for inspection of three additional clinical investigators in RECORD 4 was issued. Details of the second cycle of clinical investigator inspections are summarized in the following table:

Table 2: NDA 22-406 Second Cycle Clinical Investigator Data Validation Audits

Name of CI/Address/contact information	Protocol # and # of Subjects	Major Findings	Inspection Date	Interim Classification	Final Classifiation
Dr. John Ward Capstone Clinical Research 2018 Brookwood Medical Center Suite 314 Birmingham, AL 35209 Phone: (205) 877-2766 Fax: (205) 877-2990 Email: capstoneclin@aol.com	Protocol # 11355 RECORD 4 Site # 14010 # of subjects (Total # 203) Xarelto: 101 Enoxaprin: 102	Post-operative randomization, IRB approval expired	(b) (4)	OAI	OAI-WL
Dr. Craig Buettner West Alabama Research, Inc. Black Warrior Medical Building 100 Rice Mine Road Loop Suite 104 Tuscaloosa, AL 35406 Phone: (205) 248-6160 FAX: (205) 248-6467 Email: vredding @walresearch.com (coordinator)	Protocol #11355 RECORD 4 Site #14004 # of subjects (Total # 61) Xarelto: 31 Enoxaprin: 30	Post-operative randomization		OAI	OAI-WL
Dr. John Schwappach Colorado Orthopedic Consultants 401 W. Hampton Place Suite 220 Englewood, CO 80110 Phone: (303) 695-6060 (research dept. extension) FAX: (303) 399-9959 Email: schwappach@cocortho.com	Protocol #11355 RECORD 4 Site #14045 # of subjects (Total # 106) Xarelto: 53 Enoxaprin: 53	Protocol violations		VAI	VAI

Key to Classifications
NAI = No deviation from regulations.
VAI = Deviation(s) from regulations.
OAI = Significant deviations from regulations. Data unreliable.

Additionally, inspection of Bayer Pharmaceuticals as the sponsor of the four RECORD 4 studies revealed that the sponsor failed to 1) ensure proper monitoring of the study, 2) to ensure the study was conducted in accordance with the protocol and/or investigational plan, and 3) to ensure that FDA and all investigators were promptly informed of significant new adverse effects or risks. The sponsor inspection of Bayer revealed that some of the minor items cited in the OAI letters for Drs. (b) (4) Murray were not identified in site Monitoring Visit Reports although the CRAs were aware of them (either through the company's internal audit program or FDA inspections). The major violations at these sites were not detected by sponsor monitoring. Bayer acknowledges the failure to include the cited deficiencies in

Monitoring Visit Reports in their response letter dated April 13, 2009. The sponsor inspection of Bayer does not provide information on whether or not monitoring and/or corrective actions were inadequate at other sites classified by FDA as OAI. A limited inspection of the applicant Johnson & Johnson revealed no identifiable deviations from applicant related regulations as per 21 CFR 314.

Complete Response Letter to Applicant and Subsequent Activity

On May 27, 2009 FDA issued an NDA Complete Response letter to Johnson & Johnson for Xarelto NDA 22-406 that listed several deficiencies, including Clinical Deficiency 1 which stated that the reasons that data from 7 Clinical Investigator sites are considered unreliable include:

- Failure to conduct the study according to the signed investigator statement and the investigational plan [21 CFR 312.60]
- Failure to report to the sponsor adverse events [21 CFR 312.64]
- Failure to prepare or maintain adequate and accurate case histories with respect to observations and data pertinent to the inspection [21 CFR 312.62 (b)]
- Failure to obtain adequate informed consent [21 CFR 50]
- Failure to maintain drug accountability records [21 CFR 312.62 (a)]
- Failure to report to the IRB all unanticipated problems involving risk to human subjects [21 CFR 312.66]

On the basis of these findings, FDA requested in the CR letter that the applicant:

a. Provide the following information regarding their QA audit program:
   i. A report of the QA audit plan, including the plan for securing compliance from non-compliant clinical investigators. Included should be copies of any Standard Operating Procedures that were in place during conduct of the study to address means by which corrective actions were to be taken if or when you or the CRO identified noncompliant clinical investigators.
   ii. A report of the sponsor's audit findings, including any corrective actions taken and final outcome for the Yang, Murray, (b) (4), and Esquivel sites and for all other sites audited under the sponsor's QA program.
   iii. A description of any clinical investigators terminated for noncompliance. The list should include sites, specific violations, and whether the data were included in the NDA submission.

b. Describe Bayer's QA program with respect to the oversight of CROs that were hired to monitor the clinical sites, including (b) (4) for RECORD 4. Describe the procedures implemented to make sure that the CROs adequately monitored the clinical sites. The response should include the following information:
   i. Provide the procedures by which Bayer was kept apprised by the CROs concerning monitoring of the clinical site during the course of the study. Specifically, describe what information the CROs provided to the sponsor and provide a list of noncompliant clinical study sites reported by the CROs.
   ii. Describe how the sponsor reviewed the information provided by the CROs during the course of the study and at the end of the study. Describe what monitoring information was kept at the end of the study.

c. Independent Thirty Party Audits (b) (4)

Provide assurance that the clinical data obtained from the RECORD 1, 2, 3, and 4 studies are reliable. Specifically, perform an additional audit and supply the results of this audit within your response to this letter. Within your response, include:

i. A copy o f your audit plan, including the following information:
   - How many clinical sites were to be audited, how many subject records were examined, and a description of the process for selection of the audited sites.
   - If not all subject records at a given clinical site were to be audited, describe how subject records were sampled and how the specific data from each subject were audited.

ii. The timeline for completion of your audit (plan finalization, start date, completion date, report finalization date).

As per above, the CR letter stated that additional third party audits should be conducted to provide assurance that the RECORD 1-4 studies are reliable and requested that Johnson & Johnson submit a proposal for these audits. On June 8, 2009, Johnson & Johnson submitted "Clarification Questions" for the Complete Response Letter, which included a proposal that 24 new audits be conducted, together with submission of the reports of the 69 routine and 5 directed/for-cause audits. Johnson & Johnson proposed that the results of the new audits be submitted as an addendum to the Complete Response. In a written response preparatory to a face-to-face meeting between FDA and Johnson & Johnson on June 19, 2009, FDA proposed that 25% of the clinical investigator RECORD 1-4 sites be audited by an independent, third party. At the June 19, 2009 meeting, FDA proposed the following:

> "Selection of sites from all four RECORD studies with a total enrollment of 60 or higher results in identification of 26 sites: 9 in RECORD 1 (2 already inspected by the Agency), 4 in RECORD 2, and 13 in RECORD 4 (6 already inspected by the Agency). If 5% is the margin of error for tolerance of unreliable sites detected by the audit, then the audit of 30 sites is necessary to show with 95% confidence that the percentage of unreliable sites exceeds 5%, assuming that 25% of sites are actually unreliable. Therefore, 18 high enrolling sites not previously inspected could be included in the audit plan, which represents 11% of enrolled subjects. If 30 total sites are to be audited, an additional 12 sites could be included in the audit, which represent a random sample of sites which enrolled 40-60 subjects and sites which enrolled 10-30 subjects."

Johnson & Johnson submitted the proposed audit plan on July 8, 2009. The audit plan included audits of an additional 30 clinical sites across the entire RECORD program including all 18 high enrolling sites with $\geq$ 60 randomized subjects, and 12 moderate enrolling sites with 15-59 randomized subjects. The 12 moderate enrolling sites (3 per study) were randomly selected by the Johnson & Johnson statistics group from a pool of sites which met the stated enrollment criteria. None of the sites selected for audit had previously been inspected for this NDA by the FDA. Johnson & Johnson intended to audit all subjects if there were 35 subjects or less enrolled at the site. If there were more than 35 subjects, a random selection of subjects

was to be chosen such that if no data integrity issue was found in sample subjects, there would be 95% confidence to rule out more than a 5% error rate. The resulting sample size represented a 31% to 58% sampling (35 to 43 subjects) of sites which enrolled more than 35 subjects. Audit of these 30 sites resulted in a total of 950 subjects with data audited out of 12,729 subjects, which constituted 7.5% of all subjects in the RECORD program data base. The results of the (b) (4) audits were to be submitted with the CR.

The parameters to be verified during each audit were those contained in the Complete Response Letter (listed in Part II.1.c. below). The audit findings at each site were to be documented in an individual site audit report and provided to the FDA. In addition, a separate summary report was to be provided. Johnson & Johnson proposed that (b) (4) conduct the targeted audits. The criteria used by Johnson & Johnson to identify the independent third party auditor required that there were 1) no previous associations with the rivaroxaban development program, and 2) no current contracts with Johnson & Johnson or Bayer. Auditors utilized were full-time employees of the independent third party or regionally based contractors who were trained on the company's SOP and were overseen by a full-time employee of the independent third party. Johnson & Johnson has previously employed (b) (4) as an independent third party audit team. Johnson & Johnson proposed to provide a member of the Bayer Global Clinical Operations or Quality Assurance team to escort the third-party auditor for logistical support and translation, if needed.

On August 5, 2009, DSI communicated in writing that DSI was in agreement with the number of sites selected and the number of subjects to be audited at each site, submission of individual site reports as well as a separate summary report, and agreement with the proposed Data Verification Tool for the (b) (4) audits.

On March 5, 2010, Johnson & Johnson submitted Meeting Background Information in preparation for a face-to-face meeting on April 7, 2010. The Background Information contained a summary of the results of the (b) (4) audits. Johnson & Johnson also submitted a proposal for data verification and sensitivity analyses for RECORD 4 in order to allay concerns regarding the FDA inspectional and third party audit findings pertaining to that study. According to the proposal, Johnson & Johnson would employ (b) (4) to revisit all RECORD 4 sites to obtain unreported adverse events as well as relevant data for the sensitivity analysis. DSI responded that a review of the complete audit reports conducted for all four RECORD studies, rather than a summary, was necessary before agreement could be reached on a path forward. In addition, no recommendation could be given regarding the (b) (4) data verification proposal prior to the review of the RECORD 4 (b) (4) audits. Subsequent to this meeting, Johnson & Johnson submitted on April 19, 2010 the (b) (4) audit reports for the audits conducted between (b) (4), as well as copies of the Bayer internal company audits conducted concurrently with the clinical trials. The CR was submitted on December 23, 2010.

The following sections of this review will first evaluate the Applicant's Complete Response focusing on the adequacy of responsiveness to the items requested in the Agency's Complete Response Letter. This will be followed by a description of (b) (4) Audit findings focusing on items considered key to evaluation of data reliability. The review will then provide DSI's analysis of the specific audit findings and their impact on data reliability, followed by an

assessment of data reliability for each RECORD study. The review will then conclude with DSI's conclusions and recommendations on reliability of data for the application as a whole.

II. EVALUATION OF APPLICANT'S DECEMBER 23, 2010 SUBMISSION

In the FDA's April 29, 2009 Complete Response (CR) letter, a number of requests were outlined that the applicant needed to address to resolve the Agency's concerns with respect to data integrity issues. In the sections below, each of the items in the letter will be restated in bold font, followed by a summary of Johnson & Johnson's response, and DSI's assessment of the adequacy of the response.

1. a. Provide the following information regarding your clinical data quality assurance (QA) audit program that was in place for the four RECORD studies:

i. A report of your QA audit plan, including your plan for securing compliance from non-compliant clinical investigators. Include copies of any standard Operating Procedures (SOPs) that were in place during conduct of the study to address the means by which corrective actions were to be taken if or when you or the applicable means by which corrective actions were to be taken if or when you or the applicable contract research organization (CRO) identified noncompliant investigators.

Johnson & Johnson provided a summary of their audit plans for the RECORD 1, 2, 3, and 4 studies. They also provided a summary of their audit procedures and copies of SOPs for audit procedures. Included were SOPs which address procedures for site initiation and monitoring, study management, investigator site audits, and misconduct.

DSI Assessment of Response: Johnson & Johnson has adequately responded to this request.

ii. A report of your audit findings, including any corrective actions taken and final outcomes for the Yang, Murray, (b) (4), and Esquivel sites and for all other sites you audited under your QA program.

iii. A description of any clinical investigators terminated for non-compliance. Provide a list of these clinical investigators, their sites, the specific violations, and whether the data were included in the NDA submission.

The description of the findings requested in Parts 1.a.ii. and 1.a.iii. and the DSI assessment of these findings are combined below.

Response to 1a.ii.

Johnson & Johnson provided a summary of audit findings, corrective action plans, and outcomes for each site for clinical investigator sites that participated in the RECORD studies. There were 74 clinical investigator site audits conducted by Bayer; 69 were routine and 5 were for cause. There were 25 audits conducted at RECORD 1 sites, 15 audits conducted at RECORD 2 sites, 15 audits conducted at RECORD 3 sites, and 19 audits conducted at RECORD 4 sites. Findings during the audit were classified into Class 1, Class 2, and Class 3. Class 1 findings are findings of confirmed misconduct which endanger subject safety and/or

would lead to rejection of data by Regulatory Authorities, whereas Class 2 and Class 3 are less serious findings. There were 2 clinical investigator sites with Class 1 findings in RECORD 1, 1 clinical investigator site with Class 1 findings in RECORD 2, 3 clinical investigator sites with Class 1 findings in RECORD 3, and 2 clinical investigators with Class 1 findings in RECORD 4. Of these clinical investigator sites with Class 1 findings, 4 were the sites which were for cause inspections: Dr. Macaire Site 11354 in RECORD 1 and Site 16009 in RECORD 3, Dr. Mortele Site 28020 in RECORD 3, Dr. Dadi Site 60017 in RECORD 4, and Dr. (b) (4) (the third inspection); these inspections will be discussed below. The remaining sites with Class 1 findings included Dr. Jasey Site 26007 in RECORD 2 which had enrollment temporarily suspended due to limited access of the site by the auditors to source documents, poorly documented changes to source documents, suboptimal level of principal investigator involvement, and enrollment of a clearly ineligible subject. Enrollment was restarted 11 days later after these issues were addressed to the satisfaction of the sponsor. The 2 remaining sites with a Class 1 finding both routinely obtained coagulation studies at the site, which could potentially result in unblinding and is a protocol violation. Both sites (Dr. Schmelz Site 10010 in RECORD 1 and Dr. Debue Site 16001 in RECORD 3) corrected the problem immediately. The last site with a Class 1 finding is Dr. Esquivel Site 32006, also discussed below.

FDA requested a report of the applicant's audit findings, including any corrective actions taken and final outcomes for the Yang, Murray (b) (4), and Esquivel sites and for all other sites that were audited under their QA program. The following provides a summary of this information.

Dr. Q. Yang Site 54005 RECORD 4: This site was not included in Bayer's audit program. The regulatory violations cited by the FDA inspector are acknowledged by the applicant in the CR and reasons given for the violations. However, no evidence is presented to refute the violations observed during FDA inspections.

Dr. Michael Murray Site 14005 RECORD 4: There were no Class 1 findings at the inspections of Dr. Murray, Site 14005, and Dr. John Ward, Site 14010, who enrolled as separate sites in Birmingham, Alabama under the umbrella of an SMO. Class 2 findings included source data inadequacies, systematic data inaccuracies involving adverse event and concomitant medications, and failure to obtain protocol required venograms. The applicant presents information from Dr. Murray's letter of response to the inspectional findings. The source document issues were addressed by source verification by the site CRA, with correction as needed. These issues differ from those identified during the FDA clinical site inspection (postoperative randomization, possible unblinding) which resulted in an OAI (b) (4).

(b) (4) RECORD 4: A routine audit of this site was conducted starting on December 12, 2006. A number of Class 2 findings were identified involving problems with data quality and general GCP compliance, including lack of source documentation and lack of documentation of Principal Investigator (PI) involvement. Study activities were inappropriately delegated to unqualified study personnel, and there were extensive delays in CRF completion. Enrollment was placed on hold at the conclusion of the inspection; enrollment resumed on January 16, 2007 based on feedback from the CRA monitoring the

study. A follow-up audit was conducted starting on May 14, 2007 to determine the effectiveness of the corrective actions taken. Persistent GCP noncompliance was noted, including evidence that the original source data worksheets completed during the outpatient phase of the study had been rewritten and the original documents not maintained. Enrollment was placed on hold, and the frequency of monitoring was increased. A third audit was conducted starting January 16, 2008. This audit was precipitated by site notification to the IRB of data falsification; the IRB communicated this information to the FDA. The January, 2008 Bayer audit confirmed falsification of the signatures of the PI (and in some cases the sub-investigator) on lab reports, ECGs, hospital orders, FDA 1572s, SAE documentation, IRB submissions, and ICF documents. At least 19 patients' source data and nine submissions to the IRB were falsified.

For the NDA submission, subjects from Dr. (b) (4) site were excluded from the per protocol analyses. Patients were included in the safety and mITT analyses when validity criteria were met, and sensitivity analyses were conducted after including subjects in the per protocol analysis and excluding subjects in the mITT which revealed that the overall results were not changed.

Response to 1.a.iii.

Johnson & Johnson listed the following clinical investigators who were terminated for noncompliance:

Dr. Esquivel Gomez Site 32006 RECORD 4: A routine audit of the site starting on October 17, 2007 revealed the Class 1 finding that the site had failed to retain all available source records due to a hospital policy of periodically purging hospital and in-patient nursing notes. The nursing notes were considered to be source documents which verified the administration of the investigational product. The site had been placed on enrollment hold by the study team on August 9, 2007 due to delays in CRF completion and the hold remained in effect for the remainder of the study.

Subjects were included in the Per Protocol analyses only when it could be confirmed that eCRF data had been verified as correct by the CRA. All subjects were included in the safety and mITT populations unless the subject did not meet validity criteria.

(b) (4) RECORD 2: This site was not audited by Bayer. The inspection conducted by FDA found inadequate Investigator oversight and systematic use by the site of PlexiPulse pneumatic compression, which was not allowed by the protocol. An Investigative Committee was established and follow-up activities were conducted by Bayer, including assignment of an additional CRA to the site. Retraining was conducted. No subjects randomized were valid for the per protocol analysis due to the use of pneumatic compression or inadequate assessment of thromboembolism. All subjects were included in the safety and mITT analyses, unless they did not meet validity criteria.

Dr. Richard Rouhe Site 14062 RECORD 4: On August 16, 2007 Dr. Rouhe was notified by his IRB of his failure to report that his medical license was on probation for 5 years by the California Medical Board. Upon transmission to Bayer of this information, enrollment at this

site was terminated; six subjects had been randomized and two subjects were treated. The CRA noted that Dr. Rouhe's CV and medical license were missing at the first periodic monitoring visit on May 30, 2007; however, copies of the license was available at the August 10, 2007 CRA visit, and his CV was available at the October 15, 2007 monitoring visit. Data from this site were only included in the Safety Analysis, as the two subjects did not have an adequate assessment of venous thromboembolism.

Additionally, the efficacy data from Dr. P. Macaire's site 16009 in RECORD 1 was invalidated after a for cause inspection revealed that the CRA entered data in the eCRF and made changes outside of agreed permissible clarifications. The PI refused to confirm data entered into the eCRF. The data was considered valid for safety.

DSI Assessment of Response: Johnson & Johnson has adequately responded to this request. In general, review of the audits revealed that appropriate corrective action plans were generated and implemented for those clinical investigator sites with Class 1 findings. However, there were several areas of concern identified. Although significant findings were identified at Dr. Michael Murray's site during the Bayer audit, the issues identified by FDA inspectors which resulted in an OAI classification were not identified. Of greater significance, the initial two Bayer audits at Dr. (b) (4) site identified significant problems at this site, resulting in a temporary hold on enrollment and increased frequency of monitoring. However, the most serious issue of forging the principal investigator's signature was apparently not identified during the two audits; it came to attention after a CRA at the site reported this violation to the IRB. The information available from the Bayer audits confirms the FDA's finding that data from the sties of Drs. Yang, Murray, (b) (4), and Esquivel are not considered reliable.

b. Describe Bayer's QA program with respect to the oversight of CROs that were hired to monitor the clinical sites, including (b) (4) for the RECORD 4 study. Describe the procedures implemented to make sure that the CRO adequately monitored the clinical sites. In your response, include the following information:

i. How was Bayer kept apprised by the CROs concerning monitoring of the clinical sites during the course of the study? Specifically, what information did the CROs provide? Provide a list of non-compliant study sites reported by the CROs.
ii. How did Bayer review the information obtained from the CROs, during the course of the study and at the end of the study? What monitoring information was kept at the end of the study?
iii. What actions did Bayer take based on the monitoring reports?

Response to 1.b.i.-iii.
Bayer provided the majority of the monitoring for the RECORD 1, RECORD 2, and RECORD 3 clinical trials. The applicant presents information on the CROs that provided monitoring for RECORD 1 in Israel, RECORD 2 in Portugal and India, and RECORD 3 in Israel due to the lack of Bayer monitoring facilities in these countries. The monitoring oversight of the CRO

and processes for study documentation by the CROs were described for each of the non-Bayer CROs.

[redacted] provided the monitoring for most RECORD 4 sites. Monitoring of RECORD 4 sites in Pakistan was provided by [redacted] (by a subcontract [redacted]) and by [redacted] in Israel. The following information regarding [redacted] role in RECORD 4 was presented:

- [redacted] was responsible for the monitoring and management of RECORD 4.
- The Bayer Study Manager was responsible for overseeing the operational conduct of the CRO. This oversight included reviewing, tracking, analyzing, and summarizing the study related activities and the performance of [redacted]. The Bayer Study Manager kept the Bayer Study Team and relevant member of Bayer management informed of the overall progress of the study via meetings or reports.
- [redacted] had a Project Leader responsible for the overall management of the trial, managed by the [redacted] Director of Clinical Operations.
- Processes implemented to ensure sufficient oversight of outsourced trials and to ensure the CRO adequately monitored the clinical sites.
    - Holding the Study Kick-off Meeting chaired by the Bayer Study Manager
    - The Task Definition Document (TDD) detailed the expectations of each task from initiating and conducting through closing out the clinical trial. An outline of expectations of Bayer and [redacted] responsibilities was included in this document. The TDD detailed project management, study management, monitoring, medical management, and electronic data transfer/data management.
    - Routine meetings between Bayer and [redacted] were conducted.
    - Generation of a Monthly Status Tracking Report to track details of the study
- A Monitoring Plan was created by [redacted] for RECORD 4, reviewed, and agreed upon by the Bayer Study Manager. The Monitoring Plan detailed roles, responsibilities, training plan, lines of communication (within [redacted] external to sites), monitoring, and site management expectations.
- All CRAs were trained on the Monitoring Plan, study documents, goals, and timelines. CRAs were the primary contact with the sites, maintained the Investigator Site Files within [redacted] and informed the [redacted] Project Leader of any site issues.
- [redacted] was responsible for ensuring appropriate training and supervised monitoring activities.
- [redacted] Lead CRAs or Project Leader reviewed and approved Monitoring Reports. They ensured proper follow up and resolution of issues. The Monitoring Visit Reports were posted on the [redacted] website, and the Bayer Study Manager had access to this website. Bayer did not conduct routine reviews of the [redacted] Monitoring Visit Reports as this task was assigned to the [redacted] Lead CRA or Regional Project Leader. The applicant states that discussion of issues identified at Monitoring Visits were discussed at "frequent meetings" between [redacted] and Bayer.

DSI Assessment of Response: Johnson & Johnson has adequately responded to this request.

The methodology outline for Bayer's oversight of CROs used for the RECORD studies including (b) (4) should have been adequate. However, there are clearly monitoring inadequacies in the RECORD studies, most prominently in RECORD 4 which was monitored by (b) (4). Although there were meetings between (b) (4) and Bayer, there was no routine exchange of problematic information regarding audit findings (nor was this required by the agreements between (b) (4) & Bayer). In addition, as discussed above, critical issues identified by other means (FDA inspections, third party audits) were not routinely identified by (b) (4) site monitoring. This raises concerns, particularly, as to the adequacy of monitoring of RECORD 4 studies.

c. Independent Thirty Party Audits (b) (4)

The following was requested in the CR letter:

Provide assurance that the clinical data obtained from the RECORD 1, 2, 3, and 4 studies are reliable. Specifically, perform an additional audit and supply the results of this audit within your response to this letter. Within your response, include:

- **i. A copy o f your audit plan, including the following information:**
  - **How many clinical sites were to be audited, how many subject records were examined, and a description of the process for selection of the audited sites.**
  - **If not all subject records at a given clinical site were to be audited, describe how subject records were sampled and how the specific data from each subject were audited.**
- **ii. The timeline for completion of your audit (plan finalization, start date, completion date, report finalization date).**
- **iii. In addition to any other information within your audit report, address the following questions or requests:**
  - **At each site audited, how many violations involved each of the following specific issues? For each specific violation, list the clinical sites involved and provide a breakdown by treatment group for each site and overall for the four RECORD studies.**
    - **Enrollment of subjects that did not meet study eligibility criteria.**
    - **Failure of the Principal Investigator to ensure that all associates and colleagues assisting in the investigation were meeting the commitments of the study protocol.**
    - **Failure to report adverse events and serious adverse events**
    - **Failure to randomize subjects preoperatively**
    - **Failure to obtain informed consent from all subjects**
  - **List all clinical sites where either Bayer or CRO monitoring is determined to be ineffective, either in identifying significant violations or in taking actions towards securing compliance (such as notifying the sponsor).**

Response to 1c.i and ii.
Overview of (b) (4) Audits

The audit program was conducted by an independent third party, (b) (4). The studies included in the audit were the four pivotal Phase 3 studies of rivaroxaban 10 mg immediate-release tablets for the prophylaxis of deep vein thrombosis (DVT) and pulmonary embolism (PE) in patients undergoing hip replacement surgery or knee replacement surgery. The objective of the audit program was to provide assurance that the data obtained from the RECORD 1-4 studies are reliable. The audits assessed compliance with the protocol and appropriate Good Clinical Practice (GCP) requirements. Additionally, compliance with International Conference on Harmonization (ICH) Guidelines, the U.S. Code of Federal Regulations as set out in 21 CFR Parts 50, 54, 56, and 312, and, where applicable, local regulatory requirements was assessed. Selected documentation including protocols and monitoring visit reports was provided to the auditors by Johnson & Johnson. Bayer clinical operations representatives assisted with logistics and translations. The audit program focused on the specific areas of concern identified by the FDA in the CR letter in six categories:

- Informed Consent
- Investigational Product
- Source Data Verification and Case Report Completion
- Safety
- Study Conduct
- Monitoring

Each audit observation was grouped by (b) (4) into one of the following categories:

CRITICAL: An observation that requires prompt corrective action to ensure compliance with regulations, guidelines, company policy, or local law. These findings if unaddressed could compromise human safety, market authorizations, or the acceptability of investigational product, data, facilities, or systems intended for regulatory submission. Regulatory authority action would appear probable.

MAJOR: An observation that requires improvement to ensure compliance with regulations, guidelines, company policy, or local law. These findings if unaddressed could compromise human safety, market authorizations, or the acceptability of investigational product, data, facilities, or systems intended for regulatory submission. Regulatory authority action would appear possible.

MINOR: An observation where improvement is recommended for minor deviations from regulations, guidelines, company policy, or local law.

There were 30 sites selected across the RECORD studies for auditing, including all 18 high-enrolling sites with $\geq$ 60 randomized subjects along with 12 moderate-enrolling sites with 15-59 randomized subjects. Focused audits were performed on individual subject records for 100% of the subjects enrolled in each site that had up to 35 subjects. The 12 moderate-enrolling sites (3 per study) were randomly selected by the Johnson & Johnson statistics group suing SAS Version 9.1 from a pool of all sites that met the stated enrollment criteria. For

higher enrolling sites, focused audits were performed on a random sample of 35 to 43 subjects, depending on the number of subjects required to rule out a 5% error rate or higher with 95% confidence. The 30 site audits were conducted between (b) (4) by teams of 2 auditors for 28 sites and by 1 auditor for 2 sites. The number of audited sites and subjects by study and overall is shown below, taken from the sponsor's April 19, 2010 submission.

Table 3: NDA 22-406: (b) (4) RECORD Study Site Audits

Study	Audited sites/total sites	Audited subjects/total subjects at audited sites (%)	Audited subjects/total study subjects (%)
RECORD 1	11/217 (5.1% sites)	347/626 (55.4%)	347/4541 (7.6%)
RECORD 2	7/123 (5.7%)	216/439 (49.2%)	216/2509 (8.6%)
RECORD 3	3/147 (2.0%)	70/70 (100%)	70/2531 (2.8%)
RECORD 4	9/130 (6.9%)	312/636 (49.1%)	312/3148 (9.9%)
Overall	30/617 (4.9%)	945/1771 (53.4%)	945/12,729 (7.4%)

Draft (b) (4) audit reports were reviewed by Johnson & Johnson QA personnel and comments relating to the consistency of reporting were provided (b) (4) for their consideration before the final reports were issued. The final audit reports were reviewed by Johnson & Johnson clinical and regulatory staff for consistency. Amended reports involved only the upgrading of findings. All of the audit reports were finalized by Johnson & Johnson by November 6, 2009 and all addenda by November 30, 2009.

DSI Assessment of Response: Johnson & Johnson has adequately responded to this request. Note that across the 4 RECORD studies, 2.0-6.9% of sites were audited, with audits of 2.8-9.9% of total subjects in the studies. This will be taken in the context of audit findings as discussed below for each of the RECORD 4 studies.

iii. In addition to any other information within your audit report, address the following questions or requests:

- **At each site audited, how many violations involved each of the following specific issues? For each specific violation, list the clinical sites involved and provide a breakdown by treatment group for each site and overall for the four RECORD studies.**
  - **Enrollment of subjects that did not meet study eligibility criteria.**
  - **Failure of the Principal Investigator to ensure that all associates and colleagues assisting in the investigation were meeting the commitments of the study protocol.**
  - **Failure to report adverse events and serious adverse events**
  - **Failure to randomize subjects preoperatively**
  - **Failure to obtain informed consent from all subjects**
- **List all clinical sites where either Bayer or CRO monitoring is determined to be ineffective, either in identifying significant violations or in taking actions towards securing compliance (such as notifying the sponsor).**

Response to 1.c.iii.

J&J Analysis of (b) (4) Audits

Prior to submission of the complete set of (b) (4) audit reports, Johnson & Johnson submitted an analysis of the audits in a March 5, 2010 meeting background package. A brief summary of the Johnson & Johnson analysis is given here. Johnson & Johnson analyzed the (b) (4) audits using two approaches:

1. By six audit categories (informed consent, investigational product, SDV/CRF, safety, study conduct, monitoring).
2. By specific audit findings by classification category (critical, major, and minor).

Across the 30 audited sites, there were a total of 251 findings. Nineteen of these findings were categorized by (b) (4) auditors as critical, 121 were categorized as major and 111 were categorized as minor. The number of major findings per site ranged from 1 to a maximum of 10, with 12 of the 30 sites having 5 or more major findings (RECORD 1: 3/11 [27%], RECORD 2: 2/7 [29%], RECORD 3: 1/3 [33%], RECORD 4: 6/9 [67%]). The 19 critical findings recorded by (b) (4) occurred at 13 of the 30 audited sites in the following categories:

- 1 finding for Informed Consent
  - For one subject at one site, a signed consent form was not available.
- 2 findings for Investigational Product
  - Documentation of the Investigational Product administration during the inpatient phase of the study was either missing or insufficient.
- 6 findings for Source Data Verification and Case Report Form Completion
  - These critical findings can be further broken down into findings related to missing medical records (15 subjects at 4 sites), and significantly deficient and discrepant source documentation (2 sites).
- 4 findings for Safety
  - These findings were associated with adverse events that weren't reported and/or deficient safety reporting practices.
- 5 findings for Study Conduct
  - These can be further broken down into findings related to eligibility (9 subjects; 1 each at 2 sites, 7 at one site), protocol violations for study drug treatment outside the protocol specified time window (19 subjects at one site), and an improperly constituted ethics committee (1 site).
- 1 finding for Monitoring
  - The site monitor had failed to detect unreported adverse events, failed to detect late reporting for SAEs, and failed to meet with the principal investigator for 6 months, and failed to document training.

Further, Johnson & Johnson noted that there were a total of 603 audit identified (AI) AEs in the 931 audited subjects from 28 of 30 sites audited. The highest proportion of subjects with AI AEs were in the RECORD 4 study. There were eight AI SAEs found, all from RECORD 4 sites; five of these were newly reported events and three were upgraded AEs. Johnson & Johnson concluded the following regarding unreported AEs:

- Qualitatively, the most commonly reported AEs were similar in the audited subjects compared to those seen overall in the originally reported RECORD population.
- The AI-AEs appear to be balanced between the two treatment groups and their inclusion does not substantially alter the previously reported event rates in the audited subjects.

- RECORD 4 was found to have the largest number of AI-AEs, and all of the unreported SAEs were identified exclusively in the RECORD 4 study.
- Overall, the identification of the AI-AEs and AI-SAEs did not alter the previously reported safety profile of rivaroxaban.

The applicant notes that the efficacy endpoint in the RECORD studies was a hard composite endpoint of death, symptomatic VTE, or venographically detected VTE. They also note that the (b) (4) audits did not identify any evidence that would suggest that any of the venography data were not reliable; similarly, the audits did not identify any possibly missing or invalid symptomatic DVT or PE events. The sponsor concludes that the results of the RECORD studies are valid and reliable, but that the RECORD 4 study monitoring process should be specifically further addressed by a data validation plan, outlined in their submission.

DSI Assessment of Response: The sponsor's response is considered adequate to address the request in the CRL. In the following section, DSI will specifically analyze the (b) (4) Audits and will discuss the (b) (4) Audit findings considered critical to the evaluation of data reliability.

III. DSI Analysis of (b) (4) Audits

This section will provide DSI's analysis of the (b) (4) Audits focusing on items deemed critical to evaluations data reliability:

- Adequacy of Monitoring
- Human Subject Protections and Adverse Event Reporting
- Post-Operative Randomization
- Drug Accountability
- Eligibility

This section will also briefly touch upon (b) (4) Verification of RECORD 4 Data.

1. Adequacy of Monitoring

In one method used during the (b) (4) audits to assess adequacy of site monitoring, (b) (4) auditors reviewed each individual monitoring report. The Patient Data Check (PDC) Form was then completed for each subject, answering the question: "Was the monitoring effective, either in identifying significant violations or in taking actions towards securing compliance? The results are as follows (subjects inadequately monitored/subjects audited (%))

RECORD 1: 96/347 (27.2%)
RECORD 2: 55/216 (25.5%)
RECORD 3: 28/70 (40.0%)
RECORD 4: 197/312 (63.1%)

The (b) (4) audit reports note that inadequate monitoring was considered to be present at 2/11 (9%) of RECORD 1 sites, 2/7 (29%) of RECORD 2 sites, 1/3 (33%) of RECORD 3 sites, and 4/9 (44%) RECORD 4 sites (Table 4) according to (b) (4) assessment. Note that not all audit reports contained a specific statement regarding adequacy of monitoring. DSI review of the

audit reports yielded an additional RECORD 4 site at which (b) (4) monitoring did not detect findings which would affect the primary efficacy or safety outcome (Table 4). For 3 additional audit reports (2 at RECORD 1 sites and 1 at a RECORD 2 site), it could not be determined from review of the audit report whether key primary efficacy or safety issues detected by the (b) (4) auditors were noted by the Bayer/(b) (4) monitors. Key primary efficacy or safety issues included study drug administration inconsistencies between source documents and eCRF, drug accountability and dosing issues, identical drug dispensation times for all subjects, and inclusion of a subject with intraocular hemorrhage in violation of the exclusion criteria. Note that (b) (4) audits of many other sites demonstrated missed monitoring issues with respect to protocol deviations, adverse event reporting, source document verification, etc. However, only those instances in which monitoring omissions involved primary efficacy parameters or safety issues, which are considered critical for the evaluation of data integrity, are addressed here. In addition, instances where a single subject at a site had an issue impacting safety or efficacy are not included here since these instances would be unlikely to significantly impact overall site data reliability. Rather, review has focused on findings at sites where a substantial number of subjects were impacted at the site, such that overall data reliability of the site is in question. Please see Table 8 in Section III.5. for a listing of specific issues impacting on data reliability at individual sites.

Table 4: Monitoring Adequacy and Issues Based on (b) (4) Audit Reports

	RECORD 1	**RECORD 2**	**RECORD 3**	**RECORD 4***
# of (b) (4)-audited Sites with Monitoring Deficiencies (n)/Total # of sites audited by (b) (4) (N)	**Number sites (n/N; %)**	**Number sites (n/N; %)**	**Number sites (n/N;%)**	**Number sites (n/N;%)**
Per (b) (4) audit reports; DSI concurs	2/11 (9%)	2/7 (29%)	1/3 (33%)	4/9 (44%)
Monitors missed key primary efficacy or safety issue per DSI review of (b) (4) audit	0/11 (0%)	0/7 (0%)	0/3 (0%)	1/9 (11%)**

*(b) (4) was monitor

**Sepulveda (Site 32002): Monitoring did not detect study drug administration inconsistencies between source documents and eCRF.

The specific sites deemed by Johnson & Johnson analysis of the (b) (4) audits to have ineffective monitoring are the following:

Garces, RECORD 1, Site 240002: Monitoring was inadequate to detect some unreported AEs, medical historical information, and protocol deviations; 90% of subjects audited had a "no" response given for the PDC question.

Slappendel, RECORD 1, Site 30002: The Executive Summary of the audit states that monitoring is inadequate. 91% of subjects audited had a "no" response given for the PDC question.

Ono, RECORD 2, Site 50005: 92% of subjects audited had a "no" response given for the PDC question.

Wang, RECORD 2, Site 54001: Monitoring inadequate as judged by a significant number of eCRF versus source discrepancies; 46% of subjects audited had a "no" response given for the PDC question.

Brabants, RECORD 3, Site 28015: 100% of subjects audited had a "no" response given for the PDC question.

Kilgore, RECORD 4, Site 14034: 66% of subjects audited had a "no" response given for the PDC question.

Reddy, RECORD 4, Site 60001: Numerous protocol/GCP deviations were unreported by the monitor; 100% of subjects audited had a "no" response given for the PDC question.

V. Shah, RECORD 4, Site 60006: Numerous protocol/GCP deviations were unreported by the monitor; 100% of subjects audited had a "no" response given for the PDC question.

H. Shah, RECORD 4, Site 60004: Numerous protocol/GCP deviations were unreported by the monitor; 100% of subjects audited had a "no" response given for the PDC question.

Modi, RECORD 4, Site 60010: None of the issues noted in this report were noted as deviations by the monitor. 97% of subjects audited had a "no" response given for the PDC question.

It could not be determined from DSI evaluation of the (b) (4) audit results from Dr. Garces and Dr. Wang's sites whether inadequate monitoring of the site resulted in a deleterious effect on key primary efficacy and/or safety findings from those sites. However, review of the (b) (4) audit results themselves did not raise concerns as to data reliability of these sites.

Johnson & Johnson also submitted reports of 74 clinical investigator site audits conducted by Bayer GCP Study Audit Management for the RECORD 1-4 studies, 69 of which were routine. Review of the Bayer audit reports for the clinical investigator sites for which (b) (4) and/or DSI considered that the data was unreliable (when available) showed that in the majority of instances, the violation considered most significant by DSI was not reported in the Bayer audit report. Significant deficiencies at the sites of Drs. Lenart (RECORD 1), Porvaneckas (RECORD 1), Nararrete (RECORD 2), and Buettner (RECORD 4), described in the (b) (4) audit reports were not mentioned in the Bayer audit reports. Although significant findings were identified at Dr. Michael Murray's RECORD 4 site during the Bayer audit, the issues identified by FDA inspectors resulting in an OAI classification were not noted. The initial two Bayer audits at Dr. (b) (4) site in RECORD 4 did not report forgery of the Principal Investigator's signature, which was subsequently reported to the IRB by a site CRA. Failure to identify via site audits these serious regulatory violations identifies adequacy of monitoring as a problem in the RECORD trials, especially RECORD 4.

DSI Assessment of Response:
Based on DSI review of (b) (4) audit reports, (b) (4) auditors stated that overall study monitoring was deficient at 1 of 11 (9%) sites in RECORD 1, 2 of 7 (29%) sites audited in RECORD 2, 1 of 3 (33%) sites audited in RECORD 3, and 4 of 9 (44%) sites audited in RECORD 4. DSI concurs that monitoring was deficient at these sites. According to DSI review, (b) (4) monitoring failed to detect a key efficacy or safety issue in one additional instance in RECORD 4 (Dr. Sepulveda). It could not be determined from DSI evaluation of the (b) (4) audit results from Dr. Garces and Dr. Wang's sites whether inadequate monitoring of the site resulted in a deleterious effect on key primary efficacy and/or safety findings from those sites. It should be noted that these findings impacted a substantial number of subjects at each site, such that overall data reliability of the sites is in question.

Review of the audit reports for RECORD 1, 2, 3, and 4 submitted by Johnson & Johnson also revealed that Bayer/ (b) (4) audits did not always identify serious deficiencies.

(b) (4) assessment of monitoring ineffectiveness by PDC forms showed that 63% of subjects in RECORD 4 audited were not monitored effectively. RECORD 1 and 2 had similar levels of unreliable monitoring, 27% and 29%, respectively. The relatively high level of ineffective monitoring (40%) noted in RECORD 3 is very likely reflective of the comparatively low number of subjects audited in RECORD 3 together with the presence of a problematic site (Brabants – see Section III.3. below) which enrolled 27 subjects.

The frequency of monitoring ineffectiveness was less in RECORD 1, 2, and 3 as compared to RECORD 4; however, there was not as large a difference between monitoring ineffectiveness between RECORD 3 as compared to RECORD 4. However, as noted above, this assessment ineffectiveness by (b) (4) was based solely on PDC form checks. Note that in DSI's assessment of monitoring adequacy of all 4 RECORD studies, assessment of monitoring effectiveness/ineffectiveness was not based solely on PDC form evaluation and respective percentages, but rather on the specific findings and their impact on data reliability. As such, perhaps from a percentage standpoint, it may be noted that monitoring ineffectiveness of 40% for RECORD 3 is not substantially different from the 63% monitoring ineffectiveness for RECORD 4 based on the PDC form check; however, taking into account not only PDC form checks, but also the extent and scope of deficiencies noted in RECORD 4, particular concerns are raised regarding data reliability of RECORD 4 based on evaluation of monitoring.

Overall, monitoring deficiencies were noted for all 4 RECORD studies; however, in comparison to RECORD 1-3, the extent and scope of monitoring deficiencies noted for RECORD 4 are considered more significant and raise concerns regarding pervasiveness of monitoring deficiencies for other sites not inspected or audited, and as such undermine the confidence in reliability of the data.

2. Human Subject Projection and Adverse Event Reporting in (b) (4) Audit Reports

Human Subject Protection

In Table 5 below are presented clinical investigator sites where any instance of failure to protect human subject rights was noted during DSI review of the (b) (4) audits. Data from the sites of Drs. Brabants, Mody, and V. Shah were assessed by DSI as unreliable based on efficacy findings as given in Table 8 in Section III.5. Additionally, four women of childbearing potential were enrolled in RECORD 2 without performance of a pregnancy test; omission of the pregnancy tests were intentional, based on cultural factors. This protocol violation had the potential to significantly adversely impact any pregnancies which had been preexisting to the study. Although the events documented at the sites of Drs. Bauer, Marinoni, and Field are of substantial concern to DSI, they either involve a single individual or did not result in subject harm, and as such are unlikely to impact data reliability of these 3 specific sites.

Table 5: Clinical Investigator Sites with Instances Where Subject Safety Was Not Protected Based on DSI Review of (b) (4) Audit Reports

Study	Clinical Investigator Site number Number of subjects	Detail
RECORD 1	Bauer Site 44003 63 subjects	One subject with untreated hypertension
RECORD1	Marinoni Site 22001 15 subjects	• Subject 4003 Subject had history of disturbed vision & ITP = exclusion criteria. Subject had "pre-retinal hemorrhage" Day 1, study medication continued. • 4 subjects had epidural catheters inserted or removed outside of protocol requirements; none of these catheters were recorded on the CRF. Two were placed too soon after study drug administration (1.5 and 2 hours) and 2 were withdrawn too soon after study drug administration (1.5 and 4 hours after dose, rather than 2X the half-life)
RECORD 2	Field Site 12008 140 subjects	Subject 7989-251107 had a diagnosis of chronic renal insufficiency (CRI) per medical records, no screening labs reviewed prior to surgery (b) (6), screening labs signed by PI 10/14/06, subject withdrawn due to elevated BUN/Cr on 10/13/06.
RECORD 2	Wang Site 54001 88 subjects	Four of six women of child bearing potential did not have pregnancy test performed prior to enrollment in the trial
RECORD 3	Brabants Site 28015 27 subjects	9 of 27 subjects had screening procedures performed prior to signing Informed Consent
RECORD 4	Mody Site 60010 68 subjects	• Ethics Committee (EC) impartiality could not be confirmed, as the EC was established at the PI's request, and the members had no training or prior experience. • Clinician review of study documents (laboratory studies, ECGs) for 25/35 subjects (71%) was either not done or not done in a timely fashion. Example = ECG showing anterior wall myocardial ischemia.
RECORD 4	V. Shah	Language used to discuss the Informed Consent

Site 60006 80 subjects	document with all subjects was coercive, with documentation indicating that he said "that the study drug was completely safe, that it is the best treatment currently available, that risks were minimal (same as any other surgery). . ."

Adverse Event Reporting

The (b) (4) audit reports were reviewed in order to assess the adequacy of adverse event reporting. Only 2 of the 30 audited sites had no unreported adverse events identified during the audits. The number of unreported adverse events ranged from 1 to 54 per site. Eight unreported SAEs were identified, all at RECORD 4 sites. Unreported adverse events were assessed as "significant" by the DSI reviewer if they clearly required further expeditious medical evaluation; all events which included bleeding or elevation of liver function tests were included in this category. Anemia in itself was not considered "significant".

Table 6 below summarizes unreported AEs by clinical investigator site audited by (b) (4).

Table 6: Unreported Adverse Events

RECORD study	Investigator	Number and type of unreported SAEs	Number of unreported adverse events/number of subjects with unreported adverse events (Excludes SAEs)	Number of unreported adverse events of significance – clearly required medical evaluation	Examples of significant unreported adverse events
RECORD 1	Bauer	0	4/4	1	GGT = 205
RECORD 1	Kruczynski	0	1/1	0	-
RECORD 1	Lenart	0	1/1	0	-
RECORD 1	Marinoni	0	5/4	1	Abnormal ECG
RECORD 1	Mazurkiewicz	0	4/4	0	-
RECORD 1	Garces	0	8/6	1	Disorientation
RECORD 1	Pesola	0	2/2	0	-
RECORD 1	Porvaneckas	0	22/12	3	Allergic skin reaction, elevated BP
RECORD 1	Schwartsmann	0	0	0	-
RECORD 1	Slappendel	0	54/21	9	SOB, wound hematoma, calf red/painful, fever, low HR requiring Rx
RECORD 1	Stehlik	0	12/11	1	Hypotension and chest pain
RECORD 2	Belickas	0	8/7	2	Fever
RECORD 2	Dhanjee	0	4/4	3	Hypotension, calf pain, fever
RECORD 2	Field	0	21/13	2	Leg swelling elevated GGT
RECORD 2	Martson	0	9/5	3	Thigh hematoma, fever, hypotension
RECORD 2	Nafarrete	0	34/10	4	Infection
RECORD 2	Ono	0	37/16	7	Hypertension, nasal

Table 6: Unreported Adverse Events

RECORD study	Investigator	Number and type of unreported SAEs	Number of unreported adverse events/number of subjects with unreported adverse events (Excludes SAEs)	Number of unreported adverse events of significance – clearly required medical evaluation	Examples of significant unreported adverse events
					bleeding during surgery
RECORD 2	Wang	0	18/14	3	Hypertension, dyspnea
RECORD 3	Brabants	0	36/20	2+*	Leg hematoma;
RECORD 3	Paulsson	0	1/1	0	-
RECORD 3	Synder	0	0	0	-
RECORD 4	Dessouki	1: cholecystitis/ cholecystectomy	18/15	14	Shaking with fever & hallucinations, drug-induced pancreatitis, elevated GGT = 275, ARI, decreased platelets, Na = 119 with K = 2.5, irregular HR, Tx 2U PRBCs, burning calf
RECORD 4	Hollman	0	7/6	0	-
RECORD 4	Jove	0	33/13	7	Fever, hypotension, UTI
RECORD 4	Kilgore	1: Respiratory failure	29/25	3	SOB, Elevated AST/ALT/GGT/alk phos
RECORD 4	Mody	3: Chest infection requiring hospitalization; bedsore requiring hospitalization; hypotension & SOB requiring transfer.	47/21	7	Chest pain/breathing difficulties, Tx 2U PRBCs, fever, hypertension, amylase
RECORD 4	Reddy	3: Grade II adenoCA of the prostate; pyrexia requiring hospitalization; hospitalization more than 12 hours for catheterization	38/10	10	Fever, elevated bilirubin, left bundle branch block, decreased platelets, elevated ALT
RECORD 4	Sepulveda	0	13/25	8	Edema, hematoma, wound infection,

Table 6: Unreported Adverse Events

RECORD study	Investigator	Number and type of unreported SAEs	Number of unreported adverse events/number of subjects with unreported adverse events (Excludes SAEs)	Number of unreported adverse events of significance – clearly required medical evaluation	Examples of significant unreported adverse events
RECORD 4	H. Shah	0	44/19	7	ALT/AST > 3X ULN Probable LVH, possible MI, pitting edema, neutropenia, irregular heart beat
RECORD 4	V. Shah	0	36/17	5	Fever, LE swelling, elevated ALT > 3X ULN

*Many are unspecified abnormal hematology and chemistry values

The total number of unreported adverse events for each RECORD study is as follows:

RECORD 1 – 110; 16 significant*
RECORD 2 – 131; 24 significant
RECORD 3 – 37; 2+ significant
RECORD 4 – 265; 61 significant
Total RECORD studies – 543; 103+ significant
*see note below in "DSI Assessment of Response" as to how "significant" was defined

Although slightly more RECORD 4 subjects were audited than in other 3 studies (and RECORD 3 subjects were audited less frequently), it appears that RECORD 4 has a disproportionate number of unreported adverse events as well as unreported significant adverse events when compared with the other RECORD studies. In addition, RECORD 4 was the only study with unreported SAEs.

DSI Assessment:
(b) (4) audit reports of two clinical investigator sites of 11 audited for RECORD 1 (Drs. Bauer and Marinoni), 2 sites of 7 audited for RECORD 2 (Mr. Field and Dr. Wang), 1 site of 3 audited for RECORD 3 (Dr Brabants), and 2 sites of 9 audited for RECORD 4 (Drs. Mody and V. Shah) demonstrated instances where human subject rights were not protected during the conduct of the RECORD studies. However, the findings noted in Tables 5 and 6 above for Drs. Bauer, Marinoni, Field and Wang, are not considered pervasive in nature, and unlikely to impact data reliability for their respective RECORD 1-3 studies. The findings for Drs. Mody and Shah are concerning and provide further evidence for the distinction between study monitoring/conduct of RECORD 4 as compared to RECORD 1-3.

(b) (4) audits of the majority of sites identified unreported adverse events, ranging from 0 (2 sites) to 54 per site. When adverse events considered significant by DSI (defined as adverse events which clearly required expeditious medical evaluation and all events including bleeding or elevation of LFTs), there were 16 significant unreported AEs in RECORD 1, 24 in RECORD 2, 2+ in RECORD 3 (exact number could not be determined), and 61 in RECORD 4. Unreported AEs and SAEs identified during the data verification process conducted by (b) (4) will be presented in Section III. 6.

The finding of unreported adverse events during the (b) (4) audits did not alone result in a DSI determination that data from these sites were unreliable. However, the striking finding on examination of the number of unreported adverse events and SAEs per study is the disproportionate number of adverse events detected during the (b) (4) audits of RECORD 4 (more than twice the number of undetected AEs and significant AEs) when compared with the smaller numbers reported from RECORD 1, 2, and 3. Of additional concern, are the eight unreported SAEs noted by (b) (4) auditors from the RECORD 4 audits, whereas no undetected SAEs were reported from RECORD 1, 2, or 3. The disproportionate number of adverse events detected during the (b) (4) audits of RECORD 4 when compared with RECORD 1, 2, and 3, as well as the detection of unreported SAEs only in RECORD 4 brings into question the adequacy and completeness of the RECORD 4 safety data submitted to the Agency. In addition, the relatively large number of unreported adverse events raises further concern regarding the adequacy of study conduct and monitoring of RECORD 4.

3. Post-operative Randomization in (b) (4) Audit Reports

As noted in Table 2, post-operative randomization was identified by FDA audits for the NDA submission at 3 clinical investigator sites (Drs. Murray, Ward, and Buettner), all enrolling in RECORD 4, in violation of the protocol. This is despite the fact that (b) (4) the CRO monitoring RECORD 4, sent an email to all sites during the clinical trial reiterating the protocol requirement that subjects be randomized prior to surgery. One FDA inspection noted that the investigator gave permission to randomize after the patient stopped oozing at the surgical wound site.

As part of the CR, Johnson & Johnson determined the incidence of postoperative randomization at all RECORD sites. The results are as follows:

Postoperative randomization was assessed in most RECORD 4 (b) (4) audit reports with the following specific information regarding post-operative randomization (number of subjects randomized postoperatively/total subjects enrolled in study (%)):

RECORD 1: 18/4541 (0.4%)
RECORD 2: 13/2509 (0.5%)
RECORD 3: 9/2531 (0.4%)
RECORD 4: 1227/3148 (39.0%)

Dessouki - 18/35 randomized day of surgery, no time stamp on IVRS form
Hollman - Two subjects randomized post-operatively
Jove - No subjects randomized post-operatively

Kilgore - "Majority" of subjects randomized day of surgery, no time stamp on IVRS form
Mody - 34/35 subjects randomized day of surgery, no time stamp on IVRS form
Reddy - 12/40 subjects randomized post-operatively, deviation forms on file for 11 of these 12 subjects, in 7/40 subjects the time of randomization couldn't be determined
Sepulveda - 9 subjects were randomized on the day of surgery, no time stamp on IVRS form; there was no randomization sheet available for 1 subject
H. Shah - 1 post-operative randomization
V. Shah – no subjects noted to be randomized post-operatively

Based on these results, there are three RECORD 4 clinical investigator sites from the (b) (4) audits where subjects were randomized postoperatively (Drs. Hollman, Reddy, and H. Shah; at Dr. Reddy's site, these events were identified as protocol violations). At four additional sites (Dr. Dessouke, Kilgore, Mody and Dr. Sepulveda), it cannot be determined from the information available in the (b) (4) audit reports what proportion of the subjects were randomized postoperatively. Therefore, based on the (b) (4) audit reports, post-operative randomization occurred at a significant number of clinical investigator sites enrolling in RECORD 4. This protocol violation occurred in 3 of 5 of the sites originally inspected for the NDA, and to varying degrees in 3 additional sites audited by (b) (4) in addition, it cannot be determined from the site records whether subjects randomized on the day of surgery were in fact randomized post-operatively.

DSI Assessment of Response
According to Johnson and Johnson, postoperative randomization took place for 1227 of 3148 (39%) of RECORD 4 subjects, audited and nonaudited by (b) (4) Based on the (b) (4) audit results, 3 of the 9 sites audited for RECORD 4 randomized postoperatively; at 4 additional sites, it cannot be determined from the information available in the (b) (4) audit reports what proportion of the subjects randomized on the day of surgery were in fact randomized post-operatively. Although such postoperative randomization errors would occur in both arms of the clinical trial, it has the potential to alter the patient population included in the RECORD 4 study. If sufficient sites enrolled subjects postoperatively, especially based on specific criteria, the population included in the Xarelto product label may not reflect the population actually studied. The review division will need to assess the impact of this issue on potential product labeling. The high incidence of this protocol violation again reinforces the monitoring deficiencies in RECORD 4. Although (b) (4) was aware of the occurrence of postoperative randomization, they did not effectively enforce compliance with this protocol requirement. Post operative randomization did not occur to any significant degree in RECORD 1, 2, or 3.

4. Drug Accountability Issues in (b) (4) Audits

Review of the (b) (4) audit reports focused on identification of clinical investigator sites where there were documentation issues for study drug administration and/or storage. Attention was focused on identified problems with drug administration of accountability and/or administration, such that uncertainty existed as to whether subjects actually received the assigned study drug which had been stored appropriately to maintain activity. If subjects did not receive study drug as described in the data listings, the primary efficacy outcome could potentially be compromised.

DSI concurs with (b) (4) assessment of data from Dr. Brabants site (RECORD 3) as unreliable due to inadequacies in study drug administration documentation. Based on a review of the (b) (4) audit reports, DSI identified four additional sites for RECORD 1 (Drs. Lenart, Porvaneckas, Schwartsmann, and Slappendel), two additional sites for RECORD 2 (Drs. Naraffete and Ono), and three additional sites for RECORD 4 (Drs. Mody, Sepulveda, and Shah) which have sufficient deficits in drug administration and accountability that DSI cannot verify subjects received study drug as purported. Details of drug accountability issues for each CI are given in Table 7. At each of the additional sites, source documentation for study drug administration was missing or lacking, and/or there were significant issues with documentation of drug accountability such that it does not appear possible to verify that subjects at the site received active/correct study drug therapy.

Table 7: Clinical Investigator Sites with Drug Administration and Accountability Issues Based on (b) (4) Audits

Clinical Investigator Location	Study Site Number Number of Subjects	Assessment Source (FDA Inspections, (b) (4) Audit Reports, DSI Review of (b) (4) Audit Reports)	Major Drug Accountability/Administration Issues
Robert Slappendel Netherlands	RECORD 1 Site 30002 61 subjects	DSI review of (b) (4) site audits	• No source documentation for date/time of the pre-operative self-administered injection of enoxaparin/placebo by the subject or the date and time of last outpatient dosing • 10 of 35 subjects audited had drug accountability records which were incomplete and/or discrepant with other subject source documentation.
Endre Lenart Hungary	RECORD 1 Site 46002 87 subjects	DSI review of (b) (4) audit reports	Study coordinators log used to document drug accountability and dosing for all subjects, but entries in log were not dated/initialed
Narunas Porvaneckas, Lithuania	RECORD 1 Site 57001 72 subjects	DSI review of (b) (4) audit reports	Study drug administration times were exactly the same for all 34 subjects audited. Exact dosing times were not documented.
Edmundo Berumen Naraffete	RECORD 2 Site 32005 25 subjects	FDA review of (b) (4) site audits	Study drug administration times were exactly the same for each subject for all subjects audited
Keiske Ono Brazil	RECORD 2 Site 50005 24 subjects	FDA review of (b) (4) site audits	• Documentation of study drug administration during inpatient phase of study was missing or deficient: 8 subjects records contained

			very few notations that study drug had been given, and the remaining 16 records contained none. Doses documented on the SDW were not signed/initialed or dated • Large number of discrepancies between eCRF, SDW, and medical chart information (73 discrepancies for 20 subjects – e.g. surgery start/stop time, intraoperative blood loss, drain volume)
Karl Brabants Belgium	RECORD 3 Site 28015 27 subjects	(b) (4) site audits	• Exact time of study drug administration was rarely recorded on the inpatient medication administration records for any of the 27 subjects – only on grid with 0800, 1200, 1600, and 2000 time points • Times of study drug administration frequently do not match the times noted on the inpatient medication administration sheets • Study coordinator was unable to define a consistent primary source for many of the data points, including drug dosing, surgery start/stop times, and laboratory draw times. • Drug accountability logs provided by Bayer were not used by the study coordinator to record drug accountability and the site did not keep a log of accountability • Ambient temperatures in study drug storage room was monitored weekly, not daily
Bharat Mody India	RECORD 4 Site 60010 68 subjects	FDA review of (b) (4) site audit	Study drug not stored in permissible temperature range of 15-30^{o}C for 19 consecutive days, dropping to 10.2^{o}C each day
Victor Sepulveda Mexico	RECORD 4 Site 32002	FDA review of (b) (4) site audit	• Medical records of 10 subjects were missing from

	46 subjects		the site. Nursing notes, which include dosing entries, were missing for an additional 7 subjects • 15 of 33 subjects audited had source vs eCRF discrepancies pertaining to study drug administration noted (ranging from 1 to all doses, most = 2-3 doses)
V. Shah India	RECORD 4 Site 60006 80 subjects	DSI review of (b) (4) site audit	• Data discrepancies exits between the eCRF and site source documentation, including for study drug administration (26 subjects, 23 instances) • Missing source documentation of drug administration for 8 of 35 subjects[c]

Further information was requested by the FDA on August 2, 2010 regarding the (b) (4) audit findings at eight clinical sites (sites with significant drug accountability issues as identified in Table 7 above). This Information Request was intended to obtain any additional information which might be available at the clinical sites to clarify what the (b) (4) auditors considered to be inadequate drug accountability. Please see Appendix 2 for details of DSI requests, response/finding from Johnson & Johnson received on September 26, 2010, and DSI assessment of the additional information provided. Johnson & Johnson sent monitoring personnel to seven of the clinical sites in question; the entire team including Dr. Slappendel and the Study Coordinator is no longer present at his site, so the RECORD 1 study team attempted to provide additional clarification. The results of the site revisit to Dr. Schwartsmann's site provided sufficient evidence that study drug was given appropriately. However, the data provided for the other sites was insufficient to provide such reassurance.

DSI Assessment of Response

In conclusion, issues in drug accountability were identified across the RECORD studies, most seriously in RECORD 4. In some instances, it appears that routine hospital practice was followed (e.g., physician notes what time medication should be given and this information is copied onto a nurse's sheet, with initials/dates/times of drug administration recorded only if there were variations from this procedure). However, for purposes of a clinical trial, it is imperative that documentation sufficient to assure that medication was actually administered to study subjects be provided in the source documents. The absence of actual dates/times of drug administration as well as initials of the person administering the medication results in an inability to have confidence that the subject actually received the medication as specified in the protocol.

Overall, there were some drug accountability issues identified by (b) (4) audits at sites from all of the RECORD studies. The statistical import of the single site in RECORD 3 identified with

significant drug accountability issues is difficult to assess, given that only 3 sites were audited from RECORD 3. We acknowledge that RECORD 1 had 3 sites with significant drug accountability issues, and RECORD 2 had 2 sites. These findings for RECORD 1 and 2, when interpreted together with the failure to identify deficiencies in drug accountability in FDA inspection and the relatively small number of sites audited, do not allow extrapolation to the conclusion that all sites from RECORD 1 and 2 had drug accountability deficiencies sufficient to impugn data integrity from all sites in these studies. The ultimate decision regarding overall study reliability must be based on the totality of evidence pertinent to good clinical trial conduct. In contrast to RECORD 1, 2, and 3, however, RECORD 4 had 3 sites identified with significant drug accountability issues by (b) (4) audit, in addition to the 2 RECORD 4 sites ((b) (4) Esquivel) already identified by DSI as unreliable based on drug accountability issues, among other violations. This suggests that drug accountability deficits are more pervasive at RECORD 4 sites. Please see Section IV. Below for a further discussion of the effect of drug accountability on overall study data reliability.

5. Eligibility Criteria in the (b) (4) Audits

One item of concern identified during the initial cycle of FDA inspections was enrollment of subjects in violation of the protocol inclusion criteria. Review of the (b) (4) audit reports revealed a few subjects enrolled who did not meet eligibility criteria, but this was not a frequent finding.

DSI Assessment of Response
Enrollment of ineligible subjects does not appear to be a systematic problem in the RECORD studies.

6. (b) (4) Verification of RECORD 4 Data

As described in Section C.1. above, deficiencies in monitoring by (b) (4) and study conduct issues appeared to be more severe and widespread in the RECORD 4 study when compared with the RECORD 1, 2, and 3 studies. Therefore, the applicant proposed a data verification plan in an attempt to demonstrate the validity of the RECORD 4 data. The sponsor's plan was presented to the Division of Hematology Products and DSI on April 7, 2010. The goal of the data verification was to identify any AEs or SAEs present in the subjects' medical records that were not reported to Bayer before the time of finalization of the study, to assess overall site and investigator quality, to assess the impact of postoperative randomization, and to address the Agency's areas of concern regarding study reliability. All sites participating in RECORD 4 were to be visited by site monitors from (b) (4) , an independent CRO. Please see the CR document dated December 23, 2010 for details of the data verification plan.

After revisiting all RECORD 4 sites, there were 260 newly identified treatment emergent adverse events in the rivaroxaban arm and 244 in the enoxaparin arm. This resulted in an increase in the reported rate of adverse events from approximately 80% of subjects originally reported with adverse events to 97% of subjects following data verification; there was no change in the distribution of AEs between treatment groups. There were 28 newly reported SAEs in 25 subjects (15 rivaroxaban, 12 enoxaparin, and 1 never randomized). There were 2

newly-reported cases of ALT>3X ULN concurrent with a total bilirubin >2X ULN identified, both in subjects receiving enoxaparin. No new events of death, DVT, or PE were identified.

(b) (4) monitors were instructed to answer a series of questions regarding site and investigator overall performance. Sites and investigators were then ranked according to quality. Sensitivity analyses were performed for primary efficacy and safety by high versus low quality sites/investigators. This procedure was intended to address site performance concerns raised by the agency. Based on this procedure, the sponsor concludes that the primary efficacy and safety results remained essentially unchanged in the groups of sites with performance considered by (b) (4) as acceptable or questionable, compared to that seen in the overall patient population.

In order to address the issue of postsurgical randomization, (b) (4) compared outcomes in subjects treated preoperatively versus postoperatively in both treatment arms. The applicant states that their results demonstrate that when the rates of the efficacy and safety outcomes were calculated in the two treatment groups for subjects randomized preoperatively versus postoperatively, they appeared to be comparable and similar to those results seen overall.

DSI Assessment of Response

The (b) (4) data verification audits of the RECORD 4 study sites were conducted with the intention of reassuring the Agency of the robust nature of the RECORD 4 data. The identification of 504 new treatment emergent adverse events as well as 28 newly identified SAEs in the RECORD 4 study provokes more concern than reassurance. Although it is certainly possible that there are unreported adverse events and SAEs in clinical trials in general, the number of unreported adverse events in the RECORD 4 trial seems excessive. Additionally, these newly reported adverse events reaffirm the concern that monitoring of the RECORD 4 trial was inadequate. Similarly, it is reassuring that no difference in efficacy or safety outcome was noted in subjects randomized pre- versus postoperatively. However, the large number of subjects randomized postoperatively in violation of the protocol raises again the issue of adequacy of study monitoring. The portion of the data verification process in which (b) (4) assessed site and investigator overall performance which was then correlated with efficacy and safety outcome is interesting, but not a validated method of assessing study conduct. DSI remains concerned with the deficiencies in clinical trial conduct and monitoring of RECORD 4 with potential deleterious effects on the validity of the efficacy and safety data from the RECORD 4 study.

IV. DSI Review of (b) (4) Audits – Unreliable Sites

In order to assess whether or not the findings from the (b) (4) audits significantly impacted overall data reliability from each CI site, DSI reviewed the 30 audit reports in detail. At many sites, (b) (4) auditors identified issues with study conduct, unreported adverse events, drug disposition and accountability, informed consent, source document verification and case report completion, and monitoring. If findings at a site involved more than a few subjects or appeared to significantly impact key efficacy assessments for multiple subjects, then DSI considered data from the site to be unreliable. Please see Table 8 for details of sites with efficacy data considered unreliable by DSI, which is based on review of the totality of information available to DSI, to include Bayer audits, (b) (4) audits, as well as FDA

inspections. The identification by (b) (4) monitors that adverse events had not been fully reported did not in and of itself result in site assessment as unreliable, especially if the balance of the issues rendered the site data assessment as reliable.

As seen in Table 8 below, data from the following clinical investigators had been previously identified based on DSI review of FDA inspections as unreliable with the recommendation that it should not be used in support of the application: RECORD 2: Drs. (b) (4) Yang; and RECORD 4: Drs. (b) (4) Esquivel, Murray, Ward, and Buettner. DSI concurs with Falcon's assessment of data from Dr. Brabants site (RECORD 3) as unreliable, and this data should not be used in support of the application. Based on a review of the (b) (4) audit reports, DSI identified three additional sites for RECORD 1 (Drs. Lenart, Porvaneckas, and Slappendel), two additional sites for RECORD 2 (Drs. Naraffete and Ono), and three additional sites for RECORD 4 (Drs. Mody, Sepulveda, and Shah), which in DSI's opinion, provided unreliable data, and this data should not be used in support of the application. Note that the Executive Summary contained in the (b) (4) audit reports for each of these investigators lists multiple issues identified at each of these 8 sites, but stops short of stating that the data are unreliable. Only the data from Dr. Brabants' site was classified as unreliable by the (b) (4) auditors. At each of the additional sites, source documentation for key efficacy assessments was missing or lacking, and/or there were significant issues with documentation of drug accountability such that it does not appear possible to verify that subjects at the site received active/correct study drug therapy. The following table summarizes the reasons DSI recommends that data from individual CI sites be considered unreliable and not be used in support of the NDA. The source of the recommendation is also given as FDA inspection, (b) (4) audit report, or DSI review of (b) (4) audit report.

Table 8: Clinical Investigator Sites with Efficacy Data Considered Unreliable by DSI

Clinical Investigator Location	Study Site Number Number of Subjects	Assessment Source (FDA Inspections, (b) (4) Audit Reports, DSI Review of (b) (4) Audit Reports)	Primary Reason DSI Assesses Data from Site to be Unreliable
Endre Lenart Hungary	RECORD 1 Site 46002 87 subjects	DSI review of (b) (4) audit reports	Study coordinators log used to document drug accountability and dosing for all subjects, but entries in log were not dated/initialed, and as such can't verify accuracy of subject dosing.
Narunas Porvaneckas, Lithuania	RECORD 1 Site 57001 72 subjects	DSI review of (b) (4) audit reports	Study drug administration times were exactly the same for all 34 subjects audited. Exact dosing times were not documented, As such, can't verify accuracy of subject dosing.
Robert Slappendel[a] Netherlands	RECORD 1 Site 30002 61 subjects	DSI review of (b) (4) site audits	• No source documentation for date/time of the pre-operative self-administered injection of enoxaparin/placebo by the subject or the date and time of last outpatient dosing • 10 of 35 subjects audited had

Table 8: Clinical Investigator Sites with Efficacy Data Considered Unreliable by DSI

Clinical Investigator Location	Study Site Number Number of Subjects	Assessment Source (FDA Inspections, (b) (4) Audit Reports, DSI Review of (b) (4) Audit Reports)	Primary Reason DSI Assesses Data from Site to be Unreliable
			drug accountability records which were incomplete and/or discrepant with other subject source documentation[b]. As such, can't verify accuracy of subject dosing.
(b) (4)	RECORD 2 (b) (4)	FDA inspection	Recordkeeping and drug disposition deficiencies, considered significant enough to raise concerns regarding data reliability.
Qingming Yang China	RECORD 2 Site 54005 34 subjects	FDA inspection	Failure to report AEs, significant for evaluation of safety data as well as human subject protection
Edmundo Berumen Naraffete	RECORD 2 Site 32005 25 subjects	FDA review of (b) (4) site audits	Study drug administration times were exactly the same for each subject for all subjects audited; as such, can't verify accuracy of subject dosing.
Keiske Ono Brazil	RECORD 2 Site 50005 24 subjects	FDA review of (b) (4) site audits	• Documentation of study drug administration during inpatient phase of study was missing or deficient: 8 subjects records contained very few notations that study drug had been given, and the remaining 16 records contained none. Doses documented on the SDW were not signed/initialed or dated • Large number of discrepancies between eCRF, SDW, and medical chart information (73 discrepancies for 20 subjects – e.g. surgery start/stop time, intraoperative blood loss, drain volume) The findings raised significant concerns with respect subject dosing as well as adequacy and accuracy of data on CRFs, of significant concern to impact data reliability.
Karl Brabants Belgium	RECORD 3 Site 28015 27 subjects	(b) (4) site audits	• Exact time of study drug administration was rarely recorded on the inpatient medication administration records for any of the 27 subjects – only on grid with 0800, 1200, 1600, and 2000 time points • Times of study drug administration frequently do not

Table 8: Clinical Investigator Sites with Efficacy Data Considered Unreliable by DSI

Clinical Investigator Location	Study Site Number Number of Subjects	Assessment Source (FDA Inspections, (b) (4) Audit Reports, DSI Review of (b) (4) Audit Reports)	Primary Reason DSI Assesses Data from Site to be Unreliable
			match the times noted on the inpatient medication administration sheets • Study coordinator was unable to define a consistent primary source for many of the data points, including drug dosing, surgery start/stop times, and laboratory draw times. • Drug accountability logs provided by Bayer were not used by the study coordinator to record drug accountability and the site did not keep a log of accountability • Ambient temperatures in study drug storage room was monitored weekly, not daily
(b) (4)	RECORD 4 (b) (4)	FDA inspection	• Recordkeeping deficiencies • (b) (4) • Protocol violations
Ricardo Esquivel Mexico	RECORD 4 Site 32006 42 subjects	Bayer monitoring	• Drug disposition record deficiencies • Missing records
R. Michael Murray Alabama, U.S.A.	RECORD 4 Site 14005 152 subjects	FDA inspection	• Post-operative randomization • Possible unblinding
John Ward Alabama, U.S.A.	RECORD 4 Site 14010 203 subjects	FDA inspection	• Post-operative randomization • Study continued despite lapse of IRB approval
Craig Buettner Alabama, U.S.A.	RECORD 4 Site 14004 61 subjects	FDA inspection	Post-operative randomization
Bharat Mody India	RECORD 4 Site 60010 68 subjects	FDA review of (b) (4) site audit	Study drug not stored in permissible temperature range of 15-30°C for 19 consecutive days, dropping to 10.2°C each day
Victor Sepulveda Mexico	RECORD 4 Site 32002 46 subjects	FDA review of (b) (4) site audit	• Medical records of 10 subjects were missing from the site. Nursing notes, which include dosing entries, were missing for an additional 7 subjects • 15 of 33 subjects audited had source vs eCRF discrepancies pertaining to study drug administration noted (ranging from 1 to all doses, most = 2-3

Table 8: Clinical Investigator Sites with Efficacy Data Considered Unreliable by DSI

Clinical Investigator Location	Study Site Number Number of Subjects	Assessment Source (FDA Inspections, (b) (4) Audit Reports, DSI Review of (b) (4) Audit Reports)	Primary Reason DSI Assesses Data from Site to be Unreliable
			doses)
V. Shah[b] India	RECORD 4 Site 60006 80 subjects	DSI review of (b) (4) site audit	• Data discrepancies exits between the eCRF and site source documentation, including for study drug administration (26 subjects, 23 instances) • Missing source documentation of drug administration for 8 of 35 subjects[c] • Use of inappropriate correction techniques in all subject records • For 3 subjects, source documentation and eCRF entries were changed months after an event, sometimes in response to a query from data management. • Language used to discuss the Informed Consent document with all subjects was coercive, with documentation indicating that he said "that the study drug was completely safe, that is the best treatment currently available, that risks were minimal (same as any other surgery). . ."

[a] Evaluation of data submitted by Johnson & Johnson resulted in assessment of data from 4 of the 10 subjects in question at this site as acceptable; see Section III and Appendix 2; however, the data overall from this site is still considered unacceptable.
[b] Evaluation of data submitted by Johnson & Johnson resulted in assessment of data from 1 of the 8 subjects in question at this site as acceptable; see Section III and Appendix 2; however, the data overall from this site is still considered unacceptable.

DSI Assessment of Response:
In addition to sites previously identified, based on DSI inspections as providing unreliable data with the recommendation that data from the sites not be used in support of the NDA (Drs. (b) (4) Yang for RECORD 2, and Drs. (b) (4) Esquivel, Murray, Ward, and Buettner for RECORD 4), DSI concurs with (b) (4) auditors that data from Dr. Brabants' site enrolling in RECORD 3 be considered unreliable and that it not be used in support of the NDA. This recommendation is based on deficiencies in documentation of drug administration, such that certainty regarding study drug administration is not possible.

Based on review of the (b) (4) audit reports, DSI identified 3 additional sites for RECORD 1 (Drs. Lenart, Porvaneckas, and Slappendel), 2 additional sites for RECORD 2 (Drs. Naraffete and Ono), and 3 additional sites for RECORD 4 (Drs. Mody, Sepulveda, and V. Shah) from which DSI considers key study data to be unverifiable or unreliable and recommends that data

from these sites also not be used in support of the application. At each of these additional sites, source documentation was missing and/or there were significant issues with documentation of drug accountability such that it does not appear possible to verify that subjects at the site received active/correct study drug therapy.

As such data is not recommended for use from the following sites for their respective studies:
RECORD 1: Drs. Lenart, Porvanceckas, and Slappendal
RECORD 2: Drs. (b) (4) Yang, Naraffete, and Ono
RECORD 3: Brabants
RECORD 4: Drs. (b) (4) Esquivel, Murray, Ward, Buettner, Mody, Sepulveda, and Shah

DSI's assessment of how the inspectional/(b) (4) audit findings impact data reliability as a whole to each individual study based on the information available to DSI for review, is discussed in the next section.

V. DSI Overall Assessment of RECORD 1, 2, 3, and 4 Studies Based on (b) (4) Audits and FDA inspections

Inadequacies of study conduct and monitoring identified in the RECORD 1, 2, 3, and 4 studies during the initial NDA review cycle resulted in the request by DSI for independent third party audits of clinical investigator sites, which were conducted by (b) (4) Table 9 below summarizes the issues identified during FDA inspections and the (b) (4) audits which are considerations in the assessment of the overall integrity of each RECORD study.

Clearly, drug accountability issues at a significant number of sites in each RECORD study raises the fundamental issue of whether DSI is able (based on inspectional findings and (b) (4) audit results) to confirm that subjects at each site received study drug as given in the line listings submitted with the NDA. It can be seen in Table 9 that significant drug accountability issues (i.e. affecting more than a few subjects) were noted all 4 RECORD studies, ranging from 27 – 33% of (b) (4) audited sites. Since only three RECORD 3 sites were audited, the statistical significance of this finding for RECORD 3 is uncertain. In consideration of the potential impact of drug accountability issues on overall study data integrity, DSI evaluated other determinants of study reliability. A major determinant which enables DSI to generalize the results of audit or inspectional findings is adequacy of clinical trial monitoring. If monitoring is inadequate at the majority of sites examined, it becomes impossible for DSI to provide assurance that study conduct flaws (e.g., in drug accountability) did not occur at the vast majority of clinical sites which were not audited or inspected – or that other, undetected flaws impacting on safety and efficacy data did not occur. The same principle holds true for assessment of the number of sites assessed as unreliable after (b) (4) audit or FDA inspection. Given the relatively small percentage of subjects and sites examined, consideration must be given to interrelated study conduct issues (e.g., number of unreliable sites together with ineffective monitoring in a given study) – that is, the more essential elements of good study conduct that are defective in a given study, the more likely that overall data integrity for that study is unreliable. Lastly, DSI considered the relative number of unreported adverse events and serious adverse events in the assessment of overall study integrity. Although each RECORD study had flaws which had the potential to affect data integrity, DSI took a global

approach in applying analysis of each study conduct element to overall RECORD study reliability. We are of the opinion that assessment of significant site inadequacies in a given study across all examined study conduct issues allows a more accurate assessment of the impact of these issues on data integrity. Findings of deficits in a single area of study conduct makes extrapolation of assessment of data integrity as unreliable, problematic across an entire study, given the relatively small proportion of sites assessed. It seems reasonable, however, to have a higher level of confidence in drawing a conclusion that data integrity is unreliable, based on a small audit/inspectional sample for a given study, when all study conduct elements examined are significantly flawed. Please see discussion after Table 9 for application of these concepts to each RECORD study.

TABLE 9: EVALUATION OF RECORD 1, 2, 3, AND 4 DATA INTEGRITY

Study	Post-operative Randomization #subjects POR/total subjects (%)	Unreported Adverse Events – (b) (4) audits AEs/ significant AEs/SAEs	Unreported Adverse Events – (b) (4) audits AEs/ SAEs	Drug accountability issues (critical) Sites with issues/sites audited by (b) (4)	Inadequate monitoring (b) (4) overall assessment by subject assayed	Inadequate monitoring (b) (4) overall assessment by site assayed (sites with inadequate monitoring/sites audited) (%)	#sites unreliable (Sites unreliable/total sites audited by (b) (4) +FDA inspected)	Overall study reliability
RECORD 1 (217 sites)	18/4541 (0.4%)	110/16/0	NA	3/11 (27% of audited sites)	96/347 (27.2%)	2/11 (18%)	3/13 (23%)	Yes – except Lenart, Porvaneckas and Slappendal
RECORD 2 (123 sites)	13/2509 (0.5%)	131/24/0	NA	2/7* (29% of audited sites)	55/216 (25.5%)	2/7 (29%)	4/10 (40%)	Yes – except (b) (4) Yang Naraffete, and Ono
RECORD 3 (147 sites)	9/2531 (0.4%)	37/2+/0	NA	1/3 (33% of audited sites)	28/70 (40.0%)	1/3 (33%)	1/5 (20%)	Yes – except Brabants
RECORD 4 (130 sites)	1227/3148 (39.0%)	265/61/8	504/28	3/9* (33% of audited sites)	197/312 (63.1%)	6/9 (67%)	8/16 (50%)	No

*1 additional site each from RECORD 2 and 2 additional sites from RECORD 4 had critical drug accountability issues identified during FDA inspections.

DSI Assessment of RECORD 1 Reliability: DSI recommends that the data from this study can be used in support of the NDA. Although there were drug accountability issues identified at 27% of (b) (4) audited sites in RECORD 1, monitoring was assessed as adequate in the majority of subjects and sites, and earlier FDA inspections did not reveal drug accountability issues. Based on review of (b) (4) audit findings, however, there were 3 sites in RECORD 1 (Lenart, Porvaneckas, and Slappendal) for which DSI cannot assure data reliability (due to drug accountability issues). DSI acknowledges that there were unreported adverse events from this trial, and suggests that the review division consider additional events identified during the audit process in their safety analysis. There were no unreported SAEs noted from RECORD 1. Postoperative randomization did not occur to any significant degree in RECORD 1. In summary, despite some identified deficits in study conduct, the deficiencies do not appear pervasive enough to cast doubt on the overall reliability of RECORD 1 study data.

DSI Assessment of RECORD 2 Reliability: DSI recommends that the data from this study can be used in support of the NDA. Although there were drug accountability issues identified at 29% of (b) (4) audited sites in RECORD 2, monitoring was assessed as adequate in the majority of subjects and sites and the number of audited sites is relatively small, and earlier FDA inspections did not reveal drug accountability issues. There were 4 clinical investigator sites in RECORD 2 ((b) (4) Yang, Naraffete, and Ono) for which DSI cannot assure data reliability (due to drug accountability issues and/or issues with source documentation). DSI acknowledges that there were unreported adverse events from this trial, and DSI suggests that the review division consider additional events identified during the audit process in their safety analysis. There were no unreported SAEs noted from RECORD 2. Postoperative randomization did not occur to any significant degree in RECORD 2. In summary, despite some identified deficits in study conduct, the deficiencies do not appear pervasive enough to cast doubt on the overall reliability of RECORD 2 data.

DSI Assessment of RECORD 3 Reliability: DSI recommends that the data from this study can be used in support of the NDA. Although there were drug accountability issues identified at 33% of (b) (4) audited sites in RECORD 3, a very small number of RECORD 3 sites were audited by (b) (4) making the statistical assessment of this finding problematic. Monitoring was assessed as adequate in 42 of 70 (60%) of subjects and 2 of 3 sites audited by (b) (4) Based on (b) (4) monitoring audit strategy of focusing on a PDC (Patient Data Check) form for evaluation of monitoring adequacy, it appears that up to 40% of subjects had inadequacies in monitoring. However, note that DSI's assessment of adequacy of monitoring and data reliability did not solely focus on the PDC form, but rather on the specific types of issues that were missed by monitoring and their impact on assessment of key safety and efficacy parameters. There was 1 site in RECORD 3 (Brabants) for which DSI cannot assure data reliability (due to drug accountability/storage condition issues identified during (b) (4) audit). DSI acknowledges that there were unreported adverse events from this trial, and DSI suggests that the review division consider additional events identified during the audit process in their safety analysis. There were no unreported SAEs noted from RECORD 3. Postoperative randomization did not occur to any significant degree in RECORD 3. In summary, despite some identified deficits in study conduct, the deficiencies do not appear pervasive enough to cast doubt on the overall reliability of RECORD 3 data.

DSI Assessment of RECORD 4 Reliability: FDA inspections, the (b) (4) audits, and the (b) (4) data verification process have identified serious issues with the study conduct and monitoring of the RECORD 4 study. Postoperative randomization in violation of the protocol occurred at 1227 of 3148 (39%) of RECORD 4 subjects, despite a memo from the CRO monitoring the study ((b) (4) that postoperative randomization was not acceptable. Although this occurred equally in both study arms, the possibility exists that because of postoperative randomization, the labeled population would not be reflective of the actual study population. The number of unreported adverse events detected by (b) (4) monitors (265) was more than twice the number from any of the other RECORD trials (110, 131, and 37 for RECORD 1, 2, and 3, respectively), and there were 504 unreported adverse events detected during the (b) (4) data verification; the review division may wish to review these adverse events for safety analysis inclusion. All newly reported serious adverse events were from RECORD 4 sites: 8 from the (b) (4) audits and 28 from the (b) (4) data verification. In addition, there were serious drug accountability issues at 3 of 9 (33%) of (b) (4) audited RECORD 4 sites, in addition to 2 sites with serious drug accountability issues identified earlier by DSI ((b) (4) Esquivel). The (b) (4) audit finding that 197 of 312 (63%) of subjects and 6 of 9 (67%) of sites in RECORD 4 were monitored inadequately by (b) (4) is striking, and higher than the other RECORD studies.

Eight of 16 (50%) sites of the RECORD 4 sites audited by (b) (4) or inspected by FDA ended with an evaluation that the data from the sites was not reliable, reflective of drug accountability deficiencies and other violations of good clinical practice, including postoperative randomization, falsification, missing records, and improper study drug storage. DSI does not feel that the data verification process conducted by (b) (4) has been validated, nor does it negate the findings described above. It is important to note that these sites audited by (b) (4) represent only 7% of total sites and 10% of total subjects in the RECORD 4 study. The additional audits were conducted with the expectation that failure to identify additional sites with serious deficiencies would provide assurance that the remaining unaudited sites provided reliable data. The pervasive nature of study conduct deficiencies, including particular inadequate monitoring, raises the possibility that there may be deficiencies affecting the primary efficacy outcome which were not detected, e.g. venography conduct. Based on serious drug accountability issues, a relatively large number of unreported adverse events and serious adverse events, a high rate of postoperative randomization in violation of the protocol, and inadequate monitoring of a majority of the RECORD 4 sites as well as the relatively small proportion of sites audited, DSI recommends that the data from RECORD 4 be considered to be unreliable. While the Applicant attempted to provide further assurance that data from this study was reliable via the (b) (4) data verification process, (b) (4) findings do not negate the findings described above. Recall that the (b) (4) audit proposed by J&J was intended to be a specific methodology for analysis of the audited data, not the performance of 3rd party audits, per se, and that FDA did not agree or review as to the usage of this methodology for this intended purpose.

VI. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Executive Summary Conclusion

DSI finds that Johnson and Johnson's response to the FDA's May 27, 2009 Complete

Response Letter addresses all of the DSI items requested in the CR Letter. However DSI's review concludes that the data generated by the RECORD 4 study is unreliable, and recommends that the data not be used in support of the respective indication of prophylaxis of deep venous thrombosis and pulmonary embolism after total knee arthroplasty. Given serious drug accountability issues, a relatively large number of unreported adverse events and serious adverse events, a high rate of postoperative randomization in violation of the protocol, and inadequate monitoring of a majority of the RECORD 4 sites as well as the fact that only a subset of sites have been audited, DSI cannot provide a favorable assessment of RECORD 4 data reliability for the remaining 88% of uninspected/unaudited clinical investigator sites based on extrapolation of the (b) (4) audit findings. Although issues exist with the study conduct of RECORD 1, 2, and 3, they are not sufficiently pervasive to reflect negatively on overall study data integrity, and the data from these 3 studies are considered to be reliable, with the exception of a few sites.

Summary Assessment and Recommendation

On May 27, 2009 FDA issued an NDA Complete Response letter to Johnson & Johnson for the Xarelto NDA 22-406 for the indication of prophylaxis of deep vein thrombosis and pulmonary embolism in patients undergoing hip or knee replacement surgery. (b) (4) Inspections conducted in support of the NDA resulted in four OAI classifications, five VAI, and two NAI. Evaluation of the inspections revealed serious deficiencies in adverse event reporting, drug accountability and administration, and adherence to the protocol especially postoperative randomization. Also of serious concern were deficiencies in monitoring noted at the inspected CI and sponsor sites noted in all four RECORD studies, but particularly pervasive in RECORD 4. The CR Letter requested, in part, evidence that the four RECORD studies are reliable, and proposed that independent third party audits be conducted at additional CI sites to provide reassurance of the reliability of the RECORD 1, 2, 3, and 4 study data.

Johnson & Johnson submitted a CR on December 23, 2010. (b) (4) was selected to conduct the third party independent audits. There were 30 clinical sites audited across all four RECORD studies: all 18 high enrolling sites (previously uninspected) with > 60 randomized subjects and 12 moderately enrolling site with 15-59 randomized subjects randomly selected. All subjects at sites were audited if there were less than 35 subjects; otherwise, a random sample sufficient to provide 95% confidence to rule out a 5% error rate was chosen. Audits of these 30 sites resulted in audit of 950 subjects out of 12,729 total, which constituted 7.5% of all subjects in the 4 RECORD studies. The parameters examined during the audits were adequacy of monitoring, adverse event reporting, adherence to protocol including postoperative randomization, informed consent, investigational product, and source data verification and CRF completion. Also submitted with the CR were the reports of the Bayer audits.

Adequacy of clinical trial monitoring was assessed in several ways. (b) (4) auditors stated that overall site study monitoring was deficient at 1 of 11 (9%) of RECORD 1 sites, 2 of 7 (27%) RECORD 2 sites, 1 of 3 (33%) RECORD 3 sites, and 5 of 9 (56%) RECORD 4 sites; key efficacy and safety findings were missed during monitoring of these sites. Assessment of

monitoring by individual subjects resulted in the following assessment of inadequate monitoring: RECORD 1 96/347 (27.2%) subjects; RECORD 2 55/216 (25.5%) subjects, RECORD 3 28/70 (40.0%) subjects, and RECORD 4 197/312 (63.1%) subjects. Lastly, Johnson & Johnson submitted the results of 74 clinical investigator site audits conducted by Bayer; 69 were routine. Significant findings noted during the (b) (4) audits at the sites of Drs. Lenart (RECORD 1), Porvaneckas (RECORD 1), Nararrete (RECORD 2), and Buettner (RECORD 4) were not mentioned in the Bayer audit reports. FDA inspectional findings at the sites of Dr. Michael Murray (RECORD 4) were not described in the Bayer audit, nor did the Bayer audits detect the most serious deficiency which resulted in disqualification of Dr. (b) (4) (RECORD 4). Inspection of Bayer as the sponsor of the NDA revealed some monitoring deficiencies as well, in that the major issues at the sites of Drs. (b) (4) (RECORD 2) and Murray (RECORD 4) were not identified by Bayer monitoring. Monitoring for the RECORD 1, 2, and 3 studies was performed by Bayer, while the monitoring for RECORD 4 was conducted by the CRO (b) (4) Although issues with clinical trial monitoring inadequacies were present in all four RECORD trials, the deficiencies were most frequent in the RECORD 4 study. Deficiencies in clinical trial monitoring raise serious concern regarding the validity of data submitted in RECORD 4. In particular, the widespread monitoring deficiencies do not provide reassurance that study conduct deficiencies are not present at the approximately 90% of RECORD 4 sites which were not inspected by FDA or audited.

Based on DSI's assessment of (b) (4) audit reports, drug accountability deficiencies were present at 3/11 (27%) of RECORD 1 sites, 2/7 (29%) of RECORD 2 sites, 1/3 (33%) of RECORD 3 sites, and 3/9 (33%) of RECORD 4 sites. Site drug accountability was considered deficient if source documentation for key efficacy assessments was absent and/or there were significant issues with documentation of drug accountability such that it does not appear possible to verify that subjects at the site received study drug. Further information from Johnson & Johnson was requested that might provide assurance of drug administration at the problematic sites, such as pharmacy or nursing records. For the sites assessed as deficient here, no such documentation was located. Note that a very small number of RECORD 3 sites were audited by (b) (4) making the statistical assessment for this study problematic. We acknowledge the finding that 27-33% of RECORD 1-3 sites had deficiencies in drug accountability; however these findings were not replicated in FDA inspectional findings. In contrast with RECORD 4, however, audits of the RECORD 1, 2, and 3 studies did not demonstrate systematic deficiencies in multiple aspects of clinical trial conduct, such that data integrity from all study sites must be questioned. However, the findings that 33% of RECORD 4 sites audited by (b) (4) (as well as 2 additional sites, (b) (4) Esquivel, identified earlier by DSI) had serious drug accountability deficiencies, 67% had inadequate monitoring, and 50% of sites audited or inspected were determined to provide unreliable data, together indicate that the data from RECORD 4 cannot be considered reliable.

Failure to report adverse events was identified at all but 2 sites audited by (b) (4) There were 110 unreported AEs in RECORD 1, 131 unreported AEs in RECORD 2, 37 unreported AEs in RECORD 3, and 265 unreported AEs in RECORD 4. There were 8 unreported SAEs noted in the (b) (4) audits, all in RECORD 4. When the unreported AEs were individually examined for significance as defined by the necessity for expeditious medical evaluation, or were AEs involving bleeding or hepatic events, there were 16 in RECORD 1, 24 in RECORD 2, and 265

in RECORD 4; RECORD 3 could not be tabulated due to failure to list individual laboratory abnormalities. During the (b) (4) data verification process of RECORD 4, 504 unreported AEs were noted, as were 28 previously unreported SAEs. The (b) (4) audits identified more than twice as many AEs in RECORD 4 than in the other RECORD studies, and all of the unreported AEs were from RECORD 4. The high number of unreported AEs and SAEs from RECORD 4 may impact labeling for safety, and is again reflective of inadequate monitoring of RECORD 4.

Failure to adhere to the protocol, in particular postoperative randomization, occurred in 39% of RECORD 4 subjects. Although postoperative randomization would not be expected to affect the primary efficacy outcome since it occurred in both study arms, the concern remains that the population described in the product label may not be reflective of the actual study population if subjects are screened and enrolled by criteria other than those in the protocol. There was no other evidence of widespread failure to adhere to the inclusion criteria, and there was no significant postoperative randomization in RECORD 1, 2, or 3. Again, the failure of the CRO (b) (4) to enforce compliance with the protocol requirement for preoperative randomization is reflective of inadequate monitoring of RECORD 4.

The (b) (4) audits of the RECORD 4 study sites were conducted in an attempt to provide assurance of the validity of the data from RECORD 4. There was no difference in primary efficacy or safety outcome when sensitivity analyses were conducted on high versus low quality sites or investigators or on subjects randomized preoperatively versus postoperatively. Although interesting, the (b) (4) methodology is not validated, nor does it address the effects of inadequate monitoring of RECORD 4, which may have introduced unidentified errors not accounted for in the data verification.

In summary given the pervasive findings of deficient clinical trial monitoring, high number of clinical investigator sites with data assessed as unreliable, failure to follow the protocol including postoperative randomization, and deficient clinical trial conduct including failure to report significant adverse events and SAEs, DSI cannot provide a favorable assessment of RECORD 4 data reliability for the remaining unaudited sites based on extrapolation of the (b) (4) audit findings. Although some issues exist with the study conduct of RECORD 1, 2, and 3, they are not sufficiently pervasive to recommend an unfavorable assessment of data reliability. Therefore, the data from RECORD 1, 2, and 3, with exception of select sites as identified earlier, are considered reliable in support of the application. The data from RECORD 4 are not considered reliable in support of the respective indication.

{See appended electronic signature page}

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APPENDIX 1 SUMMARY OF [redacted] AUDIT REPORTS

CI Location Site Number	DSI Site Data Reliable Overall Y/N	Study Monitor Failure Significant (Impacts primary efficacy or safety)	[redacted] Rating C=Critical M=Major m=minor	Bayer or [redacted] missed? Y/N ?=cannot asses	Impacts primary efficacy = E Safety = S B = Both	Detail*
RECORD 1						
Bauer Austria 44003	Y	N	M	N	S	Subject 154759 was not appropriately treated for HTN, had a CVA 1 day after surgery. 4 unreported AEs: iron deficiency, diuresis, diarrhea, elevated GGT = 205
			m	N	B	12 study conduct deficiencies noted in 35 audited, including no source documentation of local lab assessments for all 35
			m	N	B	16 subjects of 35 audited subjects had discrepant entries SD vs. CRF (e.g., wound drain volumes, VS)
Kruczynski Poland 18009	Y	N	C	N	S	7 subjects randomized prior to documented eligibility evaluation; all eventually met eligibility criteria
			M	N	S	For all subjects who experienced AEs, the severity and relationship to study drug was not documented.
Lenart Hungary 46002	N	N	M	Y	S	No documentation in study files that the local IEC was notified of the 5 SAEs at this site
			M	?	E	**Study Coordinators log used to document drug accountability and dosing for all subjects, but entries in log are not signed and dated/initialed; medications and infusions administered to the study subjects recorded inconsistently; no documentation of subject training on injection techniques, dosing instructions, proper storage of study drug**.
			M	N	B	2 subjects received two pre-surgical study drug injections, as surgery was rescheduled.
			M	N	S	Preoperative laboratory results/ECGs not consistently signed and dated by investigator.
			M	N	S	For AE reporting, no source is given for seriousness, action taken with study drug, treatment, severity, and relatedness.
			m	N	B	8 subjects of 35 audited had discrepant entries SD vs. CRF, e.g. medical history, Xanax dosage

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Marinoni Italy	Y	N	M	?	S	1 subject had a hx of disturbed vision and ITP, had a "pre-retinic" hemorrhage on Day 1, study drug continued
22001			M	N	B	Source documentation deficient for all subjects enrolled: No statement Day 1 to confirm eligibility, PE/clinical assessments not recorded in source notes, entries in source notes not signed/dated, ECGs signed , not dated.
			M	N		Out of range labs not routinely annotated as "clinically significant", 1 subject with CPK elevated before and after randomization (1172) not signed or assessed by PI.
			M	N	E	Source therapy logs were not always clear as to which medication had been prescribed/dispensed and changes were made to the data in the logs for several subjects which were not initialed/dated. 3 examples cited, including 2 doses of study drug.
			M	N	S	4 subjects had their epidural catheter inserted/removed outside protocol mandated timelines; none of these catheters were recorded on the CRF. Two were placed too soon after study drug administration (1.5 and 2 hrs) and 2 were withdrawn too soon after study drug admisntraiton (1.5 and 4 hrs after dose), rather than 2X the half-life.
			M	N	S	4 subjects had unreported AEs: left lower limb paresthesia, leg edema, abnormal ECG, wound erythema/edema
			M	N	S	SAE of "infection of the surgical site" noted 10/3/06, reported late on 10/31/06
			m	N	B	6 of 15 subjects the site had discrepant entries SD vs. CRF, e.g., medical history, fever. Some source documentation was missing at the site: 1 subject central lab reports and lab culture report, 2 subjects hematology reports, and 2 subjects medical history.
			In text, not cited	N	E	3 subjects had local lab test reports during active treatment period with coagulation parameters, potentially unblinding the study team.
Mazurkiewicz Poland	Y	N	M	N	B	Documentation of PI involvement with study subjects lacking.
18019			M	N	S	4 subjects with unreported AEs: anxiety and noncooperation, cholelithiasis, and constipation in 2 subjects
Peidro	Y	N	C	N	B	1 medical record missing during audit

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Spain 24002			M	Y	B	Source documents for 12 of 19 subjects audited were missing/incomplete/not recorded to GCP standards (failure to sign/date labs, missing lab reports and/or ECGs, absent venogram results). AE descriptions in progress notes did not include severity, relationship to study drug, and outcome; this info was in eCRFs. No statement in progress notes or Inclusion/Exclusion checklist in records to document eligibility (11 of 19 subjects audited).
			M	N	B	Protocol and sponsor study procedure violations in 12 subjects (e.g., baseline ECGs not signed, date of last study medication not found in source notes, no pregnancy test, no source documentation for vital signs at Day 13, Day 36, and/or Day 65).
			M	Y	S	6 of 19 subjects audited had unreported AEs: hand edema, low potassium, nausea x 3, disorientation/anxious/depression, skin candidiasis. No SAE assessment documented for wound infection
			m	N	B	In 8 of 19 subjects audited, discrepant entries SD vs. CRF, including concomitant medications and medical history
			m	N	B	No training documentation on file for subinvestigators, and the study nurses were not identified on the Site Personnel Responsibility Log.
Pesola Finland 59005	Y	N	M	N	S	2 subjects had unreported AEs: sore calf, nausea/vomiting
			m	N	S	15 of 35 subjects audited had a single laboratory or ECG study outside of the protocol specified window.
Porvaneckas Lithuania 57001	N	N	M	N	S	The site's copy of the IC document contains only the last two signature copies.
			M	N	E	**Study drug administration times were exactly the same for each of the 34 subjects audited; exact dosing times were not documented, and it is unknown how close to the predicted time doses were given.** Pregnancy test or contraception information was missing for 2 subjects.
			M	N	S	There were unreported AEs in 12 of 34 audited subjects. Examples: suspected allergic skin reaction, hypotension, elevated blood pressure, fungal infection.

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			M	N	S	No verification sponsor notification of SAE within 24 hours were available at the site for 6 of 7 SAEs
			m	N	B	9 of 34 audited subjects had eCRF information that could not be verified in the source data or discrepancies between the source data and the eCRFs, including absence of time of blood transfusion in eCRF and in 2 subjects, discrepancy in time of study drug administration (4 and 1 hour differences).
			m	N	B	Whiteout was used to correct source documentation errors in 2 subject records
Schwartsmann Brazil 50006	N	N	M	N	B	Physical exams were not performed on Day 1, 6, 13, 36, and 65 for all 35 subjects audited in violation of the protocol.
			M	N	B	For all 35 subjects audited, post-discharge clinical assessments are not documented on the source document. For all 35 subjects audited, information entered on the source document is not signed/initialed or dated.
			M	N	E	[a]*For all 35 subjects audited, documentation of study drug administration during the inpatient phase is captured only on progress notes as "administered dose of study 11354 medication per protocol at XXX [time]". It is not clear whether the tablet or syringe were administered, or both, were administered.* *8 of 35 subjects audited lacked documentation of a single dose of study drug; 1 additional subject lacked documentation for Days 1-6.* *Documentation of study drug administration in the medical record was not contemporaneous for 4 of the 35 subjects audited.*
			m	N	B	For 5 of 35 subjects audited, discrepancies were noted between eCRF and source documents. Examples include absent eCRF entries for concomitant medication, medical history omitted from eCRF, study medication administration time discrepancy of 6 minutes
Slappendel Netherlands 30002	N	Y	M	N	B	Documentation of PI oversight, delegation, and training of study staff was deficient. Investigator review of study document was inadequate.
			M	N	B	For all 35 subjects audited, there is no documentation of protocol-required

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						physical examinations and clinical assessments for any visit days. 1 subject was randomized 2 days prior to informed consent being obtained.
			M	Y	E	[b]**10 of 35 subjects audited had drug accountability records which were incomplete and/or discrepant with other subject source documentation.**
			M	N	S	21 subjects had 54 unreported AEs. Examples include shortness of breath, hematoma around wound, tachycardia, fever, bradycardia. AE reporting for all audited subjects did not include a source of seriousness, action taken with the study drug, treatment, severity, and relatedness for AEs and/or bleeding events.
			M	Y	E	Source documentation was deficient for all audited subjects. Examples include SDWs not signed or dated for any visit days and absence of a medication record for the subject's hospital stay. **No source documentation to support the date and time of the pre-operative self administered injection of enoxaparin/placebo by the subjects or the date and time of last outpatient dosing for all subjects.**
Stehlik Czech Republic 38007	Y	N	M	N	S	1 subject had study related procedures performed prior to signing the informed consent document.
			M	N	S	There were 12 unreported AEs in 11 subjects of 34 subjects audited. Examples: Anxiety, hematoma, hypotension with chest pain, UTI, left leg swelling. No documentation in source to support the eCRF entries for severity of the AE or relationship to the study medication; the information was recorded directly onto the eCRF
			M	N	B	For 13 of the 34 subjects audited, the surgery start and stop times recorded in the eCRF could not be verified from the source documentation. Given this inconsistency, it could not be determined if the investigator complied with the minimum 6 hour post surgery study medication administration requirement.
			m	N	B	For 9 of 34 subjects audited, there were discrepancies noted between eCRF and source documents. Examples include failure to record Zyrtec as a

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						concomitant medication on the CRF, incorrect date for a pregnancy test, medical history omitted from eCRF, discrepancies in BP.
RECORD 2						
Belickas Lithuania	Y	N	M	N	S	2 SAEs were reported to the sponsor more than 24 hours after site awareness; each SAE was reported after approximately 3 months.
57001			M	N	S	7 of 35 subjects audited had unreported AEs: low hemoglobin x 3, fever x 2, RUQ pain, nausea, elevated potassium (6.2).
			M	Y (some)	B	Deficiencies, omissions, and deviations from GCP were noted in the source documentation. Examples include: alteration of dates and numbers on 2 or 3 of the local lab report slips with no explanation, missing randomization confirmation for 2 subjects, at least 95% of all blood pressure measurements appeared to be estimated or rounded, use of correction fluid was noted on progress notes.
			m	N	E	Discrepancies in number of tablets/injections returned vs the number that should have been returned for 6 subjects of 35 audited. However, compliance was not outside the protocol-allowed 80-120%.
			m	N	S	The site maintained only the last two pages of the informed consent document containing signatures for all subjects.
			m	N	B	Source documentation was inconsistent with eCRF entries for 14 of 35 subjects audited. Examples include concomitant medications not recorded on the eCRF, drainage volume inconsistency, estimated surgical loss.
			m	N	B	Dr. Belickas was not included on the Site Personnel Responsibility Logs. The assigned tasks on these logs did not include clinical assessments for safety or efficacy for the sub-investigators who performed the majority of these assessments.
Dhanjee South Africa 37001	Y	N	M	N	S	There were 4 unreported AEs: fever, calf pain, backache, and hypotension.
Field England 12008	Y	N	M	N	B	There was minimal documentation of PI involvement in the study
			M	N	S	It was unclear whether SAE reporting timelines were adhered to for 7 SAEs; reporting occurred after 3 weeks – 1 year to the sponsorfor these SAEs.

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			M	N	S	There were 21 unreported AES in 13 of the 43 subjects audited. Examples include: low hemoglobin, swelling left leg
			m	N	E	2 subjects of 43 audited had discrepant drug administration/accountability information (4 vs. 6 tablets returned, 80 minute discrepancy in drug administration time.)
			m	N	B	Discrepancies were noted between eCRF entries, SDW, and medical record information for 6 of 43 subjects audited. Examples include laboratory draw and ECG times, concomitant medication, one instance of study drug administration.
			m	N	S	Medical history in the medical record not captured in eCRF in 17 of 43 subjects audited. Examples include penicillin allergies, glaucoma.
			m	N	S	For 2 subjects laboratory pages were not signed or clinical significance documented by the PI 1 subject had a history of CRI per medical records, no screening labs documented to be reviewed prior to surgery (b) (4) screening labs signed by PI 10/14/06, subject withdrawn due to elevated BUN/Cr on 10/13/06.
			m	N	S	Qualifying information for AE data captured on eCRF (relationship to study drug, action taken, seriousness, and severity, not recorded in source documentation
			m	N	E	1 subject had venography performed unilaterally with no documentation as to reason.
Martson Estonia 63002	Y	N	M	N	B	2 subjects were enrolled despite allergy to contrast and thyroid condition; venography could not be performed for these 2 subjects.
			m	N	B	5 of 35 subjects audited had protocol deviations, including study visits out of window, venography performed too close to last dose of study drug.
			m	N (missed #3/3)	B	3 of 35 subjects had eCRF entries not supported by source documentation (no screening ECG interpretation, no reason for drug discontinuation (rash), AE of pain after venography dated earlier than venography).
			M	N	S	8 of 25 subjects had unreported AEs. Examples: thigh hematoma, swelling right foot, anxiety, knee pain
Nafarrete	N	N	M	N	B	3 of 25 medical charts could not be located

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Mexico 32005			M	?	B	**Study drug administration times were exactly the same for each subject for all subjects audited; exact times could not be documented.** 3 subjects had study drug administered too early after wound closure (1-5 hours)
			M	N	S	There were 35 unreported AEs in 10 of 25 subjects. Examples: anemia, infection, vomiting
			m	N	B	Lapses in GCP documentation were noted, including ECG tapes stapled into patient charts without identifying information, white-out in several patient charts, and an SAE report completed in pencil.
			m	N	B	Concomitant medications were listed in the medical chart, but were not reported in the CRF in 5 of 25 subjects audited: examples include magnesium sulfate, neupogen; fraxinhearina; metoclopramide, morphine, Graten, neumerabraum; metoclopramide, decorex; bicarsol, fentalyn, Dobutrex, dermakin, dopamine, precedex dexmedetomidine hydrochloride.
			m	N	B	5 of 25 subjects had discrepancies between the source data and the CRFs, including height/weight, date of ECG, side of surgery, wound drainage volume, date of ECG
			m	N	B	11 of 25 subjects had information on the CRFs that could not be verified in the source documentation. Examples include misplaced ECGs, no vital signs in source documents, no height/weight in source document, venography procedure/results absent from source document.
Ono Brazil 50005	N	Y	C	Y	E	**Documentation of study drug administration during inpatient phase of study was missing or deficient: 8 subject records contained very few notations that study drug had been given, and the remaining 16 records contained none.** **Doses of study medication documented only on SDW were not signed/initialed or dated, so it is unclear whether they are primary source entries.**
			C	Y	B	**Discrepancies were noted among eCRF entries, SDW entries, and medical chart information – 73 discrepancies for 20 subjects. Examples include surgery start/stop times, intraoperative blood loss, drain**

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						volumes.
			M	Y	B	PI oversight of study conduct was deficient – PI unaware of study procedures, no evidence that he participated in study conduct, not present in monitoring visits, and he was unaware of how many SAEs were reported from his site.
			M	Y	B	For 11 of 24 enrolled subjects, Day 1 physical examinations and clinical assessments were either not recorded or could not be verified due to missing charts.
			M	Y	S	Documentation of medical oversight was inadequate. Potential AEs were not reviewed or evaluated by a study physician; 1 subject who received 2 pre-surgery doses of enoxparin/placebo injections due to surgery rescheduling, had suctioning of blood from the nasal cavity, 2 subjects had elevated BP on 5 occasions without Rx or recorded as AEs.
			M	Y	S	5 subjects had informed consent granted by a "witness" rather than by the subject. The consent process was not documented in the medical charts for any of the subjects enrolled.
			M	Y	B	Source documentation was found to be deficient for all subjects: post-discharge PEs/CAs were not captured on the SDW; much of the information captured on the SDW had not signatures/initials/dates; information appeared to be transcribed for the medical record to the SDW, but many discrepancies were noted; central lab results were not reviewed in a timely fashion; screening ECGs were not reviewed by an MD until after randomization.
			M	Y	S	37 unreported AEs in 16 subjects. Examples include hypertension, nasal bleeding during surgery, edema, mental confusion.
			C	Y	B	1 medical record could not be located
Wang China 54001	N	Y	M	Y	S	4 of 6 women of child bearing potential did not have pregnancy tests performed prior to enrollment in the trial.
			M	Y	B	30 of 35 subject audited had discrepancies between eCRF and medical chart information. Examples include surgery start/stop times, concomitant medications, blood transfusion and venography absent from source records,

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			M	N	B	Deficiencies were noted pertaining to source documentation including: failure to document hx of alcohol abuse; PCA not listed as concomitant medications; copies of venography films sent to the adjudication committee were not kept for 13 of the 84 subjects at the site.
			M	N	S	There wers 18 unreported AEs in 14 subjects of 35 audited, including hypertension and dyspnea.
			M	N	B	4 subjects had study conduct issues identified: Discontinuation of enoxaparin/placebo 1 day late; receipt of contraindicated medication Fragmin; failure to provide clinical evaluation of lipase = 86; placement of spinal needle/epidural catheter 2 hours early in 2 subjects
			M	N	E	Source documentation of study drug administration and blood sampling times were listed as occurring at the same time for 12 of 35 subjects audited
			m	N	E	Investigational product documentation was found to be deficient in 8 of 35 subjects audited regarding doses expected vs actually returned. Compliance was not outside the 80 – 120% allowed per protocol.
			m	N	S	24 of 35 subjects audited did not have documentation of the informed consent process in the source records
RECORD 3						
Brabants Belgium 28015	Y	Y	C	Y	E	**Exact time of study drug administration was rarely recorded on the inpatient medication administration records for any of the 27 subjects – only on grid with 0800, 1200, 1600, and 2000 grids.** **Times of study drug administration frequently do not match the times noted on the inpatient medication administration sheet.**
			C	Y	B	**Study coordinator was unable to define a consistent primary source for many of the data points, including drug dosing, surgery start/stop times, and laboratory draw times.** PCAs were not verifiable in medical records Significant portions of source records were missing for 4 subjects. The start times of multiple activities were noted as occurring simultaneiously or at overlapping times in the source. Examples: oral & injectable IP; venography & lab draws.

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			M	Y	B	Documentation of PI oversight and delegation of study conduct was deficient
			M	Y	S	Documentation of medical oversight by the study was inadequate: source documentation of AEs and DVTs was missing qualifying data (stop date/time, severity, relationship, and outcome) and there were 36 unreported AEs in 20 subjects of 27 audited. Example = leg hematoma.
			M	Y	E	Documentation of investigational product accountability and storage conditions during the inpatient phase of the study was inadequate. **Drug accountability logs provided by Bayer were not used by the study coordinator to record drug accountability.** **Temperature in study drug storage area was monitored weekly, not daily.**
			M	?	S	In 9 of 27 subjects, screening procedures were conducted prior to written consent or outside of study-proscribed windows, including screening ECGs and laboratory studies
			M	Y	S	6 subjects had significant protocol deviations, including receiving study drug tablet and injection and Fraxiparine, study drug injection fewer than 12 hours and 10 hours after surgery in 2 subjects, first dose given 1.5 hours after surgery (not 6-8 hours after)
Paulsson Sweden 34003	N	N	M	N	S	1 unreported AE in 19 subjects: constipation
			m	N	S	5 subjects had source document deficiencies regarding 7 AEs: 1 subject relationship and severity in eCRF not source; 6 AEs were in eCRF not source
Synder Poland 518008	Y	N	C	N	E	All subjects received 1 or more doses of study medication outside the protocol-specified window (10 subejcts-1 dose, 9 subjects-2 doses). Time outside dosing interval ranged from approximately 2 to 5 hours
			M	N	E	6 subjects of 19 had discrepancies between eCRF and source documentation, including laboratory draw date, whether a dose of study medication was given, injection time.
			M	N	S	5 subjects of 19 had missing or incorrect PI signature and/or dates on lab reports

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			M	N	B	1 subject had an illegible time of transfusion on the source documented corrected by the monitor
			m	N	B	Correction fluid and pencils were used on the records of 1 and 2 subjects respectively and all subjects had sticky notes used as source documentation for vital signs.
RECORD 4						
Dessouki Canada 26016	Y	N	C	?	S	1 subject was hospitalized for acute cholecystitis and subsequent cholecystectomy; no SAE was reported to the sponsor or REB.
			M	N	S	1 subject had ALT = 182 on Day 13 (4x ULN). Retesting not done until 1 month later, no monitoring as specified in the protocol. PI documented this value as "NCS"
			M	Y	B	Deficiencies in documentation were noted including: approximately 75% of subjects had an alteration in the time stamp on original ECGs; 3 subjects had no documentation in source that subjects had stopped Metformin 2 days prior to venography and restarted at the earliest, 2 days after venography; most vital signs were not taken in the supine position after 5 minutes rest, as specified in the protocol; approximately 75% of the subjects audited had an AE of "post-op nausea" recorded due to receiving Gravol prophylactically, despite no source record indication of nausea; a local lab CBC including INR was obtained at Day 13 for one subject, which may result in unblinding.
			M	N	B	7 subject records were apparently backdated by the PI (lab reports, ECG, SDW worksheet).
			M	N	B	There were discrepancies between eCRF and source documentation for 7 subjects. Examples include for qualifying information for 2 AEs, ECG recorded as normal on eCRF but ECG itself read as atrial premature complex, right axis deviation, RBBB, and old inferior MI
			M	N	S	There were 18 unreported AEs in 15 of the 35 audited subjects. Examples include shaking with fever &hallucinations, drug-induced pancreatitis, elevated GGT = 275, ARI, decreased platelets, NA = 119 with K = 2.5, irregular HR, Tx 2 U PRBCs, burning calf
			M	N	S	There was no documentation that the 3 SAEs initially identified by the site

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						and reported to the sponsor were reported to the REB.
			m	N	B	No evidence that sub-investigators or study coordinators had been trained on their study-related duties
			m	N	E	18 of 35 subjects audited were randomized on the day of surgery. It was not possible from the data at the site to determine whether randomization occurred postoperatively
Hollman U.S.A, Florida 14023	Y	N	M	Y	S	6 of 35 subjects audited had unreported AEs including leg muscle spasm, rash on buttocks
			m	Y	E	Protocol violations were noted in 4 of 35 subjects audited including 1 subject randomized postoperatively
			m	Y (CAD)	S	Discrepancies were noted between source documentation and eCRFs for 8 subjects. 1 subject who refused a venogram on Day 13 and "withdrew consent for the study" per 2 site emails; however, the subject was not withdrawn from the study and continued study-related blood draws through day 42. 1 subject had coronary artery disease noted in the medical history but not recorded on the eCRF.
			m	Y	E	34 of 35 subjects were randomized on the day of surgery. Data at the site did not allow determination of which subjects were randomized postoperatively.
Jove U.S.A, Georgia 14016	Y	N	C	Y	S	1 subject was enrolled despite evidence of current EtOH abuse and elevated GGT at screening (1499)
			M	Y	E	Discrepancies were noted between eCRF and medical charts for 26/39 subjects audited. Examples include 1 dose of enoxaparin/placebo recorded in medical record not eCRF, discrepant drain volumes, discrepant vital signs, onset dates of AEs.
			M	N	S	For 2 of 4 SAEs that occurred in this audit sample, it could not be determined whether or not the SAE was reported to the sponsor within 24 hours.
			M	N	B	Data were not captured according to site practices: eCRF start and/or stop times of surgery are inconsistent with the site's practice of using operative start/stop times (2 subjects); intraoperative blood loss in eCRF is

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						inconsistent with the site's practice of using the intraoperative report to obtain blood loss (10 subjects); blood transfusion start times in eCRF are inconsistent with the site's practice of using the time pasted into the medical chart (3 subjects)
			M	Y	S	33 AEs in 13 of 39 subjects audited had unreported AEs. Examples include fever, hypotension, UTI.
			M	N	S	Drainage volumes in electronic nursing assessment system were difficult to reconcile with drain volumes in the eCRF.
			m	N	B	Training was not documented for any of the subinvestigators listed on the Form 1572 and Delegation Log.
Kilgore U.S.A., Florida 14034	Y	N	C	Y	S	25 of 35 subjects audited had 29 unreported AEs. Examples include SOB, elevated AST/ALT/GGT/alkaline phosphatase
			C	Y	B	9 of the 35 subjects audited had protocol deviations detected. Examples include 6 study visits occurring 3 days out of window, screening ECG done prior to signing of informed consent, failure of PI to sign abnormal lab report (BUN, ALT, & LD).
			M	N	S	4 of the 35 subjects audited had deficiencies in source documents, including failure of the PI to assess abnormal lab values and ECGs.
			M	N	S	The 4 SAEs that occurred at this site were not submitted to the sponsor or IRB within 24 hours of the site becoming aware of the SAE. Reports to the sponsor were made 3, 9, 11, and 14 days after site became aware.
			M	N	S	17 screening ECGs were not dated by the PI to document prerandomization review. 9 original ECG tracings were not on file and for 8/9 subjects, the photocopy was not signed and dated.
			M	N	E	Subjects were "generally" randomized on the day of surgery; neither the IVRS acknowledgement nor the source document list the time of randomization so that preoperative randomization cannot be assured.
Mody India	N	Y	C	Y	S	Site safety reporting practices were deficient: There were 47 unreported AEs in 21 of 35 subject audited. Examples: chest

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60010						pain/breathing difficulties, Tx 2U PRBCs, fever, hypertension, elevated amylase= 711 No source documentation for AE or Bleeding Event qualifying data. There were 3 unreported SAEs: chest infection requiring hospitalization; bedsore requiring hospitalization; hypotension & SOB requiring transfer.
			C	Y	S	**The EC used by the PI was formed at his request, the EC address is the PI's clinic, members include the PI, his wife and secretary, and the EC was not trained.**
			M	Y	E	**Study drug was not stored in permissible temperature range of 15-30^{o}C for 19 consecutive days, dropping to 10.2^{o}C each day.**
			M	Y	S	For 25 of 35 audited subjects, review of study documents was either not done or not done in a timely manner. This includes Progress Notes, lab reports, and ECGs
			m	Y	S	For 17 of 35 subjects, pre-study and/or concomitant medications were not recorded in the eCRF; most were Jonac suppository
			M	Y	S	For 12 of 25 subjects medical histories/conditions were not recorded in the eCRF or were documented in the CRF but not in the source documents. Examples include medication allergies, hypertension, diabetes, and bronchospasm.
			m	Y	B	There were discrepancies between the eCRF and site source documentation, including concomitant medications and ECGs interpreted as "Normal/Normal Variant" with the source document ECGs demonstrating abnormalities such as T wave depression, LBBB, and anterior wall ischemia.
			m	Y	B	Site source documents were deficient in content, missing and/or conflicting with other source documents. This included use of inappropriate correction medium and time of lab collection
			m	Y	E	For 34 of the 35 audited subjects who were randomized on the day of surgery, it could not be determined whether subjects were randomized postoperatively.
			m	Y	B	For 7 of the 35 audited subjects, there was no evidence of one (7 subjects) or 2 (2 subjects) protocol-required physical examinations.

CI Location Site Number	DSI Site Data Reliable Overall Y/N	Study Monitor Failure Significant (Impacts primary efficacy or safety)	(b) (4) Rating C=Critical M=Major m=minor	Bayer or (b) (4) missed? Y/N ?=cannot asses	Impacts primary efficacy = E Safety = S B = Both	Detail*
Reddy India 60001	Y	N	C	Y	S	There were 3 unreported SAEs from this site: adenocarcinoma of the prostate; pyrexia requiring hospitalization, hospitalization for more than 12 hours for catheterization. There were 47 unreported AEs in 21 of 40 audited subjects. Examples include fever, elevated bilirubin. LBBB, decreased platelets, elevated ALT. There were discrepancies between source documentation and eCRF for AE start and stop dates and time. Inconsistencies in the level of source documentation for AE or Bleeding Event qualifying data.
			M	N	B	There were discrepancies between the eCRF and site source documentation for 32 of 40 subjects audited. Examples include time of venography, blood transfusions not recorded on the eCRF, time of study drug administration, and differences in vital signs.
			M	N	E	12 of 40 subjects audited were randomized postoperatively; deviation forms were present for 11 of the 12 subjects. For 7 additional subjects randomized on the day of surgery, it could not be determined whether randomization occurred postoperatively.
			m	N	E	Drug accountability procedures were inadequate and/or records were incomplete and/or discrepant with other subject source documentation in 8 of 40 subjects audited. Examples include discrepancies in whether a dose of study drug was administered and discrepancies in numbers of study drug doses returned.
			m	Y	B	Pre-study medical histories/conditions were not recorded in the eCRF for 6 of 40 subjects audited. Examples include hx of TKA and drug allergies.
			m	N	B	Source documents were deficient in content, missing, and/or conflicting with other documents. For all audited subjects, inappropriate correction techniqes were noted. For the majority of subjects, the study staff did not date signatures. Several subject records contained ECG thermal printouts which were faded such that they were illegible with no photocopies.
			m	N	B	Clinician review of study documents (progress notes, lab reports, ECG tracings) was untimely and/or missing for all 40 subjects. Clinical

CI Location Site Number	DSI Site Data Reliable Overall Y/N	Study Monitor Failure Significant (Impacts primary efficacy or safety)	(b) (4) Rating C=Critical M=Major m=minor	Bayer or (b) (4) missed? Y/N ?=cannot asses	Impacts primary efficacy = E Safety = S B = Both	Detail*
						assessment of all abnormal local lab results could not be determined.
Sepulveda Mexico 32002	N	N	C	N	B	**The medical records of 10 subjects were missing from the site. Nursing notes, which include dosing entries, were missing for an additional 7 subjects.**
			C	N	S	1 of 33 subjects audited had only a blank, unsigned consent form in the study chart; this was one of the missing medical charts.
			M	Y	B	There were discrepancies between eCRF entries and medical chart information for 20 of the 33 subjects audited. Examples include surgery start and stop times, intraoperative blood loss, and venography date and time. For 1 subject a dosing worksheet was on file documenting some injection doses, but no tablets; no dosing data is entered in the eCRF.
			M	N	E	Differences were noted in number of tablets/injections returned vs number that should have been returned for 19 of 33 subjects audited. However, compliance was not outside the 80-100% allowed per protocol.
			M	N	E	**15 of the 33 subjects audited had source vs eCRF discrepancies pertaining to study drug administration noted, ranging from 1 to all doses, most = 2-3 doses.**
			M	N	S	Source documentation of AEs was inconsistent with eCRF entries or was missing qualifying data, including start and stop dates. There were 13 unreported AEs in 25 of 33 audited subjects. Examples include: edema, hematoma, wound infection, ALT/AST > 3X ULN.
			M	N	B	There were source documentation deficiencies and discrepancies relative to laboratory reports and other study procedures in 15 of 33 audited subjects. These include PI failure to review labs in a timely manner, failure of PI to sign/date lab reports, dating discrepancies, illegible ECGs on thermal paper. In addition, 1 subject withdrew consent after surgery; but per the eCRF, study procedures were performed through Visit 2/Day 1.
			m	N	E	For 9 of 33 subjects audited who were randomized on the day of surgery, it could not be determined from data at the site whether randomization occurred postoperatively.
			m	N	B	For 9 of the 33 subjects audited, medical history items were not recorded on

CI Location Site Number	DSI Site Data Reliable Overall Y/N	Study Monitor Failure Significant (Impacts primary efficacy or safety)	(b) (4) Rating C=Critical M=Major m=minor	Bayer or (b) (4) missed? Y/N ?=cannot asses	Impacts primary efficacy = E Safety = S B = Both	Detail*
						the CRF. Examples include "cardiopathy", penicillin allergy, and knee replacement.
H. Shah India 60004	Y	N	M	Y	B	For 17 of 25 subjects use of one or more pre-study medication and/or concomitant medications were not recorded in the eCRF.
			M	N	S	Site safety reporting practices were deficient. There were 44 unreported AEs in 19 of 25 subjects at the site. Examples include probable LVH, possible MI, pitting edema, neutropenia, irregular heart beat. No source documentation for AE or Bleeding Event qualifying dat
			M	N	E	1 subject was randomized postoperatively
			M	N	B	No source documentation of protocol-required clinical VTE assessments by study staff for Visits 2, 3, 4, 5, and/or 6 for 11 of 25 subjects. No source documentation of protocol-required physical examinations by study staff for specific visit days (ranging from 1 to 4 visits) for 13 of 25 subjects.
			M	N	B	PI review of study documents, including progress notes, laboratory reports, ECG tracings was untimely and/or missing for 20 of 25 subjects.
			M	N	B	Study related procedures, assessments, and examinations were performed by 2 personnel not included on the Delegation of Duties Log. The ECGs were performed by an individual with no medical or scientific background and no documentation of training in ECG performance.
			M	N	B	Protocol Amendment 1 was submitted to the EC, but no approval letter is on file.
			m	Y	B	Pre-study medical conditions/histories were not recorded in the eCRF for 11 of the 25 subjects. Examples include allergic bronchitis, hypertension, drug allergy, and knee replacement.
			m	Y	B	There were discrepancies between the eCRF and site source documentation. Examples include time of venography, date of study visits, discharge date, time of outpatient study drug administration.
			m	Y	B	Site source documents were missing or deficient. For all subjects, inappropriate correction techniques were used.

CI Location Site Number	DSI Site Data Reliable Overall Y/N	Study Monitor Failure Significant (Impacts primary efficacy or safety)	(b) (4) Rating C=Critical M=Major m=minor	Bayer or (b) (4) missed? Y/N ?=cannot asses	Impacts primary efficacy = E Safety = S B = Both	Detail*
						For 18 of 25 subjects, source documentation was missing from subjects' hospital records, including Clinic First Consultation report, laboratory reports, randomization fax, and ECG tracing.
			m	N	S	4 subjects were randomized prior to documented clinical review of screening laboratory reports and/or ECG tracings.
			m	N	E	4 subjects were randomized on the day of surgery; based on site records, it could not be determined whether they were randomized postoperatively.
V. Shah India 60006	N	N	M	N	S	**According to the documented screening visit summary, a subinvestigator used language during the informed consent process which appears to be coercive. Documented language used includes "that the study drug was completely safe, that it was the best treatment currently available, that risks were minimal (same as any other surgery).**
			M	Y	S	Site safety reporting practices were deficient. There were 36 unreported AEs in 17 of 35 subjects audited at the site. Examples include fever, LE swelling, elevated ALT > 3X ULN. No source documentation for AE or Bleeding Event qualifying data such as seriousness, action taken with study drug, treatment severity, and relatedness. For 7 subjects there were discrepancies between the source documentation and the eCRF regarding AE start/stop dates, action taken, etc.
			M	N	E	**There were data discrepancies between the eCRF and site source documentation, including for study drug administration for 26 of 35 subjects audited (25 instance of discrepancies for study drug administration).** **For 3 subjects, source documentation and eCRF entries were changed months after an event, sometimes in response to a query from data management.**
			M	Y	B	Clinician review and/or completion of study documents (for example, progress notes, lab reports, ECG tracings) was untimely and/or missing.
			M	N	E	Coagulation parameter testing was done locally for 2 subjects, potentially

CI Location Site Number	DSI Site Data Reliable Overall Y/N	Study Monitor Failure Significant (Impacts primary efficacy or safety)	(b) (4) Rating C=Critical M=Major m=minor	Bayer or (b) (4) missed? Y/N ?=cannot asses	Impacts primary efficacy = E Safety = S B = Both	Detail*
						resulting in unblinding.
			m	N	E	Drug accountability procedures were inadequate and/or records were incomplete or discrepant with other subject source documentation. For 4 subjects expected versus returned study drug was discrepant, but did not fall outside the 80-100% allowed per protocol. [c]**There was missing source documentation for 1-6 days of study medication for 8 of 35 subjects.**
			m	N	B	Pre-study medical histories or conditions were not recorded in the eCRF for 22 of 35 subjects. Examples include knee replacement, osteoarthritis.
			m	N	B	**For all subjects, inappropriate correction techniques were used in hospital records.** 4 of 25 subjects had source documentation missing from the hospital chart, including copy of venography, central lab reports.
			m	Y	E	For 12 of 35 subjects, protocol violations were noted, including study medication given 5 minutes to 8 hours 42 minutes outside the window; 10 of 12 instances were less than an hour.

Bold = Finding impacting on the primary safety or efficacy outcome which results in inability to validate data from the site.
[a] *Evaluation of data submitted by Johnson & Johnson resulted in assessment of data from this site as acceptable; see Section III.*
[b]Evaluation of data submitted by Johnson & Johnson resulted in assessment of data from 4 of the 10 subjects in question at this site as acceptable; see Section III. Data is still considered unreliable.
[c]Evaluation of data submitted by Johnson & Johnson resulted in assessment of data from 1 of the 8 subjects in question at this site as acceptable; see Section III. Data is still considered unreliable.

APPENDIX 2

SUMMARY TABLE: DSI Analysis of Johnson & Johnson Response to August 2, 2010 Information Request

Study Site	J&J Response/Finding	DSI Assessment of J&J Response/Finding
Lenart, RECORD 1, Site 46002, Hungary: Study coordinators used logs to document drug	Study drug was prescribed by the PI on the "Fever sheet." Initials on Fever sheet indicate medication administration. 35 subject	Although some initials are noted on the "Fever sheet", th day/date and time of drug administration are not noted.

accountability and dosing for all subjects, but entries in the logs were not signed and dated/initialed; medications and infusions administered to the study subjects were recorded inconsistently; no documentation of subject training on injection techniques, dosing instructions, proper storage of study drug.	medication administration records (Fever sheets) were inspected, and of these 28 were initialed twice, 3 were initialed once, and 4 were not initialed. Training on injection technique/dosing/storage was routinely done verbally and documentation regarding this was not available.	Although the Study Coordinator's notebook containing information regarding study drug dispensation is supportive, this document is not a source document. The (b) (4) finding that study drug accountability and dosing log entries for all subjects were not signed and dated/initialed and that medication administration were recorded inconsistently is unchanged.
Porvaneckas, RECORD 1, Site 57001 Brazil: Study drug administration times were exactly the same of each of the 34 subjects audited; exact dosing times were not documented.	The logs for randomly selected patients confirmed the dose of investigational medicinal product (IMP), route of dispensing, and required time of dispensing by the physician. These entries were initialed by the physician and the nurse.	The nurse's initials are not accompanied by dates/times. The sponsor submitted the Hospital Operating Procedure which state that a nurse must make a notation if the medication is given more than 5 minutes for injection or 7 minutes for oral outside the prescribed window. Since there is no other source to verify that the medication was given at the prescribed time, the (b) (4) finding is unchanged.
Schwartsmann, RECORD 1, Site 50006: For all 35 subjects audited, documentation of study drug administration during the inpatient phase is captured only on progress notes as "administered dose of study 11354 medication per protocol at XXX [time]". It is not clear whether the tablet or syringe were administered, or both. In addition, 8 of 35 subjects audited lacked documentation of a single dose of study drug; 1 additional subject lacked documentation for Days 1-6.	Study drug administration during hospitalization was documented on the source data worksheet either by the study coordinator or by the study nurse, and entries were signed and dated. These data entries were identified and the appropriate source documents obtained.	The evidence submitted by the sponsor is sufficient to ensure that drug administration was appropriately documented.
Slappendel, RECORD 1, Site 30002, Netherlands: 10 of 35 subjects audited had drug accountability records which were incomplete and/or discrepant with other subject source documentation. In addition, no source documentation to support the date and time of the preoperative self administered injection of enoxaparin/placebo by the subjects or the date and time of the last outpatient dosing for all subjects.	Alternate source documents were identified to address drug accountability and outpatient dosing.	The additional information provided was adequate to provide evidence of drug administration for four subjects 300024054-153563, 300024054-153565, 300024059-153618, and 300024021-150856. However, the evidence presented for the remaining six subjects is not considered adequate.

Nafarrete, RECORD 2, Site 32005, Mexico: Study drug administration times were exactly the same for each subject for all subjects audited; exact times could not be documented.	Study drug administration is documented in the nurse's notes which are part of the medical charts indicating 8:00, 14:00, or 20:00, but not the exact time. This is routine practice in this hospital but not documented as such in a hospital policy.	No additional information was provided to provide reassurance of drug administration. No change in conclusions.
Ono, RECORD 2, Site 50005, Brazil: Documentation of study drug administration during the inpatient phase of the study was missing or deficient: 8 subject records contained very few notations that the study drug had been given, and the remaining 16 records contained none. Doses of study medication documented only on the SDW were not signed/initialed or dated, so it is unclear whether they are primary source entries.	Source documentation to support dosing of study drug for multiple subjects was identified and provided source data worksheets.	The entries on the source data worksheets were not routinely singed and dated. Therefore, they cannot be considered to be evidence of drug administration.
Brabants, RECORD 3, Site 28015, Belgium: The exact time of drug administration was rarely recorded on the inpatient medication administration for any of the 27 subjects – the times were recorded only on a grid with times of 0800, 1200, 1600, and 2000. Times of study drug administration frequently do not match the times noted on the inpatient medication administration sheets. In addition, the drug accountability logs provided by Bayer were not used by the study coordinator to record drug accountability. In addition, the study coordinator was unable to define a consistent primary source for many of the data points, including drug dosing, surgery start/times, and laboratory draw times. Please provide this information, if available.	No additional data were available.	No change in conclusions.
V. Shah, RECORD 4, Site 60006, India: Source documentation for 16 days of study drug medication was missing for 8 of 35 subjects.	Additional source documents supporting study drug administration were obtained from study drug dispensing logs, hospital file treatment sheets, nurse's notes, study coordinator's notes and post operative orders.	The additional information provided for the eight subjects is considered adequate for one subject. However, most or all of the information for the remaining 7 subjects in question did not provide documentation of most or all drug dispensation doses.

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/s/

SUSAN D THOMPSON
05/24/2011

TEJASHRI S PUROHIT-SHETH
05/25/2011

Executive CAC
Date of Meeting: April 15, 2011

Committee: David Jacobson-Kram, Ph.D., OND-IO, Chair
Abigail Jacobs, Ph.D., OND -IO, Member
Paul Brown, Ph.D., OND-IO, Member
Karen Davis Bruno, Ph.D., DMEP, Alternate Member
Thomas Papoian, Ph.D., DCRP, Supervisor
Patricia Harlow, Ph.D., DCRP, Reviewer

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

The following information reflects a brief summary of the Committee discussion and its recommendations.

NDAs: 202-439, 22-406
Drug Name: Rivaroxaban (BAY 59-7939)
Sponsor: Ortho McNeil Janssen Pharmaceuticals Inc

Background:
Rivaroxaban is a direct Factor Xa inhibitor. In the Phase 3 trial for prevention of stroke in patients with non-valvular atrial fibrillation, the maximum daily dose was 20 mg.

Rat Carcinogenicity Study:
In a 104-week study using 50 Wistar rats/sex/group, daily doses of 0, 10, 20, and 60 mg/kg/day of rivaroxaban in ethanol/solutol HS/tap water (10/40/50 v/v) were administered by oral gavage. The exposures in the high dose males and females were 6.2 and 14.6 fold, respectively, the mean human exposure in subjects receiving 20 mg.

No significant treatment-related effect was observed on mortality, bodyweight gain, and food consumption. Although only slight effects were observed on red cell parameters on Days 184, 366, 548, and 716 , the mean values for thromboplastin time for all treated groups on all sampling days were significantly greater (up to 1.9 and 2.5-fold in males and females, respectively) than those for the control groups. Likewise, the incidence of pigment deposition increased in some organs and across all organs in the high dose groups consistent with the pharmacodynamic action of BAY 59-7939. However, the incidence of valvular fibrosis in the heart increased with dose in both males and females with the incidence in females statistically significant ($p = 0.0048$).

The incidences of a few tumors, including squamous cell carcinoma of the clitoral glands, adrenal cortical adenoma, adrenal pheochromocytoma, mammary fibroadenoma, histocytic sarcoma, and skin fibroma, were numerically increased in the higher dose groups compared to those in the control groups. However, the incidences were within historical ranges, and the attained p values do not reach the thresholds to classify these tumors as drug-related according to the CDER statistical criteria.

Mouse Carcinogenicity Study:
In a 104-week study using 60 CD-1 mice/sex/group, daily doses of 0, 10, 20, and 60

mg/kg/day of rivaroxaban in ethanol/solutol HS/tap water (10/40/50 v/v) were administered by oral gavage. The exposures in the high dose males and females were 0.8 and 0.9 fold, respectively, the mean human exposure in subjects receiving 20 mg.

No significant treatment-related effect was observed on mortality, bodyweight gain or food consumption. At study end, slight decreases in hemoglobin concentration and hematocrit, slightly prolonged thromboplastin times, and increased incidences of microscopic pigment deposits were consistent with the pharmacodynamic action of rivaroxaban.

Consistent with the increase in liver nodules macroscopically, hepatocellular tumors (adenoma and carcinoma) increased with rivaroxaban dosage in the males, but not in the females. However, the incidences of hepatocellular tumors were within historical ranges, and the attained p values do not reach the thresholds to classify these tumors as drug-related.. Similarly, the incidences of a few other tumors, including histiocytic sarcoma, malignant lymphoma, ovarian cystadenoma, uterine hemangiosarcoma, and testicular Leydig cell tumors, were numerically increased in the higher dose groups compared to those in the control groups. However, the incidences were within historical ranges, and the attained p values do not reach the thresholds to classify these tumors as drug-related.

Executive CAC Recommendations and Conclusions:

Rat:

The Committee concurred that the study was adequate, noting prior Exec CAC concurrence with the protocol.

The Committee concurred that there were no clearly drug-related neoplasms.

Mouse:

The Committee concurred that the study was adequate, noting prior Exec CAC concurrence with the protocol.

The Committee concurred that there were no clearly drug-related neoplasms.

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

cc:\
/Division File, DCRP
/T. Papoian, Team leader, DCRP
/P. Harlow, Reviewer, DCRP
/A. Blaus, CSO/PM, DCRP
/A.Seifried, OND-IO

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/s/

ADELE S SEIFRIED
04/18/2011

DAVID JACOBSON KRAM
04/18/2011

M E M O R A N D U M

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

CLINICAL INSPECTION SUMMARY ADDENDUM

DATE: May 15, 2009

TO: Marcus Cato, Regulatory Project Manager
Min Lu, Medical Officer
Division of Medical Imaging and Hematology Products

FROM: Susan D. Thompson, M.D.
Good Clinical Practice Branch 2
Division of Scientific Investigations

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

SUBJECT: Evaluation of Clinical Inspections.

NDA: 22-406

APPLICANT: Johnson & Johnson

DRUG: Xarelto (rivaroxaban)

NME: Yes

THERAPEUTIC CLASSIFICATION: Standard Review

INDICATIONS: Prophylaxis of deep vein thrombosis and pulmonary embolism in patients undergoing hip or knee replacement surgery

CONSULTATION REQUEST DATE: April 28, 2009

DIVISION ACTION GOAL DATE: May 13, 2009 for CR letter

PDUFA DATE: May 28, 2009

I. BACKGROUND:

Rivaroxaban is a highly selective direct factor Xa (FXa) inhibitor for oral administration. Inhibition of FXa produces antithrombotic effects by decreasing the amplified generation of thrombin, thus diminishing thrombin-mediated activation of both coagulation and platelets, without affecting existing thrombin levels. The sponsor states that the remaining thrombin should be sufficient to ensure primary hemostasis, resulting in a favorable efficacy to safety (bleeding) margin for rivaroxaban. The sponsor submits this NDA to support the use of rivaroxaban for the indication of prophylaxis of deep vein thrombosis (DVT) and pulmonary embolism (PE) in patients undergoing hip or knee replacement surgery.

Patients undergoing major orthopedic surgery, including total hip replacement (THR) and total knee replacement (TKR) surgeries, are a group that is at a particularly high risk for venous thromboembolism (VTE), which includes DVT and PE. Without prophylaxis, the incidence of objectively confirmed total DVT based on older studies is approximately 40 to 60% following THR or TKR, with a 10-30% incidence of proximal DVT. The most appropriate strategy to reduce the incidence of VTE is prophylaxis for all patients undergoing THR or TKR. Current therapeutic agents available for anticoagulant prophylaxis include low molecular weight heparins (LMWHs), fondaparinux, and adjusted-dose vitamin K antagonists such as warfarin. The duration of therapy is at least 10 days for both THR and TKR; for patients undergoing THR, extended prophylaxis to up to 35 days after surgery is recommended. LMWHs and fondaparinux are administered subcutaneously, which may be associated with pain and bruising as well as poor compliance. Warfarin is the only available oral anticoagulant for VTE prophylaxis after major orthopedic surgery in the U.S. However, warfarin has a narrow therapeutic window, exhibits variable dose response, has many dietary and medicinal interactions, requires dose adjustment, and has a slow onset of action. Rivaroxaban offers an alternative oral prophylactic therapy for VTE.

IND 64,892 for rivaroxaban was submitted on May 29, 2002 for the treatment and secondary prophylaxis of VTE by Bayer. All of the clinical trials submitted with the current NDA were conducted by Bayer. Approximately one month prior to the submission of this NDA, Bayer sold the rights of reference for use of the investigations to Johnson and Johnson. Johnson and Johnson submitted NDA 22-406 as the applicant on July 28, 2008. Of note, both Bayer and Johnson and Johnson submitted letters to the review division that the IND is now transferred to Johnson and Johnson.

During the conduct of the clinical studies for this NDA, complaints were received regarding two investigators enrolling subjects, one in RECORD 2 and one in RECORD 4. (b) (4)

Brief synopses of the protocols which the review division requested to be inspected are given below.

RECORD 1 Study: **Regulation of Coagulation in Orthopedic Surgery to prevent DVT and PE, controlled, double-blind, randomized study of BAY 59-7939 in the extended prevention of VTE in patients undergoing elective total hip replacement (Protocol 1134)**

RECORD 1 was a randomized, double-blind, double-dummy, active comparator controlled, multi-center and multi-national trial in patients undergoing elective THR conducted between February, (b) (4). Subjects were enrolled at 218 centers in 27 countries. The objective of the study was to assess the safety and efficacy of rivaroxaban 10 my once daily compared with once daily subcutaneously administered enoxaparin 40 mg in extended prevention of VTE in men and women aged 18 years or above undergoing elective THA. Administration of BAY 59-7939 or placebo started on the day of surgery (Day 1) 6 to 8 hours after wound closure and thereafter once daily until Day 35 (the day before venography). Enoxaparin 40 mg was administered once daily as a subcutaneous injection starting the evening prior to surgery. Subsequently, enoxaparin or placebo was administered on the day of surgery 6 to 8 hours after wound closure and thereafter once daily until Day 35. Subjects were evaluated at Day 0, 1, 7 (± 2 days), 13 (± 2 days), and 36 (± 4 days) with a follow-up visit at Day 65 (± 5 days). On Day 0 prior to surgery, a physical examination was performed, and medical history with demographics was recorded. Blood was sampled for clinical chemistry, hematology, and coagulation parameters. An ECG was performed, and a urine pregnancy test done for women of childbearing potential. On Day 1, blood samples for hematology and clinical chemistry were taken after surgery but before study medication, and a physical examination was performed. On Day 7, physical examination and blood sampling for hematology and coagulation parameter were performed. On Day 13, physical examination and

blood sampling for hematology and clinical chemistry were performed. On Day 36, blood samples for clinical chemistry, coagulation parameters, and hematology were taken, and bilateral venography was performed. Adverse events will be recorded at each visit. On Day 65, adverse events, signs and diagnosis of VTE, and cardiovascular and bleeding events during the 30 days after end of treatment will be recorded. Physical examinations were performed, and a blood sample for clinical chemistry was taken.

The primary efficacy endpoint was a composite endpoint of:

- Any DVT (proximal and/or distal)
- Non-fatal PE
- Death from all causes

The analysis of the primary efficacy endpoint was solely based on the assessments made by the Venography and VTE Adjudication Committee. Secondary efficacy endpoints were major VTE, incidence of DVT, incidence of symptomatic VTE, incidence of symptomatic VTE during follow-up, "net clinical benefit", incidence of the composite endpoint that results from the primary endpoint by substituting VTE-related death for all death, and incidence of the composite endpoint that results from major VTE by substituting all-cause mortality for VTE-related death. The main safety endpoint was the incidence of treatment-emergent major bleeding observed not later than 2 days after last intake of study drug. Major bleeding occurring after this period was considered separately. Also included as safety variables were treatment-emergent adverse events, serious adverse events, and deaths; adverse events starting more than 2 days after stop of treatment, adjudicated cardiovascular events, incidence of prolonged hospitalization, transfusion requirements, discontinuations due to adverse events, and laboratory parameters.

Brief Summary of Results

There were 4541 subjects randomized at 218 centers. Of these, 4433 subjects received study medication, and 3153 were valid for the modified intent to treat (MITT) analysis and 3029 were valid for the per-protocol (PP) analysis. In the PP analysis, 13/1537 (0.9%) subjects in the rivaroxaban arm met the primary efficacy endpoint and 50/1492 (3.4%) of subjects in the enoxaparin arm met the primary efficacy endpoint. These results demonstrated non-inferiority against enoxaparin using a non-inferiority margin of 3.5%. The results in the MITT population were similar, with the primary efficacy outcome reached by 18/1595 (1.1%) subjects in the rivaroxaban population and 58/1558 (3.7%) subjects in the enoxaparin population. This finding demonstrated statistical superiority (95% CI: -3.69%, -1.54%) of rivaroxaban over enoxaparin in preventing VTE. A total of 520 randomized subjects discontinued treatment prematurely (256 rivaroxaban subjects and 264 enoxaparin subjects). The most common reason for study withdrawal was withdrawal of consent: 121/ 2010 (5.3%) in the rivaroxaban arm and 115/2011 (5.1%) in the enoxaparin arm. The incidence of treatment-emergent major bleeding events was 0.3% in the rivaroxaban arm and <0.1% in the enoxaparin arm. There were no fatal bleeding events in either arm after start of study drug. There were 10 deaths in the study, 5 in each arm, and the incidence of treatment-emergent serious adverse events was similar between the 2 treatment groups (6.6% rivaroxaban, 8.1% enoxaparin).

RECORD 2 Study: **Regulation of Coagulation in Orthopedic Surgery to prevent DVT and PPE controlled, double-blind, randomized study of BAY- 59-7939 in the extended prevention of VTE in patients undergoing elective total hip replacement (Protocol 11357)**

RECORD 2 was a prospective, randomized, double-blind, double-dummy, active comparator controlled, multi-center and multi-national trial in patients undergoing elective THR conducted between (b) (4). Subjects were enrolled at 123 active centers in 21 countries. The objective of the study was to compare the safety and efficacy of VTE prophylaxis with rivaroxaban 10 my once daily administered for 5 weeks to enoxaparin 40 mg once daily administered for 10-14 days followed by placebo up to Day 35 in men and women aged 18 years or above undergoing elective THR. Administration of rivaroxaban or placebo started on the day of surgery (Day 1) at least 6 to 8 hours after wound closure and thereafter once daily every 24 $\pm$ 2 hours up to Day 35 $\pm$ 4 (the day before venography). All subjects in the rivaroxaban treatment group additionally received enoxaparin placebo subcutaneous injections once daily in the evening, starting on Day 0 and ending on Day 12 $\pm$ 2 (last dose). Enoxaparin 40 mg was administered once daily as a subcutaneous injection starting the evening prior to surgery (Day 0). Subsequently, enoxaparin or placebo was administered on the day of surgery 6 to 8 hours after wound closure and thereafter once daily until Day 12 $\pm$ 2. Additionally, all subjects in the enoxaparin group received rivaroxaban placebo tablets. The first rivaroxaban placebo tablet was taken on the day of surgery (Day 1), at least 6-8 hours after wound closure, and subsequently once daily every 24 $\pm$ 2 hours up to Day 35 $\pm$ 4. Subjects were evaluated at Day 0, 1, 7 ($\pm$ 2 days), 13 ($\pm$ 2 days), and 36 ($\pm$ 4 days) with a follow-up visit at Day 65 ($\pm$ 5 days). On Day 0 prior to surgery, a physical examination was performed, and medical history with demographics was recorded. Blood was sampled for clinical chemistry, hematology, and coagulation parameters. An ECG was performed, and a urine pregnancy test done for women of childbearing potential. On Day 1, blood samples for hematology and clinical chemistry were taken after surgery but before study medication, and a physical examination will be performed. On Day 7, physical examination and blood sampling for hematology and coagulation parameter were performed. On Day 13, physical examination and blood sampling for hematology and clinical chemistry were performed. On Day 36, blood samples for clinical chemistry, coagulation parameters, and hematology will be taken, and bilateral venography were performed. Adverse events will be recorded at each visit. On Day 65, adverse events, signs and diagnosis of VTE, and an assessment of cardiovascular and bleeding events during the 30 days after end of treatment were recorded. Physical examination will be performed, and a blood sample for clinical chemistry will be taken.
The primary efficacy endpoint was defined as a composite endpoint of:

- Any DVT (proximal and/or distal)
- Non-fatal PE
- Death from all causes

The analysis of the primary efficacy endpoint was solely based on the assessments made by the Independent Central Adjudication Committee and VTE Adjudication Committees. The major secondary endpoint was the incidence of the composite endpoint comprising proximal DT, non-fatal PE, and VTE-related death. Additional secondary efficacy endpoints were incidence of symptomatic VTE, incidence of symptomatic DVT (total, proximal, distal), incidence of symptomatic VTE during follow-up, incidence of PE, incidence of death, "net clinical benefit", incidence of the composite endpoint that results from the primary endpoint by substituting VTE-related death for all death, and incidence of the composite endpoint that results from major VTE by substituting all-cause mortality for VTE-related death. The main safety endpoint was the incidence of treatment-emergent major bleeding observed not later than 2 days after last intake of study drug. Major bleeding occurring after this period was considered separately. Also included as safety variables were treatment-emergent adverse events, serious adverse events, and deaths; adverse events starting after treatment initiation up to 2 days after last study treatment, adjudicated cardiovascular events, incidence of prolonged hospitalization, transfusion requirements, discontinuations due to adverse events, and laboratory parameters.

Brief Summary of Results

There were 2509 subjects randomized at 123 centers. Of these, 2457 subjects received study medication, and 1733 were valid for the MITT analysis and 1615 were valid for the PP analysis. In the PP analysis, 11/812 (1.4%) subjects in the rivaroxaban arm and 66/803 (8.2%) of subjects in the enoxaparin arm met the primary efficacy endpoint. The results in the MITT population were similar, with the primary efficacy outcome reached by 17/864 (2.0%) subjects in the rivaroxaban population and 81/869 (9.3%) subjects in the enoxaparin population. This finding demonstrated statistical superiority (95% CI: -9.41%, -5.15%) of rivaroxaban over enoxaparin in preventing VTE. A total of 300 randomized subjects discontinued treatment prematurely (135 rivaroxaban subjects and 165 enoxaparin subjects). The most common reason for study withdrawal was withdrawal of consent in the rivaroxaban arm 51/1252 (4.1%) and adverse events in the enoxaparin arm 54/1257 (4.3%). The incidence of treatment-emergent major bleeding events was very low in both treatment groups (one subject each; <0.1%). There were no fatal bleeding events in either arm after start of study drug. There were 10 deaths in the study, 2 in the rivaroxaban arm and 8 in the enoxaparin arm, and the incidence of treatment-emergent serious adverse events was slightly higher in the enoxaparin group (10.7%) than in the rivaroxaban group (7.3%).

RECORD 3 Study: Regulation of Coagulation in Orthopedic Surgery to prevent DVT and PE; a controlled, double-blind, randomized study of BAY 59-7939 in the prevention of VTE in patients undergoing elective total knee replacement (Protocol 11356)

RECORD 3 was a prospective, randomized, double-blind, double-dummy, parallel-group, active comparator controlled, multi-center and multi-national trial in patients undergoing elective TKR conducted between (b) (4). Subjects were enrolled at 147 active centers in 19 countries. The objective of the study was to assess the safety and efficacy of rivaroxaban 10 mg once daily for the prevention of VTE in male and female subjects aged 18 years or above undergoing elective TKA. Administration of rivaroxaban or placebo started on the day of surgery (Day 1) 6 to 8 hours after wound closure, and continued once daily until Day 12 $\pm$ 2 (the day before venography). Enoxaparin 40 mg or matching

placebo was administered once daily as a subcutaneous injection starting 12 hours prior to surgery (Day 0). Subsequently, enoxaparin or placebo was administered on the day of surgery at least 6 to 8 hours after wound closure and on subsequent evenings until the final evening dose administered on the evening of Day 12 ± 2. Subjects were evaluated at Day 0, 1, 7 (± 2 days), and 13 (± 2 days), with a follow-up visit at Day 42 (± 5 days). On Day 0 prior to surgery, a physical examination was performed, and medical history with demographics was recorded. Blood was sampled for clinical chemistry, hematology, and coagulation parameters. An ECG was performed. On Day 1, blood samples for hematology and clinical chemistry were taken after surgery but before study medication, and a physical examination was performed. On Day 7, physical examination and blood sampling for hematology, clinical chemistry, and coagulation parameters were performed. On Day 13, physical examination and blood sampling for hematology, clinical chemistry, and coagulation parameters were performed. On Day 42, adverse events, signs and diagnosis of DVT/PE were recorded. Physical examinations were performed, and a blood sample for clinical chemistry was taken.

The primary efficacy endpoint was defined as a composite endpoint of:

- Any DVT (proximal and/or distal)
- Non-fatal PE
- Death from all causes

The analysis of the primary efficacy endpoint was solely based on the assessments made by the Independent Central Adjudication Committee and VTE Adjudication Committees. The major secondary endpoint was the incidence of the composite endpoint comprising proximal DVT, non-fatal PE, and VTE-related death. Additional secondary efficacy endpoints were incidence of DVT (total, proximal, distal), incidence of symptomatic VTE (DVT, PE), incidence of symptomatic VTE during follow-up, "net clinical benefit" assessed by the composite endpoint comprising major VTE and treatment-emergent major bleeding, incidence of the composite endpoint that results from the primary endpoint by substituting VTE-related death for all death, and incidence of the composite endpoint that results from major VTE by substituting all-cause mortality for VTE-related death. The main safety endpoint was the incidence of treatment-emergent major bleeding observed no later than 2 days after last intake of study drug. Major bleeding observed after this period was considered separately. Also included as safety variables were treatment-emergent adverse events, serious adverse events, and deaths; adverse events starting after treatment initiation up to 2 days after last study treatment, adjudicated cardiovascular events, incidence of prolonged hospitalization, transfusion requirements, amount of intraoperative blood loss, postoperative volume of drainage, and laboratory parameters.

Brief Summary of Results

There were 2531 subjects randomized at 147 centers. Of these, 2459 subjects received study medication, and 1702 were valid for the MITT analysis and 1631 were valid for the PP analysis. In the PP analysis, 74/793 (9.3%) subjects in the rivaroxaban arm met the primary efficacy endpoint and 152/838 (18.1%) of subjects in the enoxaparin arm met the primary efficacy endpoint described by the sponsor as demonstrating noninferiority against enoxaparin, based on a noninferiority margin of 4%. The results in the MITT population were similar, with the primary efficacy outcome reached by 79/824 (9.6%) subjects in the rivaroxaban population

and 166/878 (18.9 %) subjects in the enoxaparin population, described by the sponsor as demonstrating superiority of rivaroxaban over enoxaparin in preventing VTE (95% CI: -12.40%, -5.89%). A total of 282 randomized subjects discontinued treatment prematurely (127 rivaroxaban subjects and 155 enoxaparin subjects). The most common reason for study withdrawal was withdrawal of consent in both arms: 68/ 1254 (5.4%) in the rivaroxaban arm and 60/1277 (4.7%) in the enoxaparin arm. The incidence of treatment-emergent major bleeding events was low in both treatment groups (0.6% in the rivaroxaban arm versus 0.5% in the enoxaparin arm). There were no fatal bleeding events reported in either group. There were 6 deaths in the study, all in the enoxaparin arm. The incidence of treatment-emergent serious adverse events was slightly lower in the enoxaparin group (7.4%) than in the rivaroxaban group (8.9%).

RECORD 4 Study: **Regulation of Coagulation in Orthopedic Surgery to prevent DVT and PE; a controlled, double-blind, randomized study of BAY 59-7939 (rivaroxaban) in the prevention of VTE in subjects undergoing elective total knee replacement (Protocol 11355)**

RECORD 4 was a prospective, randomized, double-blind, double-dummy, parallel-group, active comparator controlled, multi-center and multi-national trial in patients undergoing elective TKR conducted between (b) (4). Subjects were enrolled at 131 active centers in 12 countries. The objective of the study was to assess the safety and efficacy of rivaroxaban 10 mg once daily for the prevention of VTE in male and female subjects aged 18 years or above undergoing elective TKA. Administration of rivaroxaban or placebo started on the day of surgery (Day 1) 6 to 8 hours after wound closure, and continued once daily until Day 12 $\pm$ 2 (the day before venography). Enoxaparin 30 mg bid or matching placebo was administered twice daily as a subcutaneous injection starting 12-24 hours after wound closure. Thereafter, enoxaparin active or placebo was administered subcutaneously twice daily, once in the morning and once in the evening (every 12 $\pm$ 2 hours), until the final evening dose administered on the evening of Day 12 $\pm$ 2 (the day prior to venography). Subjects were evaluated at Day 0, 1, 6 ($\pm$ 2 days), and 13 ($\pm$ 2 days), with a follow-up visit at Day 42 ($\pm$ 5 days). On Day 0 prior to surgery, a physical examination was performed, and medical history with demographics was recorded. Blood was sampled for clinical chemistry, hematology, and coagulation parameters. An ECG was performed. On Day 1, blood samples for hematology and clinical chemistry were taken after surgery but before study medication, and a physical examination was performed. On Day 6, physical examination and blood sampling for hematology, clinical chemistry, and coagulation parameters were performed. On Day 13, physical examination and blood sampling for hematology, clinical chemistry, and coagulation parameters were performed. On Day 42, adverse events, signs and diagnosis of DVT/PE were recorded. Physical examinations were performed, and a blood sample for clinical chemistry was taken.

The primary efficacy endpoint was defined as a composite endpoint of:

- Any DVT (proximal and/or distal)
- Non-fatal PE
- Death from all causes

The analysis of the primary efficacy endpoint was solely based on the assessments made by the Independent Central Adjudication Committee and VTE Adjudication Committees. The major secondary endpoint was the incidence of the composite endpoint comprising proximal DVT, non-fatal PE, and VTE-related death. Additional secondary efficacy endpoints were incidence of DVT (total, proximal, distal), incidence of symptomatic VTE (DVT, PE), incidence of symptomatic VTE during follow-up, "net clinical benefit" assessed by the composite endpoint comprising major VTE and treatment-emergent major bleeding, incidence of the composite endpoint that results from the primary endpoint by substituting VTE-related death for all death, and incidence of the composite endpoint that results from major VTE by substituting all-cause mortality for VTE-related death. The main safety endpoint was the incidence of treatment-emergent major bleeding observed no later than 2 days after last intake of study drug. Major bleeding observed after this period was considered separately. Also included as safety variables were treatment-emergent adverse events, serious adverse events, and deaths; adverse events starting after treatment initiation up to 2 days after last study treatment, adjudicated cardiovascular events, incidence of prolonged hospitalization, transfusion requirements, amount of intraoperative blood loss, postoperative volume of drainage, and laboratory parameters. Other safety variables included the incidence of any treatment-emergent bleeding observed no later than 2 days after last intake of study drug, the incidence of non-major treatment–emergent bleeding observed no later than 2 days after last intake of study drug, incidence of postoperative bleeding, and incidence of surgical site bleeding associated with > 2 g/dL fall in hemoglobin or leading to infusion of > 2 units of whole blood or packed cells.

Brief Summary of Results

There were 3148 subjects randomized at 131 centers. Of these, 3034 subjects received study medication, and 1924 were valid for the MITT analysis and 1742 were valid for the PP analysis. In the PP analysis, 58/864 (6.7%) subjects in the rivaroxaban arm met the primary efficacy endpoint and 82/878 (9.3%) of subjects in the enoxaparin arm met the primary efficacy endpoint described by the sponsor as demonstrating noninferiority against enoxaparin, based on a noninferiority margin of 4%. The results in the MITT population were similar, with the primary efficacy outcome reached by 67/965 (6.9%) subjects in the rivaroxaban population and 97/959 (10.1%) subjects in the enoxaparin population, described by the sponsor as demonstrating superiority of rivaroxaban over enoxaparin in preventing VTE (95% CI: -5.67%, -0.71%). A total of 310 randomized subjects discontinued treatment prematurely (159 rivaroxaban subjects and 151 enoxaparin subjects). The most common reason for study withdrawal was adverse events in both arms: 62/ 1584 (3.9%) in the rivaroxaban arm and 56/1564 (3.6%) in the enoxaparin arm. The incidence of treatment-emergent major bleeding events was low in both treatment groups (0.7% in the rivaroxaban arm versus 0.3% in the enoxaparin arm). With regard to critical bleeding events, there was one retroperitoneal bleeding event (rivaroxaban), one intracranial bleed (enoxaparin), and one intraspinal/hemorrhagic puncture event (enoxaparin). There was one fatal bleeding event reported in the rivaroxaban treatment group. Twelve subjects died during the study, 6 in the rivaroxaban group and 6 in the enoxaparin group. The incidence of treatment-emergent serious adverse events was similar between the two groups: 5% in the rivaroxaban group and 7% in the enoxaparin group.

Rationale for Site Selection

Rivaroxaban is a new molecular entity which is an oral anticoagulant with the proposed indication of prophylaxis of VTE. The site selection is based on the review division's analysis of efficacy of rivaroxaban versus the comparator at individual sites. Sites which showed a greater efficacy of rivaroxaban in relation to comparator which had relatively high enrollment were chosen. Two sites for each of the pivotal studies were selected for inspection.

II. RESULTS (by Site):

Since the submission of the original Clinical Inspection Summary, the EIRs have been received for Andrzej Gorecki, Tadeusz Gazdzik, Qingming Yang, Cesar Valverde, and Jacek Kruczynski. Please see the Clinical Inspection Summary completed on March 16, 2009 for a full summary of these inspections. The information available and conclusions reached for these inspections is unchanged after review of the EIR. Pertinent new information is given below regarding the inspections of Bingfang Zeng, R. Michael Murray, David Fox, Bayer Pharmaceutical as the Sponsor/Monitor/CRO, and Johnson & Johnson as the applicant.

Name of CI, IRB, or Sponsor Location	Protocol # and # of Subjects	Inspection Date	Interim Classification	Final Classification
Andrzej Gorecki Szpital Kliniczny Dzieciatka Jezus – Centrum Leczenia Obrazen Klinika Ortopedii i Traumatologii Narzadu Ruchu ul. Lindleya 4 02-005 Warszawa, POLAND	Protocol # 11354, RECORD 1 Site # Poland 18006 # of subjects (Total# 71): Xarelto: 36 Enoxaparin: 35	(b) (4)	NAI	NAI
Tadeusz Gazdzik Slaska Akademia Medyczna Katedra I Oddzial Kliniczny Ortopedii Wojewodzki Szpital Specjalistyczny Nr 5 im. Sw. Barbaby Pl. Medykow 1 41-200 Sosnowiec, POLAND	Protocol # 11354, RECORD 1 Site # Poland 18012 # of subjects (Total#: 76): Xarelto: 38 Enoxaparin: 38		NAI	Pending; preliminary NAI
Qingming Yang Rui Jin Hospital, Shanghai Second Medical Univeristy Orthorpaedic Department Shanghai Ryuijin Hospital No. 197 Ruijin Second Road Shanghai, CHINA 200025	Protocol # 11357, RECORD 2 Site # China 54005 # of subjects (Total# 34): Xarelto: 17 Enoxaparin: 17		OAI	Pending; preliminary OAI
Cesar Diaz Valverde Hospital Edgardo Rebagliati Martins Av. Edgardo Rebagliati Martins S/N JESUS MARIALima Lima, 11 PERU	Protocol # 11357, RECORD 2 Site # Peru 64005 # of subjects (Total# 41): Xarelto: 20 Enoxaparin: 21		VAI	Pending; preliminary VAI
Bingfang Zeng Affiliated Sixth People's Hospital Orthorpaedic Department No. 600 Yishan Road, Xuhui District Shanghai, CHINA 200233	Protocol # 11356, RECORD 3 Site # China 54014 # of subjects (Total# 26): Xarelto: 13 Enoxaparin: 13		OAI	Pending; preliminary VAI-r requested
Jacek Kruczynski Szpital Uniwersytecki im. Antoniego Jurasze Klinika Ortopedii i Traumatologii Narzadu Ruchu ul. M. Sklodowskiej-Curie 9 85-094, Bydgoszcz POLAND	Protocol # 11356, RECORD 3 Site # Poland 18003 # of subjects (Total# 36): Xarelto: 18 Enoxaparin: 18		VAI	Pending; preliminary VAI
R. Michael Murray Capstone Clinical Research 2018 Brookwood Medical Center	Protocol # 11355, RECORD 4 Site # 14005		OAI	Pending; preliminary OAI

		(b) (4)		
Suite 314 Birmingham, AL 35209	# of subjects (Total # 152) Xarelto: 76 Enoxaprin: 76			
David Fox Unlimited Research, LP 12709 Toepperwein Road Suite 101 San Antonio, TX 78233	Protocol #11355, Record 4 Site #14022 # of subjects (Total # 64) Xarelto: 32 Enoxaparin: 32		VAI	Pending; preliminary VAI
Bayer Pharmaceutical 340 Change Bridge Rd. Pine Brook, NJ 07058	Protocol # 11354, RECORD 1 Protocol # 11357, RECORD 2 Protocol # 11356, RECORD 3 Protocol #11355, Record 4		Pending	Pending
Johnson & Johnson 920 U.S. Highway 202 Raritan, NJ 08869-0602			NAI	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. Bingfang Zeng
Affiliated Sixth People's Hospital
Orthorpaedic Department
No. 600 Yishan Road,
Xuhui District
Shanghai, CHINA 200233

a. What was inspected: The inspection was conducted in accordance with Compliance Program 7348.811. There were 26 subjects enrolled at the site. There were 23 subjects who completed the study. The observations noted are based on preliminary communications with the FDA field investigator, the Form FDA 483, Dr. Zeng's written response to the Form FDA 483, and the EIR. There were no limitations to the inspection.

b. General observations/commentary: Several deviations from FDA regulations were noted, and a Form FDA 483 was issued for these violations. The inspection documented that the investigator did not adhere to the investigational plan, in violation of 21 CFR 312.60 and did not promptly report to the sponsor adverse effects that may reasonably be regarded as caused by or probably

caused by, a investigational drug, in violation of 21 CFR 312.64. A response from Dr. Zeng to the Form FDA 483 observations dated March 12, 2009 was received. Dr. Zeng adequately addressed the issue of prohibited concomitant medications (see Protocol Violations, item 1 below). However, the remainder of the letter provided explanations for the inspector's observations rather than contradicting the deficiencies noted on the Form FDA 483.

Protocol Violations [21 CFR 312.60]

1. Two subjects were administered prohibited concomitant medications while enrolled in the clinical trial. Subjects 54014-6001 (b) (6) and 54014-6014 (b) (6) were treated with Salvia Miltiorrhiza (a platelet inhibitor) from Day 7 to Day 13 and on Day 2, respectively.

   Medical Officer's Comment: In a response letter dated March 12, 2009, Dr. Zeng responded that during the study, a sponsor medical expert stated that antiplatelet drugs were allowable during the study, although anticoagulants were not. Section 4.5.7 of the RECORD 3 protocol states that subjects on anticoagulants which cannot be stopped should be excluded; no mention is made of subjects on antiplatelet agents. Therefore this citation is not valid.

2. Subject 54014-6001 was treated with Aescuven Forte which was not listed on the concomitant drug list (eCRF).

Adverse Event Reporting [21 CFR 312.64]

1. Two subjects did not have SAEs reported within 24 hours of the investigator's awareness of the event.
   i. Subject 54014-6007 was diagnosed with a DVT in the right leg on June 27, 2006. This SAE was not reported to the Sponsor until March 2, 2007 and the IRB/EC until March 19, 2007.
   ii. Subject 54014-6014 (b) (6) was diagnosed with a DVT in the right calf on October 6, 2006. The SAE was not reported to the Sponsor and the IRB/EC until October 11, 2006.
2. Multiple subjects did not have adverse events reported to the sponsor, although the concomitant medications they received for these conditions were recorded. These include Subject 54014- 6001 (b) (6) – swelling and decreased albumin levels; Subject 54014-6006 (b) (6) – swelling at the incision site; Subject 54014-6009 (b) (6) – phlegm/sputum production; Subject 54014-6012 (b) (6) – insomnia, Subject 54014-6013 (b) (6) – constipation and phlegm; and Subject 54014-6020 (b) (6) – "dephlogisticate", fever, and wound swelling. The following subjects had unreported adverse events which are potentially of greater significance: Subject 54014-6014 (b) (6) – trophic nerve on two occasions and blood vessel constriction; Subject 54014-6015 (b) (6) – chest stress and phlegm; Subject 54014-6018 – fever and decrease in hemoglobin; and Subject 54014-6023 (b) (6) – stomach pain.

   Medical Officer's Comment: Dr. Zeng's response letter of May 12, 2009 states that these adverse events were not reported either because they were considered to be" normal for a subject post orthopedic surgery" or because they forgot. Although

some of these events may be a not unexpected consequence of surgery, they must still be reported as an adverse event.

c. Assessment of data integrity: The deviations listed above were communicated in the original CIS dated March 16, 2009. As before, DSI regards the efficacy data as acceptable in support of the NDA. In addition, most safety data appears to have been reported appropriately. Although there were two SAEs for which reporting was delayed, they were eventually reported and should be contained in the NDA data base. There was significant underreporting of non-serious adverse events at this site. There were 10 patients with unreported adverse events (listed above) of the 26 enrolled; at least 4 of these subjects had adverse events that are potentially clinically significant. DSI recommends that the review division take into consideration the underreporting of AEs in evaluation of safety.

2.. R. Michael Murray
Capstone Clinical Research
2018 Brookwood Medical Center
Suite 314
Birmingham, AL 35209

a. What was inspected: The inspection was conducted in accordance with Compliance Program 7348.811. There were 178 subjects who signed informed consent at the site, and 153 were randomized. The EIR became available since the original Clinical Inspection Summary was generated. The observations noted are based on preliminary communications with the FDA field investigator, the Form FDA 483, and Dr. Murray's written response dated March 31, 2009, and the EIR. There were no limitations to the inspection.

b. General observations/commentary: The inspection documented that the investigator did not prepare and maintain adequate and accurate case histories with respect to observations and data pertinent to the investigation, in violation of 21 CFR 312.62(b), and did not adhere to the investigational plan, in violation of 21 CFR 312.60. A response from Dr. Murray to the Form FDA 483 observations dated March 31, 2009 was received. The letter provided explanations for some of the inspector's observations; however, information to contradict the deficiencies noted on the Form FDA 483 was not presented.

<u>Recordkeeping Violations</u> [21 CFR 312.62(b)]

1. Subject 5117 experienced an elevated lipase. Site email dated 7/2/07 from Capstone Clinical Trials, Inc. President/CEO to the monitor reported that the subject "was receiving rivaroxaban in the Bayer 11355 trial". The inspector's review of the study records failed to reveal how the site became aware of the Subject's blinded treatment assignment. No documentation was observed of sponsor or site emergency unblinding of this subject.
2. The site lacked documentation of IRB approval of the following:

i. The performance of study screen visits at locations outside of routine clinical settings and not listed on the Form FDA 1572. For example screening visits including physical exams, ECGs, blood draws, etc. were conducted in subjects' homes and hotel rooms.
ii. The performance of post-enrollment study visits that included physical exams and administration of the test article at sites not listed on the Form FDA 1572 not under the PI's supervision. Subjects were sometimes moved to an inpatient rehabilitation facility together with the test article where it was dispensed and administered by the rehab center staff who had not received training on the protocol or GCP. Study visits were also conducted at subject's homes after the subjects had been discharged from the hospital, including the article administration, physical exams, and blood draws. These alternate sites included the site's (b) (4), the subject's place of employment, and an outpatient physical therapy center.
iii. Payment/reimbursement of subjects' hotel stays, mileage, and transportation costs like cab fares, despite the IRB-approved informed consent which states "the maximum total possible payment is $250.00". The consent document does not mention additional services/reimbursement.

3. The site lacked documentation that the Final Report/notice of study closure was submitted to the IRB (or that the Board acknowledged receipt of the final report/study closure). A copy of the site's computer version of the Final Report dated 4/24/08 that is unsigned/unofficial was provided during the inspection; however, there is no documentation that this report was submitted to the board.
4. The most recent status report submitted to the IRB was the Annual Review Report dated 6/26/07 and signed by the PI states in Item #8 that the site is currently enrolling patients in this study. In Item #9 it states that "this study is closed to further enrollment". In addition, the following statement was included: ". . . as this study is no longer open to enrollment. No further subjects will be consented.". According to the site enrollment logs, subjects were enrolled/randomized through 10/9/07.
5. The site Signature Sheet and Delegation of Duties Log is inaccurate in that the Log does not reflect the performance of physical exams by the Physician Assistants (who routinely conducted physical exams throughout the study). At least one physical exam was performed by an RN/study coordinator per source records. RNs are not licensed to conduct physical exams in the state of Alabama.

<u>Protocol Violations [21 CFR 312.60]</u>

1. Subjects were randomized post-surgery rather than prior to surgery. According to the protocol, randomization was to take place following screening on Day 0 or prior to surgery on Day 1.

c. Assessment of data integrity: Protocol and recordkeeping violations occurred at this site, which were described in the original Clinical Inspection Summary. Review of the EIR and Dr. Murray's written response to the Form FDA 483 revealed that the post-operative randomization described above occurred in all subjects reviewed except one. This is in spite of the fact that (b) (4) the CRO monitoring RECORD 4 sent an email to all sites reiterating the protocol requirement that subjects be randomized prior to surgery. It was stated that investigator permission to randomize was given after the patient stopped oozing at the surgical wound site. Although this randomization error would occur in both arms, it has the potential to alter the population studied at this site – i.e. the population included in the Xarelto product label after approval may not reflect the population actually studied. DSI recommends that the efficacy data from this site not be used in support of the NDA. The review division should take into consideration the effect of post-surgical randomization in their safety analysis, as this would impact absolute safety risk assessment, compared to relative safety risk assessments.

3. **David Fox**
Unlimited Research, LP
12709 Toepperwein Road
Suite 101
San Antonio, TX 78233

a. What was inspected: The inspection was conducted in accordance with Compliance Program 7348.811. There were 72 subjects screened at the site, and 64 were enrolled. There were 60 patients who completed the study. During the inspection, 23 subject records were reviewed, and all 72 informed consent documents were reviewed. The EIR became available since the original Clinical Inspection Summary was generated. The observations noted are based on preliminary communications with the FDA field investigator, the Form FDA 483, Dr. Fox's written response, and the EIR. There were no limitations to the inspection.

b. General observations/commentary: The inspection documented that the investigator did not obtain informed consent in accordance with 21 CFR 50 from each human subject prior to drug administration and that the investigator did not adhere to the investigational plan, in violation of 21 CFR 312.60. A written response to the observations contained in Form FDA 483 from Dr. Fox dated April 23, 2009 was received. The letter provided explanations for some of the inspector's observations; however, information to contradict the deficiencies noted on the Form FDA 483 was not presented.

<u>Informed Consent Violations</u> [21 CFR 50]

1. The CI failed to obtain informed consent from each human subject prior to drug administration and conducting study related tests.
    i. Subjects 5070 signed an informed consent document on September 13, 2007 that had expired on September 12, 2007, and did not sign the next approved

version.

ii. Subject 5071 signed an informed consent document on September 19, 2007 that had expired on September 12, 2007. This subject then signed the next approved version of the consent form on September 25, 2007.

2. The CI failed to have Subjects 5046, 5047, 5049, 5066, and 5068 sign a new version of the informed consent document after the original signed informed consent document is superseded.

Protocol Violations [21 CFR 312.62(b)]

1. According to the protocol, on Day 0 (the day prior to surgery), the subject will be randomized if eligible for the study. All 23 subjects reviewed were randomized on Day 1 instead of Day 0.

   Medical Officer's Comment: Dr. Fox's written response dated April 27, 2009 states that all subjects were randomized on Day 1, but prior to surgery.

2. According to the protocol, on Day 6 $\pm$ 2, blood sampling for hematology, clinical chemistry, and coagulation parameters was to be done for all subjects. Subject 5003 and 5010 did not have their coagulation parameters drawn in the correct timeframe.
3. The visit for Study Day 42 was conducted out of the visit window (Day 42 $\pm$ 5) for the following subjects: Subject 5003 – 3 days out of window; Subject 5010 – 2 days out of window; Subject 5011 - 2 days out of window; Subject 5018 – 2 days out of window; Subject 5024 – 3 days out of window; Subject 5025 – 2 days out of window; Subject 5041 – 2 days out of window; and Subject 5060 – 4 days out of window.
4. There were no Protocol Deviation Reports submitted to the IRB for any of the violations described in Parts 1-3 above.

c. Assessment of data integrity: Several informed consent and recordkeeping violations occurred at this site. The Form FDA 483 cited the violation of randomization of subjects on Day 1 rather than Day 0. Randomization on Day 1 is permitted according to protocol as long as randomization occurs prior to surgery. In his written response, Dr. Fox states that all subjects were randomized postoperatively. Subject safety was not affected. Although informed consent and protocol violations occurred at this site, it is unlikely that these errors will impact the final outcome of the study. The data appear acceptable in support of the NDA.

4. **Sponsor/Monitor/CRO**
   Bayer Pharmaceutical
   340 Change Bridge Rd.
   Pine Brook, NJ 07058

a. **What was inspected**: The FDA investigator reviewed Bayer procedures and records for protocols RECORD 1, 2, 3, and 4. The inspection began on February 24, 2009 and was concluded on March 31, 2009. The EIR was not available at the time this CIS Addendum was written. The observations noted are based on preliminary communications with the FDA field investigator and

Bayer's written response dated April 13, 2009. A second inspection summary addendum will be generated if conclusions change after receipt and review of the final EIR.

b. **General observations/commentary:** Several deviations from FDA regulations were noted, and a Form FDA 483 was issued for these violations. The investigation documented that the sponsor failed to ensure proper monitoring of the study, ensure that the study is conducted in accordance with the protocol and/or investigational plan, and ensure that FDA and all investigators are promptly informed of significant new adverse effects or risks. In Bayer's written response dated April 13, 2009, explanations for some of the inspector**'s** observations were provided; however, no information to contradict the deficiencies noted on the Form FDA 483 were presented.

1. Of the 42 Close Out Visit Reports for RECORD 4 reviewed, 18 were not properly closed out as numerous unresolved "Pending Issues" were reported at these sites during the closeout visit. There were no additional follow-up close out reports from (b) (4) or from Bayer to verify that these issues were resolved. These included Sites 14058, 14054, 14016, 14015, 14012, 14010, 14004, 14002, 26001, 18009, 18011, 18003, 18004, 18005, 18002, 32006, 26020, and 26019. Two additional sites enrolling in RECORD 1 did not have appropriately completed "Close out Visit Reports": Sites 24011 and 24015.

   Medical Officer's Comment: In the sponsor's response letter of April 13, 2009, Bayer states that in "the majority of cases", the pending items were resolved after the close out visit, and that the respective documentation is available as part of the Trial Master File. It is unclear why this information was not provided to the inspector at the time of the inspection.

2. Of the 42 sites reviewed for Periodic Monitoring Visit Reports for RECORD 3, 11 reports were not completed within an adequate timeframe to ensure adequate monitoring. Additionally, there is no documentation to indicate that these reports were reviewed in a timely manner for Sites 37003, 50010, 24010, 24003, 24002, 24004, 24005, 24006, 24008, 24010, and 37102.
3. The sponsor failed to document site specific issues such as protocol deviations/violations affecting the conduct of the clinical trial in the Periodic Site Monitoring Visit Reports and to ensure that the clinical trial was conducted in a accordance with the protocol for Site Numbers 14005 (RECORD 4), 14010 (RECORD 2), and 32006 (RECORD 4).
4. The sponsor failed to conduct monitoring visits at the frequency specified in the monitoring plan for Site 14001 and Site 26007 for RECORD 4.
5. The sponsor failed to submit the following expedited reports as required by their monitoring plan: Case 200811335 (b) (6) in RECORD 4.
6. The Periodic Site Monitoring Visit Report Number 9 for Site 14001 (RECORD 4) was not maintained and could not be located.

c. **Assessment of data integrity:** The data collected and maintained at the sponsor's site, as it pertains to the eight clinical sites audited in accordance with the sponsor-monitor oriented BIMO compliance program CP 7348. 810 demonstrate that the sponsor failed to exercise adequate oversight over the investigator sites enrolling in the four RECORD studies submitted in support of the NDA. It is unclear at present what effect this deficiency will have on data integrity.

5. **Applicant**
Johnson & Johnson
920 U.S. Highway 202
Raritan, NJ 08869-0602

a.What was inspected: The FDA inspection covered verification and definition of extent of information transmission, totality of documentation, and verification that all elements necessary to support the NDA were provided by Bayer Pharmaceuticals to Johnson & Johnson. The sponsor inspection occurred on March 24, 2009, and there were telephone conferences between the FDA inspectors and Johnson & Johnson (J&J) representatives on 3/26, 3/28, and 3/30/09. The observations noted are based on preliminary communications with the FDA field investigator and the EIR.

b. General observations/commentary: During the initial visit, J&J described a collaborative oversight arrangement between Bayer and J&J regarding the rivaroxaban clinical development program; this agreement was signed in 2005. During this time period, Bayer was performing all oversight functions, and informing J&J of any major issues or concerns. J&J stated that they were aware of the issues regarding (b) (4) Dr. Ricardo Esquivel, and (b) (4). The routine global audits conducted by Bayer were described and were to include a target of auditing at least 10% of active sites. The inspectors reviewed the Standard Operating Procedures for Study Auditing as well as Audit Tracker reports for studies RECORD 1, 2, 3, and 4. The inspectors' opinion at the conclusion of the inspection was that accurate transmission of relevant information and collaborative communication pertaining to the NDA between Bayer and J&J had occurred.

During the three subsequent teleconferences, the inspectors continued to query J&J regarding the issue of how they assured themselves of the data integrity of the studies submitted with the NDA. J&J continued to reiterate the collaborative nature of the interaction between Bayer and J&J, and also noted that Bayer was solely responsible for maintaining the IND for rivaroxaban and preparing and submitting the NDA until July 18, 2008. Ownership of the IND and NDA was assigned and transferred to J&J as of July 18, 2008. Based on this information, J&J stated that Bayer, by contract, had overall responsibility for all decisions made during the course of the trial, although J&J was informed and provided insight. J&J stated that they actively reviewed the

RECORD 1, 2, 3, and 4 studies prior to NDA submission, and did not identify issues or questionable data that warranted concern for data integrity. J&J wrote the NDA submission documents, including the clinical summary sections. J&J stated that they were informed of the findings at Dr. (b) (4) Esquivel in January, 2008; they were informed about Dr. (b) (4) later during review of the clinical study report.

No FDA Form 483 was issued.

Medical Officer's Comment: Extensive discussion noccurred during the inspection regarding the method by which J&J was able to assure themselves that the data submitted in support of the Xarelto NDA were sound, despite the earlier findings at three clinical sites of issues with data integrity. In addition, J&J was presented with information regarding BIMO inspections conducted during the NDA review which demonstrated protocol violations and deficiencies in adverse event reporting which were not reported by the sponsor's monitoring procedures. Although it is correct that Bayer was responsible for data integrity during the conduct of the RECORD studies, it is also correct that J&J is fully responsible for data integrity in the same studies now submitted in support of the NDA. Although J&J reports that no signal was apparent during the writing of the clinical sections of the NDA, the EIR includes no specific action takens by J&J to independently audit sites which enrolled in the RECORD studies in order to assure themselves that there were not more widely occurring problems similar to those found at the (b) (4), Esquivel, and (b) (4) sites.

c. Assessment of data integrity: It appears that there was accurate transmission of relevant information and collaborative communication between Bayer and J&J based on their inspectional findings. However, there is no evidence presented that J&J undertook any specific activities between acquisition and submission of the NDA in order to assure that there were no data integrity issues with the pivotal RECORD studies, similar to those described earlier at three clinical sites. In addition, there is no evidence that the adequacy of study monitoring by Bayer was independently verified by J&J prior to NDA submission.

IV. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

In general, inspection of the sites of Drs. Gorecki, Gazdzik, and Kracznski revealed that they adhered to the applicable regulations and good clinical practices governing the conduct of clinical investigations. The inspection of documents supports that audited subjects exist, met eligibility criteria, received assigned study medication, adhered to protocol, and signed informed consent documents. The inspections documented minor regulatory violations at the site of Dr. Kracznski regarding protocol violations and the site of Dr. Fox regarding both informed consent and protocol violations. In general, the studies at these four sites appear to have been conducted adequately, and the data generated by these sites may be used in support of the indication.

The inspection of Dr. Valverde's and Dr. Zeng's site raise concern regarding underreporting of adverse events. Although neither site appears to have failed to report serious adverse events, the number of unreported adverse events is significant. The data from these sites appear

acceptable for use in the NDA; however, the review division should take into consideration the specific information provided above in analysis of safety.

The findings of the inspection of Dr. Yang's site are of concern. The inspector describes an instance of apparent falsification of a subject visit by a sub-investigator, which was reportedly detected later by a second investigator. However, there was no investigation into the circumstances of the falsification incident, and the sub-investigator was allowed to continue to administer the study. In addition, the affidavit provided by the second subinvestigator at the time of the inspection and the response letter from the PI give two different versions of this event. Lastly, there is no evidence that this discrepancy was detected by the study monitor. There were four instances of unreported anemia requiring transfusion and two unreported instances of elevated liver function tests from this site. It is possible that the anemia requiring transfusions was reported as the safety variable "Bleeding event"; however, these should also have been recorded as adverse events. DSI recommends that data from this site be regarded as unreliable.

Inspection of Dr. Murray's site raised concern regarding improprieties in randomization. At this site, most subjects were randomized after surgery, rather than on Day 0 or 1 preoperatively, as required by the protocol. Although this randomization error would occur in both arms, it has the potential to alter the population studied at this site – i.e. the population included in the Xarelto product label after approval may not reflect the population actually studied. Dr. Murray's site was the second largest enroller in RECORD 4. The highest enroller (Dr. Ward) is also located in Birmingham, Alabama, and is part of the same SMO as Capstone Clinical Research (Dr. Murray), although the names differ. Therefore, DSI is inspecting Dr. Ward's site, as well as a third site under this SMO umbrella in Tuscaloosa. The results of these inspections, as well as an inspection of the site of the third highest enroller in RECORD 4 are not available at the time of this Clinical Inspection Summary Addendum.

The data collected and maintained at the sponsor's site, as it pertains to the eight clinical sites audited in accordance with the sponsor-monitor oriented BIMO compliance program CP 7348. 810 demonstrate that the sponsor failed to ensure proper monitoring of the study, ensure that the study is conducted in accordance with the protocol and/or investigational plan, and ensure that FDA and all investigators are promptly informed of significant new adverse effects**.** It is concerning that no specific procedures were implemented by J&J after acquisition of the rights to rivaroxaban to ensure the integrity of the data submitted in support of the NDA. Based on the results of the sponsor and applicant inspections as well as the results of the Clinical Investigator inspections, DSI is concerned that the sponsor failed to exercise adequate oversight over the investigator sites enrolling in the four RECORD studies submitted in support of the NDA.

Follow-Up Actions: We recommend that the applicant provide further information regarding Bayer's QA audit program, describe in detail Bayer's interactions with the oversight of contract research organizations hired by Bayer to monitor the clinical sites, and perform additional audits of clinical sites that enrolled subjects in the RECORD studies. These measures are necessary to assure the integrity of the data submitted in support of NDA 22-406

for the use of Xarelto in the indication of prophylaxis of deep vein thrombosis and pulmonary embolism in patients undergoing hip or knee replacement surgery.

{See appended electronic signature page}

Susan D. Thompson, M.D.
Good Clinical Practice Branch II
Division of Scientific Investigations

CONCURRENCE:

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Tejashri Purohit-Sheth, M.D.
Branch Chief, Good Clinical Practices 2
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/s/

Susan Thompson
5/15/2009 02:01:09 PM
MEDICAL OFFICER

Tejashri Purohit-Sheth
5/25/2009 11:15:25 PM
MEDICAL OFFICER

M E M O R A N D U M

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

CLINICAL INSPECTION SUMMARY

DATE: March 16, 2009

TO: Marcus Cato, Regulatory Project Manager
Min Lu, Medical Officer
Division of Medical Imaging and Hematology Products

FROM: Susan D. Thompson, M.D.
Good Clinical Practice Branch 2
Division of Scientific Investigations

THROUGH: Joseph Salewski
Deputy Division Director
Division of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections.

NDA: 22-406

APPLICANT: Johnson & Johnson

DRUG: Xarelto (rivaroxaban)

NME: Yes

THERAPEUTIC CLASSIFICATION: Standard Review

INDICATIONS: 1. Prophylaxis of deep vein thrombosis and pulmonary embolism in patients undergoing hip or knee replacement surgery

CONSULTATION REQUEST DATE: April 28, 2009

DIVISION ACTION GOAL DATE: May 28, 2009

PDUFA DATE: May 28, 2009

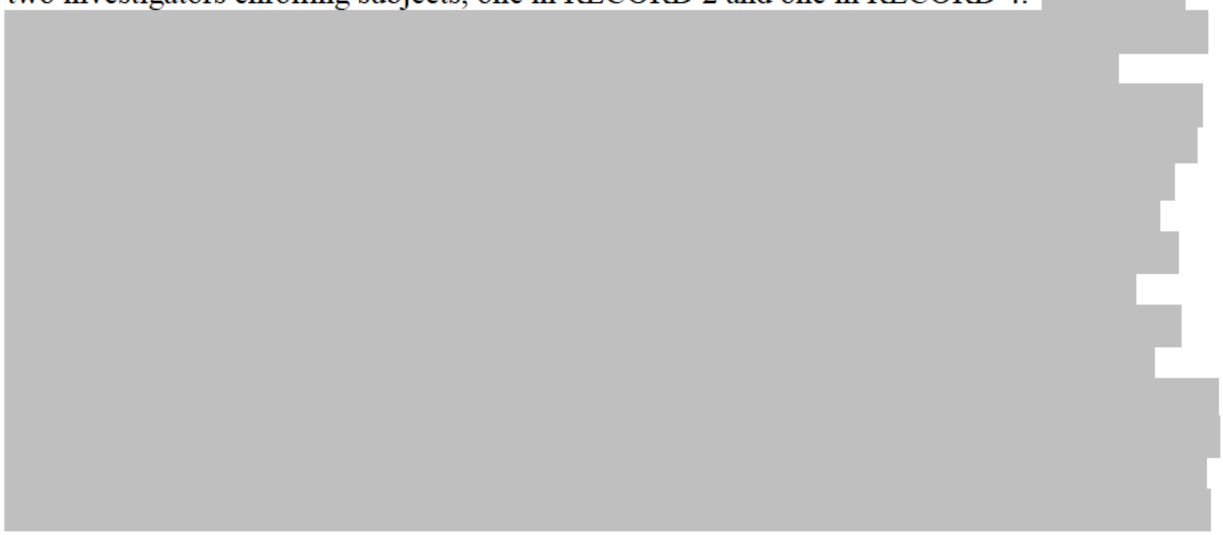
I. BACKGROUND:

Rivaroxaban is a highly selective direct factor Xa (FXa) inhibitor for oral administration. Inhibition of FXa produces antithrombotic effects by decreasing the amplified generation of thrombin, thus diminishing thrombin-mediated activation of both coagulation and platelets,

without affecting existing thrombin levels. The sponsor states that the remaining thrombin should be sufficient to ensure primary hemostasis, resulting in a favorable efficacy to safety (bleeding) margin for rivaroxaban. The sponsor submits this NDA to support the use of rivaroxaban for the indication of prophylaxis of deep vein thrombosis (DVT) and pulmonary embolism (PE) in patients undergoing hip or knee replacement surgery.
Patients undergoing major orthopedic surgery, including total hip replacement (THR) and total knee replacement (TKR) surgeries, are a group that is at a particularly high risk for venous thromboembolism (VTE), which includes DVT and PE. Without prophylaxis, the incidence of objectively confirmed total DVT based on older studies is approximately 40 to 60% following THR or TKR, with a 10-30% incidence of proximal DVT. The most appropriate strategy to reduce the incidence of VTE is prophylaxis for all patients undergoing THR or TKR. Current therapeutic agents available for anticoagulant prophylaxis include low molecular weight heparins (LMWHs), fondaparinux, and adjusted-dose vitamin K antagonists such as warfarin. The duration of therapy is at least 10 days for both THR and TKR; for patients undergoing THR, extended prophylaxis to up to 35 days after surgery is recommended. LMWHs and fondaparinux are administered subcutaneously, which may be associated with pain and bruising as well as poor compliance. Warfarin is the only available oral anticoagulant for VTE prophylaxis after major orthopedic surgery in the U.S. However, warfarin has a narrow therapeutic window, exhibits variable dose response, has many dietary and medicinal interactions, requires dose adjustment, and has a slow onset of action. Rivaroxaban offers an alternative oral prophylactic therapy for VTE.

IND 64,892 for rivaroxaban was submitted on May 29, 2002 for the treatment and secondary prophylaxis of VTE by Bayer. All of the clinical trials submitted with the current NDA were conducted by Bayer. Approximately one month prior to the submission of this NDA, Bayer sold the rights of reference for use of the investigations to Johnson and Johnson. Johnson and Johnson submitted NDA 22-406 as the applicant on July 28, 2008. Of note, both Bayer and Johnson and Johnson submitted letters to the review division that the IND is now transferred to Johnson and Johnson.

During the conduct of the clinical studies for this NDA, complaints were received regarding two investigators enrolling subjects, one in RECORD 2 and one in RECORD 4. (b) (4)



[redacted] (b) (4)

Brief synopses of the protocols which the review division requested to be inspected are given below.

RECORD 1 Study: **Regulation of Coagulation in Orthopedic Surgery to prevent DVT and PE, controlled, double-blind, randomized study of BAY 59-7939 in the extended prevention of VTE in patients undergoing elective total hip replacement (Protocol 1134)**

RECORD 1 was a randomized, double-blind, double-dummy, active comparator controlled, multi-center and multi-national trial in patients undergoing elective THR conducted between [redacted] (b) (4) Subjects were enrolled at 218 centers in 27 countries. The objective of the study was to assess the safety and efficacy of rivaroxaban 10 my once daily compared with once daily subcutaneously administered enoxaparin 40 mg in extended prevention of VTE in men and women aged 18 years or above undergoing elective THA. Administration of BAY 59-7939 or placebo started on the day of surgery (Day 1) 6 to 8 hours after wound closure and thereafter once daily until Day 35 (the day before venography). Enoxaparin 40 mg was administered once daily as a subcutaneous injection starting the evening prior to surgery. Subsequently, enoxaparin or placebo was administered on the day of surgery 6 to 8 hours after wound closure and thereafter once daily until Day 35. Subjects were evaluated at Day 0, 1, 7 (± 2 days), 13 (± 2 days), and 36 (± 4 days) with a follow-up visit at Day 65 (± 5 days). On Day 0 prior to surgery, a physical examination was performed, and medical history with demographics was recorded. Blood was sampled for clinical chemistry, hematology, and coagulation parameters. An ECG was performed, and a urine pregnancy test done for women of childbearing potential. On Day 1, blood samples for hematology and clinical chemistry were taken after surgery but before study medication, and a physical examination was performed. On Day 7, physical examination and blood sampling for hematology and coagulation parameter were performed. On Day 13, physical examination and blood sampling for hematology and clinical chemistry were performed. On Day 36, blood samples for clinical chemistry, coagulation parameters, and hematology were taken, and bilateral venography was performed. Adverse events will be recorded at each visit. On Day 65, adverse events, signs and diagnosis of VTE, and cardiovascular and bleeding events during the 30 days after end of treatment will be recorded. Physical examinations were performed, and a blood sample for clinical chemistry was taken.
The primary efficacy endpoint was a composite endpoint of:

- Any DVT (proximal and/or distal)
- Non-fatal PE
- Death from all causes

The analysis of the primary efficacy endpoint was solely based on the assessments made by the Venography and VTE Adjudication Committee. Secondary efficacy endpoints were major VTE, incidence of DVT, incidence of symptomatic VTE, incidence of symptomatic VTE during follow-up, "net clinical benefit", incidence of the composite endpoint that results from the primary endpoint by substituting VTE-related death for all death, and incidence of the composite endpoint that results from major VTE by substituting all-cause mortality for VTE-related death. The main safety endpoint was the incidence of treatment-emergent major bleeding observed not later than 2 days after last intake of study drug. Major bleeding occurring after this period was considered separately. Also included as safety variables were treatment-emergent adverse events, serious adverse events, and deaths; adverse events starting more than 2 days after stop of treatment, adjudicated cardiovascular events, incidence of prolonged hospitalization, transfusion requirements, discontinuations due to adverse events, and laboratory parameters.

Brief Summary of Results

There were 4541 subjects randomized at 218 centers. Of these, 4433 subjects received study medication, and 3153 were valid for the modified intent to treat (MITT) analysis and 3029 were valid for the per-protocol (PP) analysis. In the PP analysis, 13/1537 (0.9%) subjects in the rivaroxaban arm met the primary efficacy endpoint and 50/1492 (3.4%) of subjects in the enoxaparin arm met the primary efficacy endpoint. These results demonstrated non-inferiority against enoxaparin using a non-inferiority margin of 3.5%. The results in the MITT population were similar, with the primary efficacy outcome reached by 18/1595 (1.1%) subjects in the rivaroxaban population and 58/1558 (3.7%) subjects in the enoxaparin population. This finding demonstrated statistical superiority (95% CI: -3.69%, -1.54%) of rivaroxaban over enoxaparin in preventing VTE. A total of 520 randomized subjects discontinued treatment prematurely (256 rivaroxaban subjects and 264 enoxaparin subjects). The most common reason for study withdrawal was withdrawal of consent: 121/ 2010 (5.3%) in the rivaroxaban arm and 115/2011 (5.1%) in the enoxaparin arm. The incidence of treatment-emergent major bleeding events was 0.3% in the rivaroxaban arm and <0.1% in the enoxaparin arm. There were no fatal bleeding events in either arm after start of study drug. There were 10 deaths in the study, 5 in each arm, and the incidence of treatment-emergent serious adverse events was similar between the 2 treatment groups (6.6% rivaroxaban, 8.1% enoxaparin).

RECORD 2 Study: **Regulation of Coagulation in Orthopedic Surgery to prevent DVT and PPE controlled, double-blind, randomized study of BAY- 59-7939 in the extended prevention of VTE in patients undergoing elective total hip replacement (Protocol 11357)**

RECORD 2 was a prospective, randomized, double-blind, double-dummy, active comparator controlled, multi-center and multi-national trial in patients undergoing elective THR conducted between (b) (4). Subjects were enrolled at 123 active centers in 21 countries. The objective of the study was to compare the safety and efficacy of VTE prophylaxis with rivaroxaban 10 my once daily administered for 5 weeks to enoxaparin 40 mg

once daily administered for 10-14 days followed by placebo up to Day 35 in men and women aged 18 years or above undergoing elective THR. Administration of rivaroxaban or placebo started on the day of surgery (Day 1) at least 6 to 8 hours after wound closure and thereafter once daily every 24 ± 2 hours up to Day 35 ± 4 (the day before venography). All subjects in the rivaroxaban treatment group additionally received enoxaparin placebo subcutaneous injections once daily in the evening, starting on Day 0 and ending on Day 12 ± 2 (last dose). Enoxaparin 40 mg was administered once daily as a subcutaneous injection starting the evening prior to surgery (Day 0). Subsequently, enoxaparin or placebo was administered on the day of surgery 6 to 8 hours after wound closure and thereafter once daily until Day 12 ± 2. Additionally, all subjects in the enoxaparin group received rivaroxaban placebo tablets. The first rivaroxaban placebo tablet was taken on the day of surgery (Day 1), at least 6-8 hours after wound closure, and subsequently once daily every 24 ± 2 hours up to Day 35 ± 4. Subjects were evaluated at Day 0, 1, 7 (± 2 days), 13 (± 2 days), and 36 (± 4 days) with a follow-up visit at Day 65 (± 5 days). On Day 0 prior to surgery, a physical examination was performed, and medical history with demographics was recorded. Blood was sampled for clinical chemistry, hematology, and coagulation parameters. An ECG was performed, and a urine pregnancy test done for women of childbearing potential. On Day 1, blood samples for hematology and clinical chemistry were taken after surgery but before study medication, and a physical examination will be performed. On Day 7, physical examination and blood sampling for hematology and coagulation parameter were performed. On Day 13, physical examination and blood sampling for hematology and clinical chemistry were performed. On Day 36, blood samples for clinical chemistry, coagulation parameters, and hematology will be taken, and bilateral venography were performed. Adverse events will be recorded at each visit. On Day 65, adverse events, signs and diagnosis of VTE, and an assessment of cardiovascular and bleeding events during the 30 days after end of treatment were recorded. Physical examination will be performed, and a blood sample for clinical chemistry will be taken.
The primary efficacy endpoint was defined as a composite endpoint of:

- Any DVT (proximal and/or distal)
- Non-fatal PE
- Death from all causes

The analysis of the primary efficacy endpoint was solely based on the assessments made by the Independent Central Adjudication Committee and VTE Adjudication Committees. The major secondary endpoint was the incidence of the composite endpoint comprising proximal DT, non-fatal PE, and VTE-related death. Additional secondary efficacy endpoints were incidence of symptomatic VTE, incidence of symptomatic DVT (total, proximal, distal), incidence of symptomatic VTE during follow-up, incidence of PE, incidence of death, “net clinical benefit”, incidence of the composite endpoint that results from the primary endpoint by substituting VTE-related death for all death, and incidence of the composite endpoint that results from major VTE by substituting all-cause mortality for VTE-related death. The main safety endpoint was the incidence of treatment-emergent major bleeding observed not later than 2 days after last intake of study drug. Major bleeding occurring after this period was considered separately. Also included as safety variables were treatment-emergent adverse events, serious adverse events, and deaths; adverse events starting after treatment initiation up to 2 days after last study treatment, adjudicated cardiovascular events, incidence of prolonged hospitalization, transfusion requirements, discontinuations due to adverse events, and laboratory parameters.

Brief Summary of Results

There were 2509 subjects randomized at 123 centers. Of these, 2457 subjects received study medication, and 1733 were valid for the MITT analysis and 1615 were valid for the PP analysis. In the PP analysis, 11/812 (1.4%) subjects in the rivaroxaban arm and 66/803 (8.2%) of subjects in the enoxaparin arm met the primary efficacy endpoint. The results in the MITT population were similar, with the primary efficacy outcome reached by 17/864 (2.0%) subjects in the rivaroxaban population and 81/869 (9.3%) subjects in the enoxaparin population. This finding demonstrated statistical superiority (95% CI: -9.41%, -5.15%) of rivaroxaban over enoxaparin in preventing VTE. A total of 300 randomized subjects discontinued treatment prematurely (135 rivaroxaban subjects and 165 enoxaparin subjects). The most common reason for study withdrawal was withdrawal of consent in the rivaroxaban arm 51/1252 (4.1%) and adverse events in the enoxaparin arm 54/1257 (4.3%). The incidence of treatment-emergent major bleeding events was very low in both treatment groups (one subject each; <0.1%). There were no fatal bleeding events in either arm after start of study drug. There were 10 deaths in the study, 2 in the rivaroxaban arm and 8 in the enoxaparin arm, and the incidence of treatment-emergent serious adverse events was slightly higher in the enoxaparin group (10.7%) than in the rivaroxaban group (7.3%).

RECORD 3 Study: Regulation of Coagulation in Orthopedic Surgery to prevent DVT and PE; a controlled, double-blind, randomized study of BAY 59-7939 in the prevention of VTE in patients undergoing elective total knee replacement (Protocol 11356)

RECORD 3 was a prospective, randomized, double-blind, double-dummy, parallel-group, active comparator controlled, multi-center and multi-national trial in patients undergoing elective TKR conducted between [redacted] (b) (4). Subjects were enrolled at 147 active centers in 19 countries. The objective of the study was to assess the safety and efficacy of rivaroxaban 10 mg once daily for the prevention of VTE in male and female subjects aged 18 years or above undergoing elective TKA. Administration of rivaroxaban or placebo started on the day of surgery (Day 1) 6 to 8 hours after wound closure, and continued once daily until Day 12 $\pm$ 2 (the day before venography). Enoxaparin 40 mg or matching placebo was administered once daily as a subcutaneous injection starting 12 hours prior to surgery (Day 0). Subsequently, enoxaparin or placebo was administered on the day of surgery at least 6 to 8 hours after wound closure and on subsequent evenings until the final evening dose administered on the evening of Day 12 $\pm$ 2. Subjects were evaluated at Day 0, 1, 7 ($\pm$ 2 days), and 13 ($\pm$ 2 days), with a follow-up visit at Day 42 ($\pm$ 5 days). On Day 0 prior to surgery, a physical examination was performed, and medical history with demographics was recorded. Blood was sampled for clinical chemistry, hematology, and coagulation parameters. An ECG was performed. On Day 1, blood samples for hematology and clinical chemistry were taken after surgery but before study medication, and a physical examination was performed. On Day 7, physical examination and blood sampling for hematology, clinical chemistry, and coagulation parameters were performed. On Day 13, physical examination and blood sampling for hematology, clinical chemistry, and coagulation parameters were performed. On Day 42, adverse events, signs and diagnosis of DVT/PE were recorded. Physical examinations were performed, and a blood sample for clinical chemistry was taken. The primary efficacy endpoint was defined as a composite endpoint of:

- Any DVT (proximal and/or distal)
- Non-fatal PE
- Death from all causes

The analysis of the primary efficacy endpoint was solely based on the assessments made by the Independent Central Adjudication Committee and VTE Adjudication Committees. The major secondary endpoint was the incidence of the composite endpoint comprising proximal DVT, non-fatal PE, and VTE-related death. Additional secondary efficacy endpoints were incidence of DVT (total, proximal, distal), incidence of symptomatic VTE (DVT, PE), incidence of symptomatic VTE during follow-up, "net clinical benefit" assessed by the composite endpoint comprising major VTE and treatment-emergent major bleeding, incidence of the composite endpoint that results from the primary endpoint by substituting VTE-related death for all death, and incidence of the composite endpoint that results from major VTE by substituting all-cause mortality for VTE-related death. The main safety endpoint was the incidence of treatment-emergent major bleeding observed no later than 2 days after last intake of study drug. Major bleeding observed after this period was considered separately. Also included as safety variables were treatment-emergent adverse events, serious adverse events, and deaths; adverse events starting after treatment initiation up to 2 days after last study treatment, adjudicated cardiovascular events, incidence of prolonged hospitalization, transfusion requirements, amount of intraoperative blood loss, postoperative volume of drainage, and laboratory parameters.

Brief Summary of Results

There were 2531 subjects randomized at 147 centers. Of these, 2459 subjects received study medication, and 1702 were valid for the MITT analysis and 1631 were valid for the PP analysis. In the PP analysis, 74/793 (9.3%) subjects in the rivaroxaban arm met the primary efficacy endpoint and 152/838 (18.1%) of subjects in the enoxaparin arm met the primary efficacy endpoint described by the sponsor as demonstrating noninferiority against enoxaparin, based on a noninferiority margin of 4%. The results in the MITT population were similar, with the primary efficacy outcome reached by 79/824 (9.6%) subjects in the rivaroxaban population and 166/878 (18.9 %) subjects in the enoxaparin population, described by the sponsor as demonstrating superiority of rivaroxaban over enoxaparin in preventing VTE (95% CI: -12.40%, -5.89%). A total of 282 randomized subjects discontinued treatment prematurely (127 rivaroxaban subjects and 155 enoxaparin subjects). The most common reason for study withdrawal was withdrawal of consent in both arms: 68/ 1254 (5.4%) in the rivaroxaban arm and 60/1277 (4.7%) in the enoxaparin arm. The incidence of treatment-emergent major bleeding events was low in both treatment groups (0.6% in the rivaroxaban arm versus 0.5% in the enoxaparin arm). There were no fatal bleeding events reported in either group. There were 6 deaths in the study, all in the enoxaparin arm. The incidence of treatment-emergent serious adverse events was slightly lower in the enoxaparin group (7.4%) than in the rivaroxaban group (8.9%).

RECORD 4 Study: **Regulation of Coagulation in Orthopedic Surgery to prevent DVT and PE; a controlled, double-blind, randomized study of BAY 59-7939 (rivaroxaban) in the prevention of VTE in subjects undergoing elective total knee replacement (Protocol 11355)**

RECORD 4 was a prospective, randomized, double-blind, double-dummy, parallel-group, active comparator controlled, multi-center and multi-national trial in patients undergoing elective TKR conducted between (b) (4). Subjects were enrolled at 131 active centers in 12 countries. The objective of the study was to assess the safety and efficacy of rivaroxaban 10 mg once daily for the prevention of VTE in male and female subjects aged 18 years or above undergoing elective TKA. Administration of rivaroxaban or placebo started on the day of surgery (Day 1) 6 to 8 hours after wound closure, and continued once daily until Day 12 $\pm$ 2 (the day before venography). Enoxaparin 30 mg bid or matching placebo was administered twice daily as a subcutaneous injection starting 12-24 hours after wound closure. Thereafter, enoxaparin active or placebo was administered subcutaneously twice daily, once in the morning and once in the evening (every 12 $\pm$ 2 hours), until the final evening dose administered on the evening of Day 12 $\pm$ 2 (the day prior to venography). Subjects were evaluated at Day 0, 1, 6 ($\pm$ 2 days), and 13 ($\pm$ 2 days), with a follow-up visit at Day 42 ($\pm$ 5 days). On Day 0 prior to surgery, a physical examination was performed, and medical history with demographics was recorded. Blood was sampled for clinical chemistry, hematology, and coagulation parameters. An ECG was performed. On Day 1, blood samples for hematology and clinical chemistry were taken after surgery but before study medication, and a physical examination was performed. On Day 6, physical examination and blood sampling for hematology, clinical chemistry, and coagulation parameters were performed. On Day 13, physical examination and blood sampling for hematology, clinical chemistry, and coagulation parameters were performed. On Day 42, adverse events, signs and diagnosis of DVT/PE were recorded. Physical examinations were performed, and a blood sample for clinical chemistry was taken.

The primary efficacy endpoint was defined as a composite endpoint of:

- Any DVT (proximal and/or distal)
- Non-fatal PE
- Death from all causes

The analysis of the primary efficacy endpoint was solely based on the assessments made by the Independent Central Adjudication Committee and VTE Adjudication Committees. The major secondary endpoint was the incidence of the composite endpoint comprising proximal DVT, non-fatal PE, and VTE-related death. Additional secondary efficacy endpoints were incidence of DVT (total, proximal, distal), incidence of symptomatic VTE (DVT, PE), incidence of symptomatic VTE during follow-up, "net clinical benefit" assessed by the composite endpoint comprising major VTE and treatment-emergent major bleeding, incidence of the composite endpoint that results from the primary endpoint by substituting VTE-related death for all death, and incidence of the composite endpoint that results from major VTE by substituting all-cause mortality for VTE-related death. The main safety endpoint was the incidence of treatment-emergent major bleeding observed no later than 2 days after last intake of study drug. Major bleeding observed after this period was considered separately. Also included as safety variables were treatment-emergent adverse events, serious adverse events, and deaths; adverse events starting after treatment initiation up to 2 days after last study treatment, adjudicated cardiovascular events, incidence of prolonged hospitalization, transfusion requirements, amount of intraoperative blood loss, postoperative volume of drainage, and laboratory parameters. Other safety variables included the incidence of any treatment-emergent bleeding observed no later than 2 days after last intake of study drug, the incidence of non-major

treatment–emergent bleeding observed no later than 2 days after last intake of study drug, incidence of postoperative bleeding, and incidence of surgical site bleeding associated with > 2 g/dL fall in hemoglobin or leading to infusion of > 2 units of whole blood or packed cells.

Brief Summary of Results

There were 3148 subjects randomized at 131 centers. Of these, 3034 subjects received study medication, and 1924 were valid for the MITT analysis and 1742 were valid for the PP analysis. In the PP analysis, 58/864 (6.7%) subjects in the rivaroxaban arm met the primary efficacy endpoint and 82/878 (9.3%) of subjects in the enoxaparin arm met the primary efficacy endpoint described by the sponsor as demonstrating noninferiority against enoxaparin, based on a noninferiority margin of 4%. The results in the MITT population were similar, with the primary efficacy outcome reached by 67/965 (6.9%) subjects in the rivaroxaban population and 97/959 (10.1%) subjects in the enoxaparin population, described by the sponsor as demonstrating superiority of rivaroxaban over enoxaparin in preventing VTE (95% CI: -5.67%, -0.71%). A total of 310 randomized subjects discontinued treatment prematurely (159 rivaroxaban subjects and 151 enoxaparin subjects). The most common reason for study withdrawal was adverse events in both arms: 62/ 1584 (3.9%) in the rivaroxaban arm and 56/1564 (3.6%) in the enoxaparin arm. The incidence of treatment-emergent major bleeding events was low in both treatment groups (0.7% in the rivaroxaban arm versus 0.3% in the enoxaparin arm). With regard to critical bleeding events, there was one retroperitoneal bleeding event (rivaroxaban), one intracranial bleed (enoxaparin), and one intraspinal/hemorrhagic puncture event (enoxaparin). There was one fatal bleeding event reported in the rivaroxaban treatment group. Twelve subjects died during the study, 6 in the rivaroxaban group and 6 in the enoxaparin group. The incidence of treatment-emergent serious adverse events was similar between the two groups: 5% in the rivaroxaban group and 7% in the enoxaparin group.

Rationale for Site Selection

Rivaroxaban is a new molecular entity which is an oral anticoagulant with the proposed indication of prophylaxis of VTE. The site selection is based on the review division's analysis of efficacy of rivaroxaban versus the comparator at individual sites. Sites which showed a greater efficacy of rivaroxaban in relation to comparator which had relatively high enrollment were chosen. Two sites for each of the pivotal studies were selected for inspection.

II. RESULTS (by Site):

Name of CI, IRB, or Sponsor Location	Protocol # and # of Subjects	Inspection Date	Interim Classification	Final Classification
Andrzej Gorecki Szpital Kliniczny Dzieciatka Jezus – Centrum Leczenia Obrazen Klinika Ortopedii i Traumatologii Narzadu Ruchu ul. Lindleya 4 02-005 Warszawa, POLAND	Protocol # 11354, RECORD 1 Site # Poland 18006 # of subjects (Total# 71): Xarelto: 36 Enoxaparin: 35	Pending	NAI	Pending
Tadeusz Gazdzik Slaska Akademia Medyczna Katedra I Oddzial Kliniczny Ortopedii Wojewodzki Szpital Specjalistyczny Nr 5 im. Sw. Barbaby Pl. Medykow 1 41-200 Sosnowiec, POLAND	Protocol # 11354, RECORD 1 Site # Poland 18012 # of subjects (Total#: 76): Xarelto: 38 Enoxaparin: 38	Pending	NAI	Pending
Qingming Yang Rui Jin Hospital, Shanghai Second Medical Univeristy Orthorpaedic Department Shanghai Ryuijin Hospital No. 197 Ruijin Second Road Shanghai, CHINA 200025	Protocol # 11357, RECORD 2 Site # China 54005 # of subjects (Total# 34): Xarelto: 17 Enoxaparin: 17	(b) (4)	OAI	Pending
Cesar Diaz Valverde Hospital Edgardo Rebagliati Martins Av. Edgardo Rebagliati Martins S/N JESUS MARIALima Lima, 11 PERU	Protocol # 11357, RECORD 2 Site # Peru 64005 # of subjects (Total# 41): Xarelto: 20 Enoxaparin: 21		VAI	Pending
Bingfang Zeng Affiliated Sixth People's Hospital Orthorpaedic Department No. 600 Yishan Road, Xuhui District Shanghai, CHINA 200233	Protocol # 11356, RECORD 3 Site # China 54014 # of subjects (Total# 26): Xarelto: 13 Enoxaparin: 13		OAI	Pending
Jacek Kruczynski Szpital Uniwersytecki im. Antoniego Jurasze Klinika Ortopedii i Traumatologii Narzadu Ruchu ul. M. Sklodowskiej-Curie 9 85-094, Bydgoszcz POLAND	Protocol # 11356, RECORD 3 Site # Poland 18003 # of subjects (Total# 36): Xarelto: 18 Enoxaparin: 18		VAI	Pending

R. Michael Murray Capstone Clinical Research 2018 Brookwood Medical Center Suite 314 Birmingham, AL 35209	Protocol # 11355, RECORD 4 Site # 14005 # of subjects (Total # 152) Xarelto: 76 Enoxaprin: 76	(b) (4)	Pending	Pending
David Fox Unlimited Research, LP 12709 Toepperwein Road Suite 101 San Antonio, TX 78233	Protocol #11355, Record 4 Site #14022 # of subjects (Total # 64) Xarelto: 32 Enoxaparin: 32		Pending	Pending
Bayer Pharmaceutical 340 Change Bridge Rd. Pine Brook, NJ 07058	Protocol # 11354, RECORD 1 Protocol # 11357, RECORD 2 Protocol # 11356, RECORD 3 Protocol #11355, Record 4	Pending	Pending	Pending
Johnson & Johnson 920 U.S. Highway 202 Raritan, NJ 08869-0602		Pending	Pending	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. Andrzej Gorecki
Szpital Kliniczny Dzieciatka Jezus – Centrum Leczenia Obrazen
Klinika Ortopedii i Traumatologii
Narzadu Ruchu
ul. Lindleya 4
02-005 Warszawa, POLAND

a. **What was inspected**: The inspection was conducted in accordance with Compliance Program 7348.811. There was no screening log maintained at the site; all subjects listed in the Subject ID log were randomized. There were 71 subjects enrolled and 69 subjects completed the study; 1 subject discontinued due to withdrawal of consent and one subject discontinued due to a protocol violation (concomitant oral anticoagulant). The informed consent of all subjects were reviewed, and the medical file and venography films were verified for all subjects. The files of 20 subjects were reviewed/translated, with a review focus on adverse events. The EIR was not available at the time this CIS was written. The observations noted are based on preliminary communications with the FDA field investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the final EIR. There were no

limitations to the inspection.

b. **General observations/commentary**: No issues were noted with the Informed Consent Documents, record review, study drug accountability, or general conduct of the study. The primary efficacy endpoint was verifiable. No Form FDA 483 was issued to the investigator. The inspector notes that there was some underreporting of non-serious adverse events. The Sponsor was aware of this underreporting and allowed the investigator to report non-serious adverse events that were unexpected for the patient and/or atypical for the procedure. In addition, the dispensing log was completed in a retrospective manner; however, the actual administration log book was completed at administration.

c. **Assessment of data integrity**: The data from Dr. Gorecki's site appear acceptable for use in support of the NDA.

2. **Tadeusz Gazdzik**
Slaska Akademia Medyczna
Katedra I Oddzial
Kliniczny Ortopedii
Wojewodzki Szpital
Specjalistyczny Nr 5
im. Sw. Barbaby
Pl. Medykow 1
41-200 Sosnowiec, POLAND

a. **What was inspected**: The inspection was conducted in accordance with Compliance Program 7348.811. There was no screening log maintained at the site; all subjects listed in the Subject ID log were randomized. There were 76 subjects enrolled and 69 subjects completed the study; 4 subjects were discontinued due to withdrawal of consent, one subject was discontinued because surgery was not done, one subject discontinued due to a history of liver disease, and one discontinued due to a SAE (myocardial infarction). The informed consent documents of all subjects were reviewed, and the medical file and venography films were verified for all subjects. The files of 36 subjects were reviewed in part; 12 subject files had all progress notes translated, with a review focus on adverse events. The EIR was not available at the time this CIS was written. The observations noted are based on preliminary communications with the FDA field investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the final EIR. There were no limitations to the inspection.

b. **General observations/commentary**: No issues were noted with the Informed Consent Documents, record review, study drug accountability, adverse event reporting, or general conduct of the study. The primary efficacy endpoint was verifiable. No Form FDA 483 was issued to the investigator.

c. **Assessment of data integrity**: The data from Dr. Gazdzik's site appear acceptable for use in support of the NDA.

3. **Qingming Yang**
Rui Jin Hospital, Shanghai Second Medical University
Orthorpaedic Department
Shanghai Ryuijin Hospital
No. 197 Ruijin Second Road
Shanghai, CHINA 200025

a. **What was inspected**: The inspection was conducted in accordance with Compliance Program 7348.811. There were 34 subjects screened at the site, and all 34 were enrolled. There were 23 subjects who completed the study. The EIR was not available at the time this CIS was written. The observations noted are based on preliminary communications with the FDA field investigator and the Form FDA 483. In addition, a letter responding to the Form FDA 483 dated March 3, 2009 from Dr. Yang was reviewed as well as an affidavit generated during the inspection by a subinvestigator, (b) (6) An inspection summary addendum will be generated if conclusions change upon receipt and review of the final EIR. There were no limitations to the inspection.

b. **General observations/commentary**: Several deviations from FDA regulations were noted, and a Form FDA 483 was issued for these violations. The inspection documented that the investigator did not adhere to the investigational plan, in violation of 21 CFR 312.60, failed to report to the sponsor adverse events, in violation of 21 CFR 312.64, did not prepare and maintain adequate and accurate case histories with respect to observations and data pertinent to the investigation, in violation of 21 CFR 312.62(b), failed to include contact information for subject questions in the Informed Consent Document (ICD), in violation of 21 CFR 50, and failed to include in the ICD the possibility that the FDA may inspect the study records.

<u>Protocol Violations [21 CFR 312.60]</u>

1. The Principal Investigator (PI) did not ensure that all associates and colleagues assisting in the investigation were meeting the commitments of the study protocol and regulations. Sub-Investigator (b) (6) was discovered to have recorded a Visit on Day 65 for Subject 54005-7005 (b) (6) However, Sub-Investigator (b) (6) contacted the subject and confirmed that the patient visit never took place; according to the inspector, the visit was struck out in the record. However, there was no further investigation into this incident, nor into whether the same issue may emerge in other subject records. An affidavit was taken from the Sub-Investigator regarding this incident; the PI also addressed this incident in a letter responding to all the findings listed in the Form FDA

483. However, the versions of this incident in the affidavit and the letter are not the same.

Adverse Event Reporting [21 CFR 312.64]

1. There were two subjects (54005-7021 (b) (6) and 54005-7006 (b) (6)) who experienced a ≥ 2 g/dL drop in hemoglobin requiring transfusion of 400 mL of Red Blood Cells (RBCs) and 200 mL of Fresh Frozen Plasma (FFP). Two additional subjects (54005-7005 (b) (6) and 54005-7017 (b) (6)) had a ≥ 2 g/dL drop in hemoglobin and received transfusion of RBCs and FFPs. None of these were reported as adverse events. In his response letter the PI states that blood loss and transfusion is normal for a subject post orthopedic surgery and therefore was not considered an adverse event. However, the definition of adverse events contained in the protocol does not exclude such conditions.

   Medical Officer Comment: It is possible that these adverse events were reported as "Bleeding Events", a safety variable in this study. However, such reporting does not obviate the requirement to report them as adverse events, as the protocol does not exclude postoperative conditions.
2. There were two subjects (54005-7020 (b) (6) and 54005-7012 (b) (6)) with elevations of AST and/or ALT of 1.5 to > 3 times the upper limit of normal on several occasions which were not reported as Adverse Events.
3. Subject 54005-7021 experienced nausea which was not reported as an adverse event.
4. Subject 54005-7006 experienced constipation for 3 days which was not reported as an adverse event.
5. Subject 54005-7005 had a decreased albumin on two occasions (Day 3 and Day 7) for which albumin infusions on Day 5 and Day 6 were administered.

Recordkeeping Violations [21 CFR 312.62(b)]

1. There is no source data maintained by the Clinical Investigator (CI) of the actual investigational drug administration times for all subjects. The CI assumes that the study nurse administers IV and oral doses according to the Long-Term orders in the medical records. The PI's response indicates that this procedure is standard Chinese medical practice, and that nurses maintain their own temporary notes regarding drug administration which are later discarded.
2. The CI did not maintain a complete copy of the informed consent forms for all subjects; only the last two pages were retained in the subject record for Subjects 54005-7021 (b) (6), 54005-7029 (b) (6) 54005-7030 (b) (6) 54005-7032 (b) (6), 54005-7033- (b) (6), and 54005-7034 (b) (6)
3. Source documents for Day 36 and 65 were not always completed and signed by the Sub-investigator completing the forms, and they were not reviewed by the PI. These source documents included In-Patient Study

Drug Administration, Adverse Event Reports, Blood Transfusion, Drug Administration After-Discharge, and end of treatment records for Subjects 54005-7004 (b) (6) 54005-7005 (b) (6), 54005-7012 (b) (6) 54005-7020 (b) (6), and 54005-7021 (b) (6).

Informed Consent Violations [21 CFR 50]

1. The version of the ICD signed by all 33 subjects lacked the contact information of the CI and the IRB/EC. This version of the IC was approved by the IRB/Ethics Committee.
2. The ICD signed by all 33 subjects enrolled in the clinical trial did not include the statement that the U.S. FDA may inspect the study records.

c. **Assessment of data integrity**: There were protocol, adverse event reporting, recordkeeping, and informed consent violations reported from this site. Of most concern is the apparent falsification of data by a subinvestigator for a patient visit. However, of even more significance is that there was no investigation into this incident by the PI or his representative, and the Sub-investigator who entered the erroneous data continued to perform study-related procedures. Lastly, the lack of consistency between the Sub-Investigator's affidavit and the PI's letter raises concern regarding the veracity of the information provided. In addition, there appears to be significant underreporting of adverse events from this site, including anemia/bleeding requiring transfusion and liver function abnormalities. DSI recommends that the data from subjects enrolled in RECORD 2 at Dr. Yang's site not be considered acceptable for use in support of the NDA. In addition, any data obtained from subjects enrolled in RECORD 3 at this site should also be regarded as unreliable. Although data from RECORD 3 at Dr. Yang's site was not audited, the Sub-investigator in question may have participated in study activities, and the lack of oversight appears to be significant at this clinical trial site.

4. **Cesar Diaz Valverde**
Hospital Edgardo Rebagliati Martins
Av. Edgardo
Rebagliati Martins S/N
JESUS MARIALima
Lima, 11 PERU

a. What was inspected: The inspection was conducted in accordance with Compliance Program 7348.811. There were 41 subjects enrolled at the site; a screening log was not maintained. There were 39 subjects who completed the study; 1 subject withdrew due to a SAE and 1 subject withdrew consent. The EIR was not available at the time this CIS was written. The observations noted are based on preliminary communications with the FDA field investigator and the Form FDA 483. An inspection summary addendum will be generated if conclusions change upon receipt and review of the final EIR. There were no limitations to the inspection.

b. General observations/commentary: Several deviations from FDA regulations were noted, and a Form FDA 483 was issued for these violations. The inspection documented that the investigator did not adhere to the investigational plan, in violation of 21 CFR 312.60 and did not prepare and maintain adequate and accurate case histories with respect to observations and data pertinent to the investigation, in violation of 21 CFR 312.62(b).

Protocol Violations [21 CFR 312.60]

1. The following adverse events were not reported as required by the protocol: Subject 7001 – abdominal distention, nausea, and vomiting; Subject 7002 – constipation and nausea; Subject 7004 – sore throat; Subject 2006 – short of breath; Subject 7012 – headache and gastric discomfort; Subject 7026 – headache; blurred vision, vertigo, and vomiting; Subject 7036 – gluteal dermatitis and cough; Subject 7038 – liquid stools; rash and itching; headaches on 3 occasions; Subject 7039 – nausea and 2 episodes of chest pain; and Subject 7041 - gastric discomfort.
2. The following concomitant medications were not documented: Subject 7001 – Glycerin suppository; Subject 7002 – Glycerin suppository; and Subject 7008 – Timolol eye drops.
3. Subject 7009 did not have a 12 lead ECG printout in the medical or source records, although the CRF indicates that one was done.
4. The protocol requires that venography studies (performed for DVT diagnosis) be done in the respective hospital radiology unit. The subjects at this site did not have the bilateral venography performed at the respective hospital radiology unit, and there is no documentation for the CI fully explaining this deviation.
5. There was no source documentation for the receipt of the Coagulation blood samples by the (b) (4) for Subject 7024 on Day 0.
6. The source hospital medical record for Subject 7013 was not available for the inspector's review and was reported to be lost from the central archive.

Recordkeeping Violations [21 CFR 312.62(b)]

1. The source hospital medical record for Subject 7013 was not available for the inspector's review and was reported to be lost from the central archive.
2. Subject 7009 did not have a 12 lead ECG printout in the medical or source records, although the CRF indicates that one was done.
3. There was no source documentation for the receipt of the Coagulation blood samples by the (b) (4) for Subject 7024 on Day 0.

c. **Assessment of data integrity**: Although protocol and recordkeeping violations occurred at this site, it is unlikely that these errors will impact the final outcome of the study. However, significant underreporting of adverse events at this site raises the question of whether the rights, safety, and welfare of any of the randomized subjects

was compromised due to these inaccuracies. The data appear acceptable for use in support of the NDA.

5. **Bingfang Zeng**
Affiliated Sixth People's Hospital
Orthorpaedic Department
No. 600 Yishan Road,
Xuhui District
Shanghai, CHINA 200233

a. What was inspected: The inspection was conducted in accordance with Compliance Program 7348.811. There were 26 subjects enrolled at the site. There were 23 subjects who completed the study. The EIR was not available at the time this CIS was written. The observations noted are based on preliminary communications with the FDA field investigator and the Form FDA 483. An inspection summary addendum will be generated if conclusions change upon receipt and review of the final EIR. There were no limitations to the inspection.

b. General observations/commentary: Several deviations from FDA regulations were noted, and a Form FDA 483 was issued for these violations. The inspection documented that the investigator did not adhere to the investigational plan, in violation of 21 CFR 312.60 and did not promptly report to the sponsor adverse effects that may reasonably be regarded as caused by or probably caused by, a investigational drug, in violation of 21 CFR 312.64.

Protocol Violations [21 CFR 312.60]

1. Two subjects were administered prohibited concomitant medications while enrolled in the clinical trial. Subjects 54014-6001 (b) (6) and 54014-6014 (b) (6) were treated with Salvia Miltiorrhiza (a platelet inhibitor) from Day 7 to Day 13 and on Day 2, respectively.
2. Subject 54014-6001 was treated with Aescuven Forte which was not listed on the concomitant drug list (eCRF) .

Adverse Event Reporting [21 CFR 312.64]

1. Two subjects did not have SAEs reported within 24 hours of the investigator's awareness of the event.
    i. Subject 54014-6007 was diagnosed with a DVT in the right leg on June 27, 2006. This SAE was not reported to the Sponsor until March 2, 2007 and the IRB/EC until March 19, 2007.
    ii. Subject 54014-6014 (b) (6) was diagnosed with a DVT in the right calf on October 6, 2006. The SAE was not reported to the Sponsor and the IRB/EC until October 11, 2006.
2. Multiple subjects did not have adverse events reported to the sponsor, although the concomitant medications they received for these conditions were recorded. These include Subject 54014- 6001 (b) (6) – swelling and

decreased albumin levels; Subject 54014-6006 (b) (6) – swelling at the incision site; Subject 54014-6009 (b) (6) – phlegm/sputum production; Subject 54014-6012 (b) (6) – insomnia; Subject 54014-6013 (b) (6) – constipation and phlegm; Subject 54014-6014 (b) (6) – trophic nerve on two occasions and blood vessel constriction; Subject 54014-6015 (b) (6) chest stress and phlegm; Subject 54014-6018 – fever and decrease in hemoglobin; Subject 54014-6020 (b) (6) – "dephlogisticate", fever, and wound swelling; Subject 54014-6023 (b) (6) – stomach pain.

c. **Assessment of data integrity**: Although protocol and adverse event reporting violations occurred at this site, it is unlikely that these errors will impact the final outcome of the study. However, significant underreporting of adverse events at this site raises the question of whether the rights, safety, and welfare of any of the randomized subjects was compromised due to these inaccuracies. The data appear acceptable for use in support of the NDA.

6. **Jacek Kruczynski**
Szpital Uniwersytecki im.
Antoniego
Jurasze
Klinika Ortopedii i Traumatologii
Narzadu Ruchu
ul. M. Sklodowskiej-Curie 9
85-094, Bydgoszcz
POLAND

a. **What was inspected**: The inspection was conducted in accordance with Compliance Program 7348.811. There were 36 subjects enrolled at the site; there was no screening log at the site. There were 34 subjects who completed the study; 2 subjects did not have surgery. The informed consent documents of all subjects were reviewed, and the medical file and venography films were verified for all subjects. The progress notes in the files of 13 subjects were translated and reviewed. The EIR was not available at the time this CIS was written. The observations noted are based on preliminary communications with the FDA field investigator and the Form FDA 483. An inspection summary addendum will be generated if conclusions change upon receipt and review of the final EIR. There were no limitations to the inspection.

b. **General observations/commentary**: Several deviations from FDA regulations were noted, and a Form FDA 483 was issued for these violations. The inspection documented that the investigator did not adhere to the investigational plan, in violation of 21 CFR 312.60.

Protocol Violations [21 CFR 312.60]

1. Subjects were randomized prior to required screening activities. Subjects 6006, 6010, 6011, 6012, 6014, 6019, 6020, and 6025 were randomized prior to obtaining subjects' ECG's and/or blood sampling for hematology, clinical chemistry, coagulation parameters, and serology retention sample.
2. ECG interpretation by Internal Medicine/Cardiology was not implemented/recorded in source documentation until approximately June, 2006. ECGs performed prior to this time were retrospectively reviewed and documented for source/CRF entry.
3. Investigational drug disposition records were not adequate with respect to dates, quantity and use by subjects in source subject drug administration records (temperature charts) were completed by subinvestigators not administering or witnessing the administration of the study drugs. The records do not document the identity and signature of administering/dispensing person.

   Medical Officer's Comment: The inspector notes in an accompanying email that the actual administration log book at the site was completed at administration. Therefore, although this citation represents a protocol violation, it does not affect data integrity.

c. Assessment of data integrity: Although protocol violations occurred at this site, it is unlikely that these errors will impact the final outcome of the study. The data appear acceptable for use in support of the NDA.

7. R. Michael Murray
Capstone Clinical Research
2018 Brookwood Medical Center
Suite 314
Birmingham, AL 35209

a. What was inspected: The inspection was conducted in accordance with Compliance Program 7348.811. There were 178 subjects who signed informed consent at the site, and 153 were randomized. The EIR was not available at the time this CIS was written. The observations noted are based on preliminary communications with the FDA field investigator and the Form FDA 483. An inspection summary addendum will be generated if conclusions change upon receipt and review of the final EIR. There were no limitations to the inspection.

b. General observations/commentary: The inspection documented that the investigator did not prepare and maintain adequate and accurate case histories with respect to observations and data pertinent to the investigation, in violation of 21 CFR 312.62(b), and did not adhere to the investigational plan, in violation of 21 CFR 312.60.

Recordkeeping Violations [21 CFR 312.62(b)]

1. Subject 5117 experienced an elevated lipase. Site email dated 7/2/07 from Capstone Clinical Trials, Inc. President/CEO to the monitor reported that the subject "was receiving rivaroxaban in the Bayer 11355 trial". The inspector's review of the study records failed to reveal how the site became awar of the Subject's blinded treatment assignment. No documentation was observed of sponsor or site emergency unblinding of this subject.
2. The site lacked documentation of IRB approval of the following:
    i. The performance of study screen visits at locations outside of routine clinical settings and not listed on the Form FDA 1572. For example screening visits including physical exams, ECGs, blood draws, etc. were conducted in subjects' homes and hotel rooms.
    ii. The performance of post-enrollment study visits that included physical exams and administration of the test article at sites not listed on the Form FDA 1572 not under the PI's supervision. Subjects were sometimes moved to an inpatient rehabilitation facility together with the test article where it was dispensed and administered by the rehab center staff who had not received training on the protocol or GCP. Study visits were also conducted at subject's homes after the subjects had been discharged from the hospital, including the article administration, physical exams, and blood draws. These alternate sites included the site's sister company, [redacted] (b) (4), the subject's place of employment, and an outpatient physical therapy center.
    iii. Payment/reimbursement of subjects' hotel stays, mileage, and transportation costs like cab fares, despite the IRB-approved informed consent which states "the maximum total possible payment is $250.00". The consent document does not mention additional services/reimbursement.
3. The site lacked documentation that the Final Report/notice of study closure was submitted to the IRB (or that the Board acknowledged receipt of the final report/study closure). A copy of the site's computer version of the Final Report dated 4/24/08 that is unsigned/unofficial was provided during the inspection; however, there is no documentation that this report was submitted to the board.
4. The most recent status report submitted to the IRB was the Annual Review Report dated 6/26/07 and signed by the PI states in Item #8 that the site is currently enrolling patients in this study. In Item #9 it states that "this study is closed to further enrollment". In addition, the following statement was included: ". . . as this study is no longer open to enrollment. No further subjects will be consented.". According to the site enrollment logs, subjects were enrolled/randomized through 10/9/07.
5. The site Signature Sheet and Delegation of Duties Log is inaccurate in that the Log does not reflect the performance of physical exams by the Physician Assistants (who routinely conducted physical exams throughout the study). At least one physical exam was performed by an RN/study coordinator per

source records. RNs are not licensed to conduct physical exams in the state of Alabama.

Protocol Violations [21 CFR 312.60]

1. Subjects were randomized post-surgery rather than prior to surgery. According to the protocol, randomization was to take place following screening on Day 0 or prior to surgery on Day 1.

c. Assessment of data integrity: Although protocol and recordkeeping violations occurred at this site, it is unlikely that these errors will impact the final outcome of the study. The data appear acceptable for use in support of the NDA.

8. David Fox
Unlimited Research, LP
12709 Toepperwein Road
Suite 101
San Antonio, TX 78233

a. What was inspected: The inspection was conducted in accordance with Compliance Program 7348.811. There were 72 subjects screened at the site, and 64 were enrolled. There were 60 patients who completed the study. During the inspection, 23 subject records were reviewed, and all 72 informed consent documents were reviewed. The EIR was not available at the time this CIS was written. The observations noted are based on preliminary communications with the FDA field investigator and the Form FDA 483. An inspection summary addendum will be generated if conclusions change upon receipt and review of the final EIR. There were no limitations to the inspection.

b. General observations/commentary: The inspection documented that the investigator did not obtain informed consent in accordance with 21 CFR 50 from each human subject prior to drug administration and that the investigator did not adhere to the investigational plan, in violation of 21 CFR 312.60.

Informed Consent Violations [21 CFR 50]

1. The CI failed to obtain informed consent from each human subject prior to drug administration and conducting study related tests.
    i. Subjects 5070 signed an informed consent document on September 13, 2007 that had expired on September 12, 2007, and did not sign the next approved version.
    ii. Subject 5071 signed an informed consent document on September 19, 2007 that had expired on September 12, 2007. This subject then signed the next approved version of the consent form on September 25, 2007.
2. The CI failed to have Subjects 5046, 5047, 5049, 5066, and 5068 sign a new version of the informed consent document after the original signed informed consent document is superceded.

Protocol Violations [21 CFR 312.62(b)]

1. According to the protocol, on Day 0 (the day prior to surgery), the subject will be randomized if eligible for the study. All 23 subjects reviewed were randomized on Day 1 instead of Day 0.
2. According to the protocol, on Day 6 ± 2, blood sampling for hematology, clinical chemistry, and coagulation parameters was to be done for all subjects. Subject 5003 and 5010 did not have their coagulation parameters drawn in the correct timeframe.
3. The visit for Study Day 42 was conducted out of the visit window (Day 42 ± 5) for the following subjects: Subject 5003 – 3 days out of window; Subject 5010 – 2 days out of window; Subject 5011 - 2 days out of window; Subject 5018 – 2 days out of window; Subject 5024 – 3 days out of window; Subject 5025 – 2 days out of window; Subject 5041 – 2 days out of window; and Subject 5060 – 4 days out of window.
4. There were no Protocol Deviation Reports submitted to the IRB for any of the violations described in Parts 1-3 above.

c. Assessment of data integrity: Although informed consent and recordkeeping violations occurred at this site, it is unlikely that these errors will impact the final outcome of the study. The data appear acceptable for use in support of the NDA.

9. **Sponsor/Monitor/CRO**
   Bayer Pharmaceutical
   340 Change Bridge Rd.
   Pine Brook, NJ 07058

   a. **What was inspected**: This inspection is ongoing; no information regarding the results of the inspection has been received.

9. **Applicant**
   Johnson & Johnson
   920 U.S. Highway 202
   Raritan, NJ 08869-0602

   a. **What was inspected**: This inspection has not yet been conducted.

IV. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

In general, inspection of the Drs. Gorecki, Gazdzik, Kracznski, Murray, and Fox sites revealed that they adhered to the applicable regulations and good clinical practices governing the conduct of clinical investigations. The inspection of documents supports that audited subjects exist, met eligibility criteria, received assigned study medication, adhered to protocol, and signed informed consent documents. The inspections documented minor regulatory violations at the sites of Drs. Gorecki, Gazkzik, Kracznski, Murray, and Fox regarding protocol, recordkeeping, and informed consent violations. In general, the studies at these sites appear to have been conducted adequately, and the data generated by these sites may be used in support

of the indication. The results of the inspection of the sponsor Bayer Pharmaceuticals are not yet available, and the inspection of the applicant Johnson & Johnson has not yet taken place.

The inspection of Dr. Valverde's and Dr. Zeng's site raise concern regarding underreporting of adverse events. Although neither site appears to have failed to report serious adverse events, the number of unreported adverse events is significant. The data from these sites appear acceptable for use in the NDA.

Of greatest concern are the findings of the inspection of Dr. Yang's site. The inspector describes an instance of apparent falsification of a subject visit by a sub-investigator, which was reportedly detected later by a second investigator. However, there was no investigation into the circumstances of the falsification incident, and the Sub-Investigator was allowed to continue to administer the study. In addition, the affidavit provided by the second subinvestigator at the time of the inspection and the response letter from the PI give two different versions of this event. Lastly, there is no evidence that this discrepancy was detected by the study monitor. There were four instances of unreported anemia requiring transfusion and two unreported instances of elevated liver function tests from this site. It is possible that the anemia requiring transfusions was reported as the safety variable "Bleeding event"; however, these should also have been recorded as adverse events. DSI recommends that data from this site be regarded as unreliable.

At the present time, we cannot comment on the adequacy of clinical trial monitoring by the sponsor and the CRO (b) (4) When the sponsor inspection is completed and the results transmitted to DSI, we will generate an inspection summary addendum.

Follow-Up Actions: All observations above are based on preliminary communications with the FDA Field investigators and the Form FDA 483. An inspection summary addendum will be generated if conclusions change upon receipt and review of the final EIR. For the ongoing and pending inspections, an inspection summary addendum will be generated after the inspections have been completed and the results have been evaluated by DSI.

{See appended electronic signature page}

Susan D. Thompson, M.D.
Good Clinical Practice Branch II
Division of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Joseph Salewski
Deputy Division Director
Division of Scientific Investigations

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

/s/

Susan Thompson
3/16/2009 03:11:52 PM
MEDICAL OFFICER

Joseph Salewski
3/17/2009 01:37:09 PM
CSO

NDA/BLA REGULATORY FILING REVIEW

(Including Memo of Filing Meeting)

Application Information		
NDA # 22-406 BLA#	NDA Supplement #:S- BLA STN #	Efficacy Supplement Type SE-
Proprietary Name: Xarelto™ Established/Proper Name: Rivaroxaban Dosage Form: Tablets Strengths: 10 mg		
Applicant: Johnson and Johnson Agent for Applicant (if applicable): N/A		
Date of Application: July 22, 2008 Date of Receipt: July 28, 2008 Date clock started after UN: N/A		
PDUFA Goal Date: May 28, 2009	Action Goal Date (if different):	
Filing Date: September 26, 2008 Date of Filing Meeting: September 2, 2008		
Chemical Classification: (1,2,3 etc.) (original NDAs only) Factor Xa Inhibitor		
Proposed Indication(s): Prophylaxis of deep vein thrombosis and pulmonary embolism in patients undergoing hip replacement surgery and knee replacement surgery.		
Type of Original NDA: AND (if applicable) Type of NDA Supplement: ***Refer to Appendix A for further information.***		☒ 505(b)(1) ☐ 505(b)(2) ☐ 505(b)(1) ☐ 505(b)(2)
Review Classification: ***If the application includes a complete response to pediatric WR, review classification is Priority.*** ***If a tropical disease Priority review voucher was submitted, review classification defaults to Priority.***		☒ Standard ☐ Priority ☐ Tropical disease Priority review voucher submitted
Resubmission after withdrawal? ☐ Resubmission after refuse to file? ☐		
Part 3 Combination Product? ☐		☐ Drug/Biologic ☐ Drug/Device ☐ Biologic/Device
☐ Fast Track ☐ Rolling Review ☐ Orphan Designation ☐ Rx-to-OTC switch, Full ☐ Rx-to-OTC switch, Partial ☐ Direct-to-OTC Other:		☐ PMC response ☐ PMR response: ☐ FDAAA [505(o)] ☐ PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] ☐ Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) ☐ Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR

	601.42)
Collaborative Review Division (*if OTC product*):	
List referenced IND Number(s): 64,892	
PDUFA and Action Goal dates correct in tracking system? ***If not, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.***	☒ YES ☐ NO
Are the proprietary, established/proper, and applicant names correct in tracking system? ***If not, ask the document room staff to make the corrections. Also, ask the document room staff to add the established name to the supporting IND(s) if not already entered into tracking system.***	☒ YES ☐ NO
Are all classification codes/flags (e.g. orphan, OTC drug, pediatric data) entered into tracking system? ***If not, ask the document room staff to make the appropriate entries.***	☒ YES ☐ NO
Application Integrity Policy	
Is the application affected by the Application Integrity Policy (AIP)? ***Check the AIP list at:*** ***http://www.fda.gov/ora/compliance_ref/aiplist.html*** **If yes**, explain: **If yes**, has OC/DMPQ been notified of the submission? **Comments**:	☐ YES ☒ NO ☐ YES ☐ NO
User Fees	
Form 3397 (User Fee Cover Sheet) submitted	☒ YES ☐ NO
User Fee Status **Comments:**	☒ Paid ☐ Exempt (orphan, government) ☐ Waived (e.g., small business, public health) ☐ Not required
Note: *505(b)(2) applications are no longer exempt from user fees pursuant to the passage of FDAAA. It is expected that all 505(b) applications, whether 505(b)(1) or 505(b)(2), will require user fees unless otherwise waived or exempted (e.g., business waiver, orphan exemption).*	
Exclusivity	

Does another product have orphan exclusivity for the same indication? ***Check the Electronic Orange Book at: http://www.fda.gov/cder/ob/default.htm***	☐ YES ☒ NO
If yes, is the product considered to be the same product according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]? ***If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007)*** **Comments**:	☐ YES ☐ NO
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? ***(NDAs/NDA efficacy supplements only)*** ***Note:*** *An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.* **Comments**:	☒ YES # years requested: 5 ☐ NO
If the proposed product is a single enantiomer of a racemic drug previously approved for a different therapeutic use (***NDAs only***): 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)? ***If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.***	☒ Not applicable ☐ YES ☒ NO
505(b)(2) (NDAs/NDA Efficacy Supplements only)	
	☒ **Not applicable**
1. Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?	☐ YES ☐ NO
2. 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)).	☐ YES ☐ NO
3. 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))?	☐ YES ☐ NO

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).*	

4. 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*** **If yes**, please list below:	☐ YES ☒ NO

Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration

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.

Format and Content	
Do not check mixed submission if the only electronic component is the content of labeling (COL). **Comments**:	☐ All paper (except for COL) ☐ All electronic ☐ Mixed (paper/electronic) ☒ CTD ☐ Non-CTD ☐ Mixed (CTD/non-CTD)
If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?	
If electronic submission: paper forms and certifications signed (non-CTD) or electronic forms and certifications signed (scanned or digital signature)(CTD)? ***Forms*** *include: 356h, patent information (3542a), financial disclosure (3454/3455), user fee cover sheet (3542a), and clinical trials (3674);* ***Certifications*** *include: debarment certification, patent certification(s), field copy certification, and pediatric certification.* **Comments**:	☒ YES ☐ NO
If electronic submission, does it follow the eCTD guidance? (*http://www.fda.gov/cder/guidance/7087rev.pdf*) **If not,** explain (e.g., waiver granted):	☒ YES ☐ NO

Form 356h: Is a signed form 356h included? ***If foreign applicant, <u>both</u> the applicant and the U.S. agent must sign the form.*** Are all establishments and their registration numbers listed on the form? **Comments**:	☒ YES ☐ NO ☒ YES ☐ NO
Index: Does the submission contain an accurate comprehensive index? **Comments**:	☒ YES ☐ NO
Is the submission complete as required under 21 CFR 314.50 (*NDAs/NDA efficacy supplements*) or under 21 CFR 601.2 (*BLAs/BLA efficacy supplements*) including: ☒ legible ☒ English (or translated into English) ☒ pagination ☒ navigable hyperlinks (electronic submissions only) **If no**, explain:	☒ YES ☐ NO
Controlled substance/Product with abuse potential: Abuse Liability Assessment, including a proposal for scheduling, submitted? Consult sent to the Controlled Substance Staff? **Comments**:	☒ Not Applicable ☐ YES ☐ NO ☐ YES ☐ NO
BLAs/BLA efficacy supplements only: Companion application received if a shared or divided manufacturing arrangement? **If yes**, BLA #	 ☐ YES ☐ NO
Patent Information (NDAs/NDA efficacy supplements only)	
Patent information submitted on form FDA 3542a? **Comments**:	☒ YES ☐ NO
Debarment Certification	
Correctly worded Debarment Certification with authorized signature? ***If foreign applicant, <u>both</u> the applicant and the U.S. Agent must***	☒ YES ☐ NO

sign the certification. ***Note:*** *Debarment Certification should use wording in FD&C Act section 306(k)(l) 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…"* **Comments**:	
Field Copy Certification (NDAs/NDA efficacy supplements only)	
Field Copy Certification: that it is a true copy of the CMC technical section (***applies to paper submissions only***) ***If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.***	☒ Not Applicable (*electronic submission or no CMC technical section*) ☐ YES ☐ NO
Financial Disclosure	
Financial Disclosure forms included with authorized signature? ***Forms 3454 and/or 3455 must be included and must be signed by the APPLICANT, not an Agent.*** ***Note:*** *Financial disclosure is required for bioequivalence studies that are the basis for approval.* **Comments**:	☒ YES ☐ NO
Pediatrics	
PREA ***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.* Are the required pediatric assessment studies or a full waiver of pediatric studies included? **If no,** is a request for full waiver of pediatric studies OR a request for partial waiver/deferral and a pediatric plan included? • ***If no, request in 74-day letter.*** • **If yes**, 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) **Comments**:	☐ Not Applicable ☐ YES ☒ NO ☒ YES ☐ NO ☒ YES ☐ NO

BPCA (NDAs/NDA efficacy supplements only): Is this submission a complete response to a pediatric Written Request? ***If yes, contact PMHS (pediatric exclusivity determination by the Pediatric Exclusivity Board is needed).*** **Comments**:	☐ YES ☒ NO
Prescription Labeling	
Check all types of labeling submitted. **Comments**:	☐ **Not applicable** ☒ Package Insert (PI) ☐ Patient Package Insert (PPI) ☐ Instructions for Use ☐ MedGuide ☒ Carton labels ☒ Immediate container labels ☐ Diluent ☐ Other (specify)
Is electronic Content of Labeling submitted in SPL format? ***If no, request in 74-day letter.*** **Comments**:	☒ YES ☐ NO
Package insert (PI) submitted in PLR format? **If no**, was a waiver or deferral requested before the application was received or in the submission? **If before**, what is the status of the request? ***If no, request in 74-day letter.*** **Comments**: Preliminary comments regarding the PLR format will be conveyed in the 74 day letter.	☒ YES ☐ NO ☐ YES ☐ NO
All labeling (PI, PPI, MedGuide, carton and immediate container labels) consulted to DDMAC? **Comments**: The consult will be sent to DDMAC later in the review when the labeling review is closer to being completed.	☒ YES ☐ NO
MedGuide or PPI (plus PI) consulted to OSE/DRISK? (*send WORD version if available*) **Comments**:	☒ Not Applicable ☐ YES ☐ NO
REMS consulted to OSE/DRISK? **Comments**:	☒ Not Applicable ☐ YES ☐ NO
Carton and immediate container labels, PI, PPI, and proprietary name (if any) sent to OSE/DMEDP?	☐ Not Applicable ☒ YES

Comments:	☐ NO

OTC Labeling	
Check all types of labeling submitted. **Comments**:	☒ **Not Applicable** ☐ Outer carton label ☐ Immediate container label ☐ Blister card ☐ Blister backing label ☐ Consumer Information Leaflet (CIL) ☐ Physician sample ☐ Consumer sample ☐ Other (specify)
Is electronic content of labeling submitted? ***If no, request in 74-day letter.*** **Comments**:	☐ YES ☐ NO
Are annotated specifications submitted for all stock keeping units (SKUs)? ***If no, request in 74-day letter.*** **Comments**:	☐ YES ☐ NO
If representative labeling is submitted, are all represented SKUs defined? ***If no, request in 74-day letter.*** **Comments**:	☐ YES ☐ NO
Proprietary name, all labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEDP? **Comments**:	☐ YES ☐ NO
Meeting Minutes/SPA Agreements	
End-of Phase 2 meeting(s)? ***If yes, distribute minutes before filing meeting.*** **Comments**:	☒ YES Date(s): July 5, 2005; November 18, 2005; August 23, 2006 ☐ NO
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? ***If yes, distribute minutes before filing meeting.*** **Comments**:	☒ YES Date(s): December 13, 2007; January 29, 2008 ☐ NO
Any Special Protocol Assessment (SPA) agreements? ***If yes, distribute letter and/or relevant minutes before filing meeting.*** **Comments**:	☒ YES Date(s): 4/18/06; (2) 4/25/06; 4/28/06 ☐ NO

ATTACHMENT

MEMO OF FILING MEETING

DATE: September 2, 2008

NDA/BLA #: 22-406

PROPRIETARY/ESTABLISHED NAMES: Xarelto®

APPLICANT: Johnson and Johnson

BACKGROUND: Xarelto™ (Rivaroxaban) tablets is a new molecular entity. It is a direct factor Xa inhibitor. The product is being reviewed for prophylaxis of deep vein thrombosis (DVT) and pulmonary embolism (PE) in orthopedic surgery patients (short-term use). It is also being studied for acute coronary syndrome (ACS) and Atrial Fibrillation indications in the Division of Cardiovascular and Renal Products (longer-term use). The product was approved in the European Union on July 24, 2008. Bayer HealthCare, Inc. plans to launch the product in the European Union in October 2008.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Diane Leaman	Yes
	CPMS/TL:	Florence Moore	No
Cross-Discipline Team Leader (CDTL)			
Clinical	Reviewer:	Dr. Min Lu	Yes
	TL:	Dr. Kathy Robie-Suh	Yes
Social Scientist Review (*for OTC products*)	Reviewer:	N/A	
	TL:		
Labeling Review (*for OTC products*)	Reviewer:	N/A	
	TL:		
OSE	Reviewer:	Tim Lape	No
	TL:	Todd Bridges	No
Clinical Microbiology (*for antimicrobial*	Reviewer:	N/A	

products)			
	TL:		

Clinical Pharmacology	Reviewer:	Joseph Grillo, Ph.D. Christoffer Tornoe, Ph.D. and Yaning Wang, Ph.D	Yes Yes No
	TL:	Dr. Young-Moon Choi	Yes
Biostatistics	Reviewer:	Qing Xu, Ph.D. Satish Misra, Ph.D.	Yes No
	TL:	Jyoti Zalkikar, Ph.D	Yes
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Yash Chopra, M.D., Ph.D.	Yes
	TL:	Adebayo Laniyonu, Ph.D.	No
Statistics, carcinogenicity	Reviewer:	N/A	
	TL:		
Product Quality (CMC)	Reviewer:	Josephine Jee, Ph.D.	Yes
	TL:	Eldon Leutzinger, Ph.D.	Yes
Facility (*for BLAs/BLA supplements*)	Reviewer:	N/A	
	TL:		
Microbiology, sterility (*for NDAs/NDA efficacy supplements*)	Reviewer:	N/A	
	TL:		
Bioresearch Monitoring (DSI) [redacted] (b) (4) Data from site with Dr. [redacted] (b) (4) is not usable (RECORD 4)	Reviewer:	Susan Thompson, M.D.	Yes
	TL:		
Other reviewers	Charles Cooper, M.D George Rochester, Ph.D. Mark Levenson, Ph.D.		Yes No Yes

OTHER ATTENDEES: Rafel (Dwaine) Rieves, Division Director

505(b)(2) filing issues? **If yes,** list issues: Minor PLR formatting issues All the chemistry information was submitted under DMFs.	☐ Not Applicable ☒ YES ☐ NO

Per reviewers, are all parts in English or English translation? **If no**, explain:	☒ YES ☐ NO

Electronic Submission comments **List comments**: format acceptable	☐ Not Applicable
CLINICAL **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical study site(s) inspections(s) needed? **If no,** explain:	☒ YES ☐ NO
• Advisory Committee Meeting needed? **Comments**: ***If no, for an original NME or BLA application, include the reason. For example:*** o ***this drug/biologic is not the first in its class*** o ***the clinical study design was acceptable*** o ***the application did not raise significant safety or efficacy issues*** o ***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***	☒ YES Date if known: March 19, 2009 ☐ NO ☒ To be determined Reason:
• 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 permit review based on medical necessity or public health significance? **Comments**:	☒ Not Applicable ☐ YES ☐ NO
CLINICAL MICROBIOLOGY	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE

Comments:	☐ Review issues for 74-day letter
CLINICAL PHARMACOLOGY **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical pharmacology study site(s) inspections(s) needed?	☐ YES ☒ NO
BIOSTATISTICS **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
PRODUCT QUALITY (CMC) **Comments**: All chemistry is under DMFs	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Categorical exclusion for environmental assessment (EA) requested? **If no**, was a complete EA submitted? **If EA submitted**, consulted to EA officer (OPS)? **Comments**: done by CMC reviewer	☐ Not Applicable ☒ YES ☐ NO ☐ YES ☐ NO ☒ YES ☐ NO
• Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to DMPQ?	☐ Not Applicable ☒ YES ☐ NO ☐ Not Applicable ☒ YES ☐ NO

Comments:	
• Sterile product? **If yes**, was Microbiology Team consulted for validation of sterilization? (**NDAs/NDA supplements only**)	☐ YES ☒ NO ☐ YES ☒ NO
FACILITY (BLAs only) **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter

REGULATORY PROJECT MANAGEMENT

Signatory Authority: Dr. Richard Pazdur

GRMP Timeline Milestones: Filing letter 10/10/08
Midcycle December 2, 2008
Primary and Secondary Reviews due April 28, 2009
Advisory Committee Meeting TBD
Action Package and letter to Division Director May 7, 2009
Action Package and letter to Office Director May 14, 2009

Comments:

REGULATORY CONCLUSIONS/DEFICIENCIES

☐	The application is unsuitable for filing. Explain why:
☒	The application, on its face, appears to be suitable for filing. ☐ No review issues have been identified for the 74-day letter. ☒ Review issues have been identified for the 74-day letter. List (optional): ☒ Standard Review ☐ Priority Review

ACTIONS ITEMS

☒	Ensure that the review and chemical classification codes, as well as any other pertinent classification codes (e.g., orphan, OTC) are correctly entered into tracking system.
☐	If RTF action, notify everybody who already received a consult request, OSE PM., and Product Quality PM. Cancel EER/TBP-EER.

☐	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.
☐	If BLA or priority review NDA, send 60-day letter.
☒	Send review issues/no review issues by day 74
☐	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.

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

/s/

Diane V Leaman

10/3/2008 12:23:58 PM

CSO

DSI CONSULT: Request for Clinical Inspections

Date: September 25, 2008

To: Tejashri S. Purohit-Sheth, Branch Chief, Good Clinical Practices Branch I (GCP1), HFD-47
Primary Reviewer: Susan Thompson
Office of Compliance/CDER/GCPBII
Division of Scientific Investigations, HFD-45

Through: Dr. Min Lu, Medical Officer, Division of Medical Imaging and Hematology Products (DMIHP)/HFD-160
Dr. Kathy Robie-Suh, Medical Teamleaer and Dr. Rafel (Dwaine) Rieves, Division Director/ HFD-160

From: Diane Leaman, Regulatory Health Project Manager/DMIHP/HFD-160

Subject: **Request for Clinical Site Inspections**

I. General Information

Application#: NDA 22-406
Sponsor/Sponsor contact information (to include phone/email):
Drug: Trade Name (rivaroxaban)
NME: Yes
Standard or Priority: Standard
Study Population < 18 years of age: No
Pediatric exclusivity: No

PDUFA: May 28, 2009
Action Goal Date: May 28, 2009
Inspection Summary Goal Date: April 28, 2009

II. Background Information

Include a brief introduction about the application and include the following:

- *New application: Yes.*
- *Proposed indication:* Prophylaxis of DVT and PE in patients undergoing hip or knee replacement surgeries.
- *Brief information*

- *on drug:* Rivaroxaban is a highly selective direct factor Xa (FXa) inhibitor that can be orally administered.
- *Disease:* Venous thromboembolism (VTE), which includes deep vein thrombosis (DVT) and pulmonary embolism (PE), is a serious condition that is a common cause of mortality and morbidity.
- *pivotal studies (to include brief summary of protocols, pertinent endpoints, and concerns with application)*
  1. **RECORD 1 Study**: randomized, double-blind, double-dummy, active comparator controlled, multi-center and multi-national trial in patients undergoing elective total hip replacement. A total of 4541 subjects were randomized at 218 centers.
  2. **RECORD 2 Study**: randomized, double-blind, double-dummy, active comparator controlled, multi-center and multi-national trial in patients undergoing elective total hip replacement. A total of 2509 subjects were randomized at 123 centers.
  3. **RECORD 3 Study**: randomized, double-blind, double-dummy, parallel-group, active comparator controlled, multicenter, and multinational trial in patients undergoing elective total knee replacement. A total of 2531 subjects were randomized at 147 centers.
  4. **RECORD 4 Study**: randomized, double-blind, double-dummy, parallel-group, active comparator controlled, multicenter, and multinational trial in patients undergoing elective total knee replacement. A total of 3148 subjects were randomized.

  The primary efficacy endpoint for all 4 studies was a composite endpoint of:
  - Any deep vein thrombosis (DVT) (proximal and/or distal).
  - Non-fatal pulmonary embolism (PE).
  - Death from all causes.

III. Protocol/Site Identification

Study Include the Protocol Title/# for all protocols to be audited. Complete the following table.

Study Protocol Titles:

RECORD 1 Study: REgulation of Coagulation in ORthopedic Surgery to prevent DVT and PE, controlled, double-blind, randomized stiudy of BAY 59-7939 in the extended prevention of VTE in patients undergoing elective total hip replacement (Protocol 11354).

RECORD 2 Study: REgulation of Coagulation in ORthopedic Surgery to prevent DVT and PE, controlled, double-blind, randomized stiudy of BAY 59-7939 in the extended prevention of VTE in patients undergoing elective total hip replacement (Protocol 11357).

RECORD 3 Study: REgulation of Coagulation in ORthopedic Surgery to prevent DVT and PE; a controlled, double-blind, randomized study of BAY 59-7939 in the prevention of VTE in patients undergoing elective total knee replacement (Protocol 11356).

RECORD 4 Study: REgulation of Coagulation in ORthopedic Surgery to prevent DVT and PE; a controlled, double-blind, randomized study of BAY 59-7939 (rivaroxban) in the prevention of VTE in subjects undergoing elective total knee replacement (Protocol 11355).

Site # (Name,Address, Phone number, email, fax#)	Protocol #	Number of Subjects	Indication
Poland 18006 Andrzej GÓRECKI Szpital Kliniczny Dzieciatka Jezus -Centrum Leczenia ObrazenKlinika Ortopedii i Traumatologii Narzadu Ruchu I Wydzial Lekarski ul. Lindleya 4 02-005 Warszawa	**11354 RECORD 1**	Xarelto: 36 Enoxaparin: 35	Prophylaxis of DVT and PE in patients undergoing hip replacement surgery
Poland 18012 Tadeusz GAŹDZIK Wojewodzki Szpital Specjalistyczny nr 5 Katedra i Oddzial Kliniczny Ortopedii SlAM pl. Medyków 1 41-200 Sosnowiec	**11354 RECORD 1**	Xarelto: 38 Enoxaparin: 38	Prophylaxis of DVT and PE in patients undergoing hip replacement surgery
China 54005 Qingming YANG Rui Jin Hospital, Shanghai Second Medical University Orthorpaedic Department, Shanghai Ruijin Hospital No.197 Ruijin Second Road, Shanghai, China 200025	**11357 RECORD 2**	Xarelto: 17 Enoxaparin: 17	Prophylaxis of DVT and PE in patients undergoing hip replacement surgery
Peru 64005 Cesar DIAZ VALVERDE Hospital Edgardo Rebagliati Jr. Domingo Cueto s/n LIMA 11 Lima	**11357 RECORD 2**	Xarelto: 20 Enoxaparin: 21	Prophylaxis of DVT and PE in patients undergoing hip replacement surgery
China 54014 Bingfang ZENG Shanghai No.6 Hospital Orthorpaedic Department No.600 Yishan Road, Xuhui District, Shanghai, China 200233 Shanghai, 200233 CHINA	**11356 RECORD 3**	Xarelto: 13 Enoxaparin: 13	Prophylaxis of DVT and PE in patients undergoing knee replacement surgery

Site # (Name,Address, Phone number, email, fax#)	Protocol #	Number of Subjects	Indication
Poland 18003 Jacek KRUCZYŃSKI Szpital Uniwersytecki im. Antoniego Jurasza Klinika Ortopedii i Traumatologii Narzadu Ruchu ul. M. Sklodowskiej-Curie 9 Bydgoszcz, 85-094 POLAND	**11356 RECORD 3**	Xarelto: 18 Enoxaparin: 18	Prophylaxis of DVT and PE in patients undergoing knee replacement surgery
United States 14005 R. Michael MURRAY Capstone Clinical Trials, Inc. 2018 Brookwood Medical Center Drive Suite 314 Birmingham, AL 35209 UNITED STATES	**11355 RECORD 4**	Xarelto: 76 Enoxaparin: 76	Prophylaxis of DVT and PE in patients undergoing knee replacement surgery
United States 14022 David FOX Unlimited Research, LP 12709 Toepperwein Road Suite 101 San Antonio, TX 78233 UNITED STATES	**11355 RECORD 4**	Xarelto: 32 Enoxaparin: 32	Prophylaxis of DVT and PE in patients undergoing knee replacement surgery

IV. Site Selection/Rationale

Summarize the reason for requesting DSI consult and then complete the checklist that follows your rationale for site selection. Medical Officers may choose to consider the following in providing their summary for site selection.

Rivaroxaban is a new molecular entity and an oral anticoagulant for prophylaxis of VTE. The site selection is based on the efficacy. These sites showed a greater efficacy of Rivaroxaban as compared active comparator than other sites.

Scientific misconduct at more than one site has been reported in the clinical studies.

Things to consider in decision to submit request for DSI Audit

- *Evaluate site specific efficacy. Note the sites with the greatest efficacy compared to active or placebo comparator. Are these sites driving the results?*
- *Determine the sites with the largest number of subjects. Is the efficacy being driven by these sites?*
- *Evaluate the financial disclosures. Do sites with investigators holding financial interest in the sponsor's company show superior efficacy compared to other sites?*
- *Are there concerns that the data may be fraudulent or inconsistent?*
    - *Efficacy looks too good to be true, based on knowledge of drug based on previous clinical studies and/or mechanism of action*

  - *Expected commonly reported AEs are not reported in the NDA*
- *Evaluate the protocol violations. Are there a significant number of protocol violations reported at one or more particular sites? Are the types of protocol violations suspicious for clinical trial misconduct?*
- *Is this a new molecular entity?*
- *Is the data gathered solely from foreign sites?*
- *Were the NDA studies conducted under an IND?*

Rationale for DSI Audits

- *A specific safety concern at a particular site based on review of AEs, SAEs, deaths, or discontinuations*
- *A specific efficacy concern based on review of site specific efficacy data*
- *Specific concern for scientific misconduct at one or more particular sites based on review of financial disclosures, protocol violations, study discontinuations, safety and efficacy results*

Domestic Inspections:

Reasons for inspections (please check all that apply):

____ Enrollment of large numbers of study subjects
____ High treatment responders (specify):
__x__ Significant primary efficacy results pertinent to decision-making
__x__ 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
__x__ Domestic and foreign data show conflicting results pertinent to decision-making
__x__ There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, or significant human subject protection violations.
____ Other (specify) (Examples include: Enrollment of large numbers of study subjects and site specific protocol violations. This would be the first approval of this new drug and most of the limited experience with this drug has been at foreign sites, it would be desirable to include one foreign site in the DSI inspections to verify the quality of conduct of the study).

Five or More Inspection Sites *(delete this if it does not apply)*:
We have requested these sites for inspection (international and/or domestic) because of the following reasons: *state reason(s) and prioritize sites*.
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.

Scientific misconduct at more than one site has been reported in the clinical studies.

The listed sites under each study have been prioritized in order based on the efficacy results.

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

If you have specific data that needs to be verified, please provide a table for data verification, if applicable.

Should you require any additional information, please contact Diane Leaman at Ph: *301-796-1424 or Dr. Min Lu, Medical Officer* at Ph: 301-796-1406.

Concurrence: (as needed)

_____ Medical Team Leader
_____ Medical Reviewer
Rafel (Dwaine) Rieves, M.D., Director, Division of Medical Imaging and Hematology Products (for foreign inspection requests only)

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/s/

Diane V Leaman
10/27/2008 05:27:16 PM

Rafel Rieves
10/27/2008 05:30:57 PM

Interdisciplinary Review Team for QT Studies Consultation: Thorough QT Study Review

NDA	22, 406
Brand Name	Xarelto™
Generic Name	Rivaroxaban (BAY 59-7939)
Sponsor	Johnson & Johnson
Indication	Prophylaxes of Deep Vein Thrombosis and Pulmonary Embolism in Patients undergoing Hip & Knee Replacement Surgery
Dosage Form	Tablets
Drug Class	Direct Factor Xa (FXa) Inhibitor
Therapeutic Dosing Regimen	10 mg once daily
Duration of Therapeutic Use	Acute
Maximum Tolerated Dose	50 mg
Submission Number and Date	N000, 28 July 2008
Review Division	DMIHP / HFD 160

1 SUMMARY

1.1 OVERALL SUMMARY OF FINDINGS

No significant QT prolongation effect of BAY 59-7939 (15 mg and 45 mg) was detected in this TQT study. The largest upper bounds of the 2-sided 90% CI for the mean difference between BAY 59-7939 (15 mg and 45 mg) and placebo were below 10 ms, the threshold for regulatory concern as described in ICH E14 guidance. The largest lower bound of the two-sided 90% CI for the ΔΔQTcF for moxifloxacin was greater than 5 ms, and the moxifloxacin profile over time is adequately demonstrated in Figure 4, indicating that the assay sensitivity of the study was established.

In this randomized, double-blinded, four-way crossover study with 27 male and 27 female subjects single oral doses of 15 and 45 mg BAY 59-7939, placebo, and 400 mg of moxifloxacin. The overall summary of findings is presented in Table 1.

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/s/

Joanne Zhang
3/4/2009 10:08:48 AM
BIOMETRICS

Lihan K Yan
3/4/2009 10:12:14 AM
BIOMETRICS

Christine Garnett
3/4/2009 02:49:04 PM
BIOPHARMACEUTICS

Kevin Krudys
3/4/2009 03:34:16 PM
BIOPHARMACEUTICS

Monica Fiszman
3/5/2009 08:50:22 AM
PHARMACOLOGIST

Norman Stockbridge
3/5/2009 11:36:41 AM
MEDICAL OFFICER

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications

MEMORANDUM

Pre-Decisional Agency Information

Date: December 19, 2008

To: Diane Leaman – Senior Regulatory Project Manager
Division of Medical Imaging and Hematology Products (DMIHP)

From: Michelle Safarik, PA-C – Regulatory Review Officer
Division of Drug Marketing, Advertising, and Communications (DDMAC)

Subject: DDMAC labeling comments for Xarelto (rivaroxaban) film coated oral tablets
NDA 22-406

DDMAC has reviewed the proposed product labeling (PI) and proposed carton and container labeling for Xarelto (rivaroxaban) film coated oral tablets (Xarelto) submitted for consult on December 16, 2008. We offer the following comments.

Highlights

Boxed Warning

1. For consistency with the Boxed Warning section of the Lovenox PI, we recommend replacing [redacted] (b) (4) with "Rivaroxaban." As proposed, this statement minimizes the risks of Xarelto.

Dosage and Administration

1. The Highlights section of the proposed PI should summarize the most important information about Xarelto. As proposed, this section omits important material facts regarding the dosage and administration of Xarelto. Therefore, we recommend including when dosing should be initiated and the duration of use for each type of orthopedic surgery.

Warnings and Precautions

1. According to the *Guidance for Industry: Labeling for Human Prescription Drug and Biological Products – Implementing the New Content and Format Requirements*, the Warnings and Precautions section in Highlights should include "[r]ecommendations for patient monitoring to ensure safe use of the drug, and

measures that can be taken to prevent or mitigate harm." We recommend including such important information (e.g., "An epidural catheter should not be removed earlier than 18 hours after the last administration of XARELTO. The next XARELTO dose is not to be administered earlier than 6 hours after the removal of the catheter. If traumatic puncture occurs, the administration of XARELTO is to be delayed for 24 hours. . . .Any unexplained fall in hemoglobin or blood pressure should lead to a search for a bleeding site").

Full Prescribing Information

Warnings and Precautions

1. The phrase, [redacted] (b) (4) is promotional in tone and minimizes the risks of Xarelto therapy. Therefore, we recommend deleting.

Adverse Reactions

1. The following statements are redundant and unnecessary, and we recommend deleting:

[redacted] (b) (4)

Commonly-Observed Adverse Drug Reactions in Double-Blind Controlled Clinical Studies

1. [redacted] (b) (4)

   This phrase minimizes the risks of bleeding with Xarelto, and contradicts the incidences of major, non-major clinically relevant, and any bleeding events reported with Xarelto. Therefore, we recommend deleting this misleading phrase.

2. [redacted] (b) (4)

   This claim is promotional in tone and minimizes the risks of Xarelto therapy. Therefore, we recommend deleting.

Other Adverse Drug Reactions Observed During the Premarketing Evaluation of XARELTO

(b) (4)

It does not appear that LFTs >3x ULN have any clinical implication with Xarelto dosing (i.e., it does not preclude a patient starting or discontinuing Xarelto). Therefore, do these findings have clinical significance to Xarelto dosing? If not, we recommend deletion. If so, is this superiority claim supported by substantial evidence? If not, we recommend deleting.

Discontinuations Due to Adverse Drug Reactions

(b) (4)

Are the differences in the discontinuation rates between Xarelto and enoxaparin statistically significant? If not, we recommend deleting. Is the lower frequency of DVT/PE in the Xarelto group truly the primary reason for these lower discontinuation rates? Are there other reasons that should be presented in the proposed PI?

Use in Specific Populations

Pregnancy

(b) (4)

[redacted] Therefore, we recommend revising the Pregnancy Category to either C or X.

Geriatric Use

[redacted]

The above phrase is promotional in tone and minimizes the risks of Xarelto therapy. Therefore, we recommend deleting.

<u>Clinical Pharmacology</u>

Mechanism of Action

1. Is Xarelto indeed a [redacted] direct Factor Xa inhibitor? If not, we recommend deletion of this phrase.

Pharmacokinetics – Absorption and Bioavailability

1. "The absolute bioavailability of rivaroxaban is [redacted] (80% to 100%) for the 10 mg dose. Rivaroxaban is [redacted] absorbed with maximum concentrations (C_{max}) appearing 2 to 4 hours after tablet intake." (emphasis added)

   [redacted] are promotional in tone. We recommend deleting as context ("80% to 100%" and "2 to 4 hours," respectively) is provided.

Pharmacokinetics – Special Populations – Body Weight

1. "[e]xtremes in body weight (>50 kg or >120 kg) had [redacted] influence (less than 25%) on rivaroxaban plasma concentrations." (emphasis added)

   [redacted] is promotional in tone. We recommend deleting as context ("less than 25%") is provided.

Pharmacokinetics – Special Populations – Hepatic Impairment

1. "Cirrhotic subjects with mild hepatic impairment (classified as Child-Pugh A) exhibited [redacted] (1.2-fold increase in rivaroxaban AUC on average). . . ." (emphasis added)

   The phrase [redacted] is promotional in tone. We recommend deleting as context ("1.2-fold increase in rivaroxaban AUC on average") is provided.

Clinsical Studies

1. We note that this section contains several discussions of (b) (4) of major VTE and pooled analyses of the four RECORD studies and of symptomatic events in double-blind and active-controlled treatment periods. Are these (b) (4) considered substantial evidence to be included in labeling? If not, we recommend deleting.

Patient Counseling Information

1. We recommend instructing prescribers to ask patients if they have renal and/or hepatic impairment for consistency with the Dosage and Administration and Use in Specific Populations sections of the proposed PI.

Carton and Container Labeling

We have reviewed the proposed carton and container labeling and have no comments at this time.

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/s/

Michelle Safarik
12/19/2008 12:33:47 PM
DDMAC REVIEWER

MEMORANDUM

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

DATE: December 17, 2008

TO: File

FROM: Diane Leaman

SUBJECT: **NDA 22-406, Xarelto (Rivaroxaban) Tablets
Information Request from the Division of Scientific Investigations to go to Johnson & Johnson regarding the clinical site inspections.**

In response to a request for information from Dr. Susan Thompson, DSI, GCPBII, Diane Leaman, SRPM sent the following e-mail to Andrea Kollath, Director, regulatory Affairs, Johnson & Johnson Pharmaceutical Research & Development, L.L.C. on December 16, 2008:

"Andrea,
Please send us the following information:

"We are requesting the compilation of data listings for use as background material in upcoming clinical investigator inspections for NDA 22-406 Xarelto. The data listings should include the following parameters:

- Protocol and protocol amendments
- Blank CRF
- Blank ICF
- Primary efficacy endpoint
- Secondary efficacy endpoint
- Concomitant medications
- Adverse events
- Withdrawals
- Deaths
- Serious adverse events
- Protocol violations/deviations
- Randomization list for the site
- Laboratory values (biochemistry, hematology, coagulation parameters, etc.)

The data listings should be formatted separately for each of the following eight investigators:

Investigator	Protocol	Center/Site Number
Andrzej Gorecki	RECORD 1	Poland 18006
Tadeusz Gazkzik	RECORD 1	Poland 18012
Qingming Yang	RECORD 2	China 54005
Cesar Diaz Valverde	RECORD 2	Peru 64005

Bingfang Zeng	RECORD 3	China 54014
Jacek Kruczynski	RECORD 3	Poland 18003
R. Michael Murray	RECORD 4	U.S. 14005
David Fox	RECORD 4	U.S. 14022

For each parameter listed in the bullets above, the file should contain a listing of each patient enrolled by that investigator with the pertinent data - e.g., "Primary efficacy endpoint" should contain a listing of Patient 1, 2, 3, 4, etc. with the appropriate outcome of the primary efficacy endpoint. If possible, we would like the data listings transmitted electronically by January 7, 2009."

Diane”

Diane Leaman, SRPM
Division of Medical Imaging and Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

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/s/

Diane V Leaman
12/17/2008 08:47:24 AM
CSO

Division of Medical Imaging and Hematology Products (DMIHP)

REGULATORY PROJECT MANAGER LABELING REVIEW

Application Number: NDA 22-406

Name of Drug: Xarelto™ (rivaroxabaqn) Tablets

Sponsor: Johnson and Johnson

Materials Reviewed: Package Insert (PI)

Submission Date: July 28, 2008
Receipt Date: July 28, 2008

Background and Summary

Background

Xarelto™ was submitted July 28, 2008 (received July 28, 2008) for the indication: as an anticoagulant direct Factor Xa inhibitor for the prophylaxis of deep vein thrombosis (DVT) and pulmonary embolism (PE) in patients undergoing hip replacement surgery or knee replacement surgery.

Review

PACKAGE INSERT

The PI for Xarelto (rivaroxaban) tablets submitted in the original submission dated July 28, 2008 (received July 28, 2008) follows the PLR format with the following exceptions:

I. **HIGHLIGHTS OF PRESCRIBING INFORMATION** section

A. In the Drug names, dosage form, route of administration and controlled substance symbol section, the sponsor called XARELTO™ (b) (4)

Reviewer Comment: The line should read "Xarelto™ (rivaroxaban) tablets." The chemistry reviewer should comment on the term (b) (4)

B. The sponsor included a **Boxed Warning** with the following information:,

(b) (4)

(b) (4)

Reviewer Comment: The black box warning for Arixtra, an anti Xa pentasaccharide has the following black box warning:

"WARNING: SPINAL/EPIDURAL HEMATOMAS

See full prescribing information for complete boxed warning.

- **Patients receiving low molecular weight heparins, heparinoids, or fondaparinux sodium who undergo spinal puncture or neuraxial anesthesia are at risk of epidural or spinal hematoma which can result in long-term or permanent paralysis. (5.6)**
- **Risk is increased by use of indwelling epidural catheters, by concomitant use of drugs affecting hemostasis, by traumatic or repeated epidural or spinal puncture. (5.6)**
- **Monitor for signs and symptoms of neurologic impairment. (5.6)**
- **Consider risk/benefit before neuraxial intervention in anticoagulated patients or those to be anticoagulated for thromboprophylaxis. (5.6)"**

Lovenox (enoxaparin sodium) Injection has the following Black Box Warning:

"WARNING: SPINAL/EPIDURAL HEMATOMA

See *full prescribing information for complete boxed warning.*

- **Enoxaparin use in patients undergoing spinal/epidural anesthesia or spinal puncture increases the risk of spinal or epidural hematoma, which may cause long-term or permanent paralysis (5.1)**
- **Risk is increased by:**
  - **Indwelling epidural catheters for analgesia (5.1)**
  - **Drugs affecting hemostasis [*e.g.*, nonsteroidal anti-inflammatory drugs, platelet inhibitors, anticoagulants] (5.1, 7)**
  - **Traumatic or repeated spinal or epidural puncture (5.1)"**

The black box warning should list "Xarelto" (b) (4) **in the first bullet. The medical officer should comment on the Black Box Warning.**

C. **CONTRAINDICATIONS** section

1. The first bullet reads (b) (4)

   Reviewer Comment: This bullet should be shortened to read "Active major bleeding."

2. The second bullet reads (b) (4)

   Reviewer Comment: This bullet should be shortened to read "Hepatic disease with coagulopathy."

3. [redacted] (b) (4)

Reviewer Comment: This bullet should be shortened to read "Pregnancy or Breast-feeding (4)."

D. **ADVERSE REACTIONS** section

[redacted] (b) (4)

Reviewer Comment: This item should be revised to read "6.2 Postmarketing."

E. **USE IN SPECIFIC POPULATIONS** section

[redacted] (b) (4)

Reviewer Comment: These bullets should be deleted.

2. The **Renal Impairment** subsection

[redacted] (b) (4)

Reviewer Comment: The subsection should be revised to not have sub-bullets and to shorten the bullets. It could read for example,

"Severe Renal Impairment: Use with caution; use with concomitant medications (e.g., strong CYP3A4 inhibitors); may increase rivaroxaban plasma concentrations
Kidney failure: Do not use
Hepatic impairment: association with coagulopathy may lead to bleeding (8.7)."
The review team should comment on the wording in this subsection.

F. S**ee 17 PATIENT COUNSELING INFORMATION.**

[redacted] (b) (4)

Reviewer Comment: This phrase should not be included in the labeling.

III. FULL PRESCRIBING INFORMATION section

A. Throughout the labeling the sponsor refers to the tradename with all capital letters.

Reviewer Comment: The tradename should be in Title format "Xarelto" and should not include the trademark notation "™" after the first usage in the INDICATIONS AND USAGE section.

B. **6.2 Postmarketing Experience** subsection

The sponsor titled section **6.2** [redacted] (b) (4)

Reviewer Comment: The subsection should be entitled "6.2 Postmarketing Experience". The contents may need to be revised as the information in the subsection may need to be placed in another section and this subsection may need to be deleted until data after approval of the drug product has been collected.

C. **DRUG INTERACTIONS**

The sponsor entitled the fourth subsection [redacted] (b) (4)

Reviewer Comment: The title should be revised to clarify more clearly the specific items in this subsection.

D. **USE IN SPECIFIC POPULATIONS** section

1. [redacted] (b) (4)

Reviewer Comment: The sponsor should provide an explanation [redacted] (b) (4)

CONCLUSIONS

1. The comments listed (above) should be sent to the sponsor in an information request letter.

2. The entire labeling should be reviewed by the review team, including the clinical (especially Item I.B.), chemistry and manufacturing (especially Item I.A.), pharmacology/toxicology, statistical, and clinical pharmacology reviewers for further comments on labeling content.

3. A consult will be sent to the SEALD team for review.

Diane Leaman, B.S.
Safety Regulatory Project Manager
Division of Medical Imaging and
Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

Florence Moore
Acting Project Management Team Leader
Division of Medical Imaging and
Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

Cc:
Archival NDA 22-406
Drafted by: dm/8/25/08
Initialized:
Final: August 26, 2008
Filename:N22406RPMRev.doc
RPM LABELING REVIEW

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/s/

Diane V Leaman
8/27/2008 12:58:45 PM
CSO

Florence Moore
8/27/2008 06:12:11 PM
CSO