

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

206316Orig1Orig2s000

OTHER REVIEW(S)

The goal of this study is to gain efficacy and safety data in pediatric patients

(b) (4)

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.

This is one of three agreed-upon pediatric studies.

Study 3: A Phase 3, multicenter, open-label, randomized, active control study in pediatric patients with VTE. The Sponsor proposes (b) (4) (b) (4) The trial will enroll (b) (4) pediatric patients with documented VTE. The objective of the trial is (b) (4)

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)
- 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

Continuation of Question 4

- 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?

Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

- There is a significant question about the public health risks of an approved drug
- There is not enough existing information to assess these risks
- Information cannot be gained through a different kind of investigation
- The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
- The trial will emphasize risk minimization for participants as the protocol is developed

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/

JANET G HIGGINS
01/05/2015

KATHY M ROBIE SUH
01/05/2015

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.

NDA/BLA # 206316
Product Name: Savaysa (edoxaban) tablets

PMR/PMC Description: Perform, complete and submit the full study report for a single-dose study of pharmacokinetic and pharmacodynamics (PK/PD) of edoxaban in pediatric patients at risk for VTE, requiring anticoagulation or recently completing standard of care anticoagulation in accordance with your October 31, 2013 Agreed Upon iPSP.

PMR/PMC Schedule Milestones:	Final Protocol Submission:	Completed
		<u>2/19/2014</u>
	Study/Trial Completion:	<u>6/30/2017</u>
	Final Report Submission:	<u>12/31/2017</u>
	Other: _____	_____

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

Oral anti Factor Xa anticoagulants are associated with risk of bleeding and hepatotoxicity. In addition there are no antidotes or proven effective methods to reverse bleeding in patients receiving these agents; it was prudent to defer the pediatric development of such agent to after safety and effectiveness demonstrated in adults.

(b) (4)

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 goal of this pharmacokinetic/pharmacodynamic (PK/PD) study is to evaluate the PK and PD characteristics of edoxaban in pediatric patients at risk for VTE, requiring anticoagulation or recently completing standard of care anticoagulation to allow selection of appropriate doses for further study.

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.

This is one of three agreed-upon pediatric studies.

- Study 2: Title: "A Phase 1, Open-Label, Single-Dose, Non-Randomized Study to Evaluate Pharmacokinetics and Pharmacodynamics of Edoxaban in Pediatric Patients." The study proposes to start in June 2014. The study will enroll (b) (4) pediatric patients at risk for VTE requiring anticoagulant or recently completing standard of care anticoagulation. Patients from 4 age cohorts, <18-12, <12-6, <6- 2, and <2-0 years (12 patients per age cohort) will receive a single dose of edoxaban. Patients will be evaluated for PK to identify the dose for the phase 3 trial.

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)
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Continuation of Question 4

- 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
PK/PD and safety

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?

Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

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PMR/PMC Development Coordinator:

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/s/

JANET G HIGGINS
01/05/2015

KATHY M ROBIE SUH
01/05/2015

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

Memorandum

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

Date: January 2, 2015

To: Alison Blaus
Regulatory Project Manager
Division of Cardiovascular and Renal Products

From: Zarna Patel, Pharm.D.
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

James Dvorsky, Pharm.D.
Regulatory Review Officer
OPDP

Subject: Savaysa (edoxaban) tablets for oral use
NDA: 206316
Comments on draft labeling

OPDP has reviewed the proposed Package Insert (PI) submitted for consult on January 23, 2014, for Savaysa (edoxaban) tablets. OPDP's comments are provided directly on the attached copy of the proposed PI. Our comments are based on the proposed labeling at the following location:

[http://sharepoint.fda.gov/orgs/CDER-CRP/Alison%20Blaus/NDA%20206316%20\(Edoxaban\)/Labeling/NDA%20206316%20-%20Daiichi%20Proposed%20label%2029Dec2014.doc](http://sharepoint.fda.gov/orgs/CDER-CRP/Alison%20Blaus/NDA%20206316%20(Edoxaban)/Labeling/NDA%20206316%20-%20Daiichi%20Proposed%20label%2029Dec2014.doc)

Thank you for the opportunity to review the proposed PI.

If you have any questions on the comments, please contact Zarna Patel at zarna.patel@fda.hhs.gov and James Dvorsky at james.dvorsky@fda.hhs.gov.

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/s/

ZARNA PATEL
01/02/2015

JAMES S DVORSKY
01/02/2015

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

PATIENT LABELING REVIEW

Date: January 2, 2015

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

Ann Farrell, MD
Director
Division of Hematology Products (DHP)

Robert Kane, MD
Deputy Director for Safety
Division of Hematology Products (DHP)

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Associate Director for Patient Labeling
Division of Medical Policy Programs (DMPP)

Barbara Fuller, RN, MSN, CWOCN
Team Leader, Patient Labeling
Division of Medical Policy Programs (DMPP)

From: Sharon R. Mills, BSN, RN, CCRP
Senior Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

Zarna Patel, Pharm.D.
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

James Dvorsky, Pharm.D.
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: Review of Patient Labeling: Medication Guide (MG)

Drug Name (established name): SAVAYSA (edoxaban)

Dosage Form and Route: tablets for oral use

Application Type/Number: NDA 206316, Original 1, Original 2 (b) (4)

Applicant: Daiichi Sankyo, Inc.

1 INTRODUCTION

On January 8, 2014, Daiichi Sankyo, Inc. submitted for the Agency's review an original New Drug Application (NDA) 206316 for SAVAYSA (edoxaban) tablets. On January 22, 2014, the Division of Cardiovascular and Renal Products (DCRP) issued an Acknowledgment letter to the Applicant for NDA 206316. The Acknowledgment letter notified the Applicant that for administrative purposes the NDA would be split by indications as follows:

- NDA 206316/Original 1- Reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation.
- NDA 206316/Original 2- Treatment of deep vein thrombosis and pulmonary embolism.

(b) (4)

Original 1 will be reviewed by DCRP. Originals 2 (b) (4) will be reviewed by the Division of Hematology Products (DHP).

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Cardiovascular and Renal Products (DCRP) on June 17, 2014, and January 23, 2014, respectively, for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) for SAVAYSA (edoxaban) tablets.

2 MATERIAL REVIEWED

- Draft SAVAYSA (edoxaban) tablets MG received on January 8, 2014, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on December 23, 2014.
- Draft SAVAYSA (edoxaban) tablets Prescribing Information (PI) received on January 8, 2014, revised by the Review Division throughout the review cycle and received by DMPP and OPDP on December 23, 2014 and on December 30, 2014.
- ELIQUIS (apixaban) tablets for oral use comparator labeling dated August 21, 2014.

3 REVIEW METHODS

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

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using

fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We have reformatted the MG document using the Verdana font, size 11.

In our collaborative review of the MG we have:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the MG is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the MG is consistent with the approved comparator labeling where applicable.

4 CONCLUSIONS

The MG is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the MG is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG.

Please let us know if you have any questions.

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/s/

SHARON R MILLS
01/02/2015

ZARNA PATEL
01/02/2015

JAMES S DVORSKY
01/02/2015

BARBARA A FULLER
01/02/2015

LASHAWN M GRIFFITHS
01/02/2015

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

Memorandum

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

Date: January 2, 2015

To: Alison Blaus
Regulatory Project Manager
Division of Cardiovascular and Renal Products

From: Zarna Patel, Pharm.D.
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

James Dvorsky, Pharm.D.
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OPDP

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Thank you for the opportunity to review the proposed PI.

If you have any questions on the comments, please contact Zarna Patel at zarna.patel@fda.hhs.gov and James Dvorsky at james.dvorsky@fda.hhs.gov.

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/s/

ZARNA PATEL
01/02/2015

JAMES S DVORSKY
01/02/2015

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.

NDA # 206316
Product Name: Savaysa (Edoxaban Immediate Release) Tablets

PMR/PMC Description: 1) Development of a discriminating and canonical dissolution method, and
2) Setting of dissolution acceptance criterion based on data from at least 12 commercial batches.

PMR/PMC Schedule Milestones: Final Protocol Submission: 2/20/2015
Study/Trial Completion: 3/8/2016
Final Report Submission: 4/8/2016
Other: NA

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

During the review cycle it was determined that the dissolution method proposed by the Applicant did not have adequate discriminating ability. Even more, it was determined that (b) (4) a new dissolution method was needed for the proposed drug product. Since the development and validation of an appropriate dissolution method and setting of the dissolution acceptance criterion using the new method require longer than the remaining review clock time, a PMC is necessary. It is noted that the current product's control strategy (e.g., operating closely to the normal operating ranges) ensures the quality of the drug product.

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 currently proposed dissolution method shows

(b) (4)

The goals of the in vitro dissolution study under the PMC are: 1) to develop and validate a discriminating dissolution method, which follows a canonical behavior so that it can serve its purpose of being a quality control test, and 2) to set an adequate acceptance for the drug product using the dissolution profile data generated with the new dissolution method from at least 12 commercial batches.

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.

The Post-Marketing Commitment should be fulfilled within 15 months from action date:

1) develop a new dissolution method, which shows greater discriminating ability ^{(b) (4)}

_____ and set the final dissolution acceptance criterion for your drug product using the new method and the overall multipoint dissolution profile data from a minimum of 12 commercial batches (if twelve batches are made), manufactured under the same conditions as those used for the manufacture of the batches used in pivotal clinical trials. .

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)
- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
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- Dosing trials

Continuation of Question 4

- 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., development of a discriminating dissolution method)
- 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?

- Do 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?

Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

- There is a significant question about the public health risks of an approved drug
- There is not enough existing information to assess these risks
- Information cannot be gained through a different kind of investigation
- The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
- The trial will emphasize risk minimization for participants as the protocol is developed

PMR/PMC Development Coordinator:

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(Signature line for BLAs)

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/s/

Lori A WACHTER
12/18/2014

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum: December 15, 2014

Requesting Office or Division: Division of Cardiovascular and Renal Products (DCRP) and
Division of Hematology Products (DHP)

Application Type and Number: NDA 206316

Product Name and Strength: Savaysa (edoxaban) tablets, 15 mg, 30 mg, and 60 mg

Submission Date: December 5, 2014

Applicant/Sponsor Name: Daiichi-Sankyo

OSE RCM #: 2014-64-1

DMEPA Primary Reviewer: Tingting Gao, PharmD

DMEPA Team Leader: Chi-Ming (Alice) Tu, PharmD

1 PURPOSE OF MEMO

Division of Cardiovascular and Renal Products (DCRP) and Division of Hematology Products (DHP) requested that we review the revised container labels and carton labeling for Savaysa 15 mg, 30 mg, and 60 mg strengths (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.¹

2 CONCLUSIONS

The revised container labels and carton labeling for Savaysa 15 mg, 30 mg, and 60 mg strengths are acceptable from a medication error perspective. We have no further recommendations at this time.

¹ Baugh D. Label and Labeling Review for Savaysa (NDA 206316). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2014-Oct-15. 24 p. OSE RCM No.: 2014-64.

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/s/

TINGTING N GAO
12/15/2014

CHI-MING TU
12/15/2014

MEMORANDUM

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

DATE: November 17, 2014

TO: Norman Stockbridge, M.D.
Director
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I

FROM: Hansong Chen, Ph.D., Pharm.D.
Pharmacologist
Division of Bioequivalence and GLP Compliance
Office of Scientific Investigations

THROUGH: Sam H. Haidar, Ph.D., R.Ph.
Chief, Bioequivalence Branch
Division of Bioequivalence and GLP Compliance
Office of Scientific Investigations

William H. Taylor, Ph.D.
Director
Division of Bioequivalence and GLP Compliance
Office of Scientific Investigations

SUBJECT: Review of EIR Covering NDA 206316, Edoxaban, Sponsored
by Daiichi Sankyo Inc., Edison, NJ

At the request of the Division of Cardiovascular and Renal Products, Office of Drug Evaluation I, the Division of Bioequivalence and GLP Compliance (DBGLPC) arranged the inspections of the following in vivo bioequivalence study:

Study Number: DU176b-A-U142
Study Title: "An Open-label, Phase I, Randomized, Two-treatment, Replicated Crossover Bioequivalence Study of the Round Shape Tablet and the Current Tablet Formulation of Edoxaban in Healthy Subjects under Fasting Conditions."

Clinical site: Celerion, Neptune, NJ

FDA investigator, Michael Serrano (ORA) performed the inspection at Celerion, Neptune, NJ, from Oct 16 to Oct 24,

2014. The audit included a thorough review of the study records, study protocol compliance, informed consent documents, IRB approvals, case report forms, examination of facilities and test article accountability, as well as interviews and discussions with the firm's management and staff.

During the audit, the FDA investigator did not observe any significant violations and Form FDA-483 was not issued.

Analytical site: [REDACTED] (b) (4)

FDA investigators [REDACTED] (b) (4) Chen (OSI) con [REDACTED] (b) (4) spection at [REDACTED] (b) (4) from [REDACTED] (b) (4) to [REDACTED] (b) (4). The audit included a thorough review of the study records, examination of facilities and equipment, and interviews and discussions with the firm's management and staff.

During the audit, FDA investigators did not observe any objectionable conditions, and did not issue Form FDA-483 at the conclusion of the inspection.

Conclusion:

Following the above inspections, this DBGLPC scientist concludes that both clinical and bioanalytical data from study DU176b-A-U142 are acceptable for further Agency review.

Hansong Chen, Ph.D., Pharm.D.
Pharmacologist

Final Classification:

NAI- Celerion, Neptune, NJ

NAI- [REDACTED] (b) (4)
FEI#: [REDACTED] (b) (4)

cc:

OSI/DBGLPC/Taylor/Haidar/Bonapace/Skelly/Choi/Dasgupta/Chen
OSI/DBGLPC/Turner-Rinehardt/Dejernett/Fenty-Stewart/Johnson
CDER/OTS/OCP/DCPI/Menon-Andersen
CDER/OND/ODEI/DCRP/Stockbridge/Blaus
ORA/ [REDACTED] -DO/ [REDACTED] no
ORA/ [REDACTED] (b) (4) -DO/ [REDACTED] (b) (4)

Draft: HC 10/31/2014

Edit: YMC 10/31/2014; SHH 10/31/2014

Page 3 - NDA 206316, Edoxaban, Sponsored by Daiichi Sankyo Inc.,
Edison, NJ

OSI File #: BE 6670

ECMS: Cabinets/CDER_OC/OSI/Division of Bioequivalence & Good
Labora (b) (4) ce/Inspections/BE Program/Analytical
sites/

ECMS: Cabinets/CDER_OC/OSI/Division of Bioequivalence & Good
Laboratory Practice Compliance/Inspections/BE Program/Clinical
sites/Celerion, Neptune, NJ

FACTS: 8748798

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

/s/

HANSONG CHEN
11/17/2014

WILLIAM H TAYLOR
11/17/2014

MEMORANDUM

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

CLINICAL INSPECTION SUMMARY

DATE: October 28, 2014

TO: Martin Rose, Team Leader
Melanie Blank, Medical Officer Clinical
Tzu-Yun McDowell, Medical Officer Safety
Alison Blaus, Regulatory Health Project Manager
Division of Cardio-Renal Drug Products

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

THROUGH: Susan Thompson, M.D.
Team Leader
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

Kassa Ayalew, M.D., M.P.H.
Branch Chief
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: 206316

APPLICANT: Daiichi Sankyo, Inc.

DRUG: SAVAYSA™ (edoxaban tosylate)

NME: Yes

THERAPEUTIC CLASSIFICATION: Priority

INDICATION: Reduction in the risk of stroke and systemic embolism in nonvalvular atrial fibrillation (AF).

PROTOCOL: DU176b-C-U301: A Phase 3 Randomized, Double-Blind, Double-Dummy, Parallel Group, Multi-Center, Multi-National Study for Evaluation of Efficacy and Safety of DU 176b versus Warfarin in Subjects with Atrial Fibrillation” – Effective aNticoaGulation with factor xA next GEneration in Atrial Fibrillation (ENGAGE AF-TIMI 48)

CONSULTATION REQUEST DATE:	April 9, 2014
INSPECTION SUMMARY GOAL DATE:	November 8, 2014
ADVISORY COMMITTEE	October 29, 2014
DIVISION ACTION GOAL DATE:	January 8, 2015
PDUFA DATE:	January 8, 2015

I. BACKGROUND:

Daiichi Sankyo submits NDA 206316 (under IND #63,266), for edoxaban tablets (15 mg, 30 mg, 60 mg) with a proposed indication of reducing the risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation. This was a multicenter study of approximately 21,000 randomized subjects at approximately 1420 sites in six regions: North America, Latin America, Western Europe, Eastern Europe, Asia Pacific, South Africa, and Japan, encompassing 46 countries. The first subject was randomized on November 19, 2008. The last subject completed the study on May 24, 2013.

Protocol DU176b-C-U301 was an event-driven (672 primary endpoint events), Phase 3, multi-national, multi-center, randomized, double-blind, double dummy, parallel-group study in subjects with documented atrial fibrillation (AF) within the preceding 12 months and in whom anticoagulation therapy was indicated and planned for the duration of the study. Eligible subjects were stratified by CHADS 2 risk score at randomization.

- Stratum 1: CHADS 2 risk score 2 and 3
- Stratum 2: CHADS 2 risk score 4, 5, and 6

Within each CHADS 2 stratum, subjects were further stratified based on whether or not a subject required edoxaban dose reduction for factors such as low creatinine clearance, low body weight, or a need for concomitant treatment with P-glycoprotein inhibitors such as quinidine and/or verapamil.

After this second stratification, subjects were randomly assigned to 1 of the following 3 treatment groups in a 1:1:1 ratio:

- Edoxaban Low Exposure group (30 mg QD with dosage reduction to 15 mg QD for moderate renal impairment, low body weight, or specified concomitant medications), referred to as edoxaban 30 mg group hereafter.
- Edoxaban High Exposure group (60 mg QD with dosage reduction to 30 mg QD for moderate renal impairment, low body weight, or specified concomitant medications), referred to as edoxaban 60 mg group hereafter;
- Warfarin group (warfarin once daily with dose adjusted to maintain INR between 2.0 and 3.0).

Efficacy: The primary efficacy endpoint was the composite of stroke and Systemic Embolic Event (SEE). Secondary efficacy endpoints included:

- Composite of stroke, SEE, and CV mortality;
- Major adverse cardiovascular event (MACE), which is the composite of non-fatal MI, non-fatal stroke, non-fatal SEE, and death due to CV cause or bleeding;
- Composite of stroke, SEE, and all-cause mortality

Safety: The primary safety endpoint was major bleeding. Other safety assessments included, but were not limited to, all bleeding or non-bleeding AEs (including malignancies, bone fractures, hepatic, and all other AEs), and laboratory assessments. Liver enzymes and bilirubin abnormalities were evaluated as safety events of special interest.

Reasons for Site Selection:

The following sites with relatively high enrollment were chosen for inspection. Other factors for selecting sites for clinical inspection included the following:

- Site #1930 (Spinar) had high favorable effect size, low deaths and discontinuations, and low reported bleeding adverse event.
- Site #3805 (Monteiro) had high favorable effect size, and a high ratio of NSAEs to SAEs.
- Site #7017 (Maxwell) had no events in the active arm, a low death rate, a high ratio of NSAEs to SAEs, and a high number of discontinuations.
- Site #1028 (Slaby) had no major bleeding events.
- Site #1007 (Awasty, U.S. site) had high favorable effect size, high number of adverse events, deaths and discontinuations.

II. Results

Name of CI/ Site #	Protocol #, # of Subjects enrolled	Inspection Dates	Final Classification
Vivek Awasty Site 1007	DU176b-C-U301 72 subjects	May 19 – 23, 2014	NAI
Tom Maxwell Site 7017	DU176b-C-U301 99 subjects	July 14 – 18, 2014	Preliminary NAI
Pedro Monteiro Site 3805	DU176b-C-U301 137 subjects	July 7 – 15, 2014	Preliminary NAI
Josef Slaby Site 1928	DU176b-C-U301 66 subjects	July 21 – 25, 2014	Preliminary VAI
Jindrich Spinar Site 1930	DU176b-C-U301 152 subjects	June 13 – 28, 2014	Preliminary NAI (
Daiichi Sankyo Pharma Development	Sponsor Inspection DU176b-C-U301	August 4 – September 9, 2014	VAI

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. Vivek Awasty (Site 1007)

R&R Research
980 South Prospect St
Marion, OH 43302

- a. **What was inspected:** The inspection was conducted according to Compliance Program 7348.811. Dr. Awasty has fifteen IND studies in the CDER database and was last inspected in September, 2008, wherein the inspection was classified as NAI.

Dr. Awasty's site had relatively high enrollment, and high site favorable effect size for the active arm. The site screened 107 subjects and enrolled 72 subjects. A total of 17 subjects died during the study. The FDA field investigator reviewed records for 40 enrolled subjects, and 22 screen failures. At this site, the first subject was screened on January 29, 2009, and the last subject screened on November 19, 2010.

The inspection reviewed the following: Informed Consent Documents, adverse events, correspondences between the Sponsor and IRB, drug accountability records, screening and enrollment logs, laboratory results, medical records with progress notes, 1572 forms, financial disclosure statements, visit schedules, and monitoring. The field investigator corroborated the sponsor's data listings with the source records for all adverse events, including serious adverse events, protocol deviations, primary and secondary efficacy events, and subject disposition (deaths, drop-outs, discontinuations).

- b. **General observations/commentary:** There was no under-reporting of adverse events and the primary efficacy endpoint data was verifiable. The field investigator found that data documented in the subject records corroborated with data entered into the e-CRF and data listings. Monitoring was done on a regular basis during the study. No Form FDA-483 was issued, and no objectionable issues were observed.
- c. **Assessment of data integrity:** The study appears to have been conducted adequately, and the data generated by this site appear acceptable in support of the respective indication.

2. Tom Maxwell (Site 7017)

Little Common Surgery
82 Cooden Sea Road
Bexhill on Sea, E.SUSX TN39 4SP
Great Britain, Europe

- a. **What was inspected:** This inspection was conducted according to Compliance Program 7348.811. Dr. Maxwell has eight INDs in the CDER database and no prior inspections. This site was selected for inspection because: no endpoint events in the active drug arm, low number of deaths, high number of discontinuations, and high ratio of NSAEs to SAEs.
- b. **General observations/commentary:** Dr. Maxwell's site screened 128 subjects, enrolled 99 subjects. A total of 89 subjects completed the study. There were 29

screen failures, and ten discontinuations. The field investigators reviewed seventeen subject files for informed consent, inclusion and exclusion criteria, ECGs, laboratory results, INR values, concomitant medications, investigational drug disposition, corroboration of source documents to sponsor's data listings for treatment assignment, primary efficacy endpoints, AEs, SAEs, subject disposition (deaths, drop-outs, discontinuations), and endpoint events submitted to the Clinical Event Committee (CEC) for adjudication. There were no discrepancies in the corroboration of data listings to source data. Adverse events were reported, and the primary efficacy endpoint was verifiable for subject records reviewed. No Form FDA-483 was issued, because no objectionable issues were observed.

- c. **Assessment of data integrity:** The study appears to have been conducted adequately, and the data generated by this site appear acceptable in support of the respective indication.

Note: The final EIR for Dr Maxwell was not available at the time this clinical inspection summary was written. The observations noted are based on preliminary EIRs or email communications with the field investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the EIRs.

3. Pedro Monteiro (Site 3805)
Hospitais da Universidade de Coimbra
Avenida Bissaya Barreto 52
Coimbra, N/A 3000-075

- a. **What was inspected:** This inspection was conducted according to Compliance Program 7348.811. Dr. Monteiro has three IND studies in the CDER database and no prior inspections. This site was chosen to inspect because of having a high favorable effect size and a high ratio of non-serious adverse events (NSAEs) to SAEs.

Dr. Monteiro's site screened 148 subjects, and enrolled 137 subjects. There were eleven screen failures. Of the 14 dropouts, 12 were due to death and 2 were due to consent withdrawal. The field investigators reviewed records for fourteen subjects. Primary endpoint was the determining factor in choosing subject source data for review. All subject's reviewed had a reported endpoint event.

The following items were reviewed: informed consent documents; inclusion and exclusion criteria; ECGs; laboratory reports; INR values; concomitant medications; source records matching data listings for treatment assignment, primary efficacy endpoint, adverse events, serious adverse events, and deaths. As per the assignment, the inspection made sure that primary and secondary efficacy endpoint events were submitted to the Clinical Events Committee (CEC). Bleeding events were reviewed to ensure appropriate reporting. Drug accountability records were briefly reviewed.

- b. **General observations/commentary:** Dr. Monteiro was significantly involved during the conduct of the study, as evidenced by extensive documentation in source documentation and CRFs.

In the review of source data, no instances were observed of a patient having a bleeding event or stroke without documentation of the event in the e-CRF. Data listings corroborated well with source documents. The AEs and SAEs were appropriately reported. No significant discrepancies were observed while comparing source data to data provided by the sponsor (data listings). There was no under-reporting of adverse events and the primary and secondary efficacy endpoints were verifiable and accurate, for all subject records reviewed.

Monitoring was done by the sponsor and done often throughout the study. No issues were identified with respect to monitoring.

At the conclusion of the inspection, no Form FDA-483 was issued. The inspection was classified as NAI.

- c. **Assessment of data integrity:** The study appears to have been conducted adequately, and the data generated by this site may be used in support of the respective indication.

Note: The final EIR for Dr. Monteiro was not available at the time this clinical inspection summary was written. The observations noted are based on preliminary EIRs or email communications with the field investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the EIRs.

4. Josef Slaby (Site 1928)
Oblastni nemocnice Kolin,
Zizkova 146
Kolin, N/A 280 02
Czech Republic, Eastern Europe

- a. **What was inspected:** This inspection was conducted according to Compliance Program 7348.811. Dr. Slaby has one IND study in the CDER database and no prior inspections. This site was chosen to inspect because of having no major bleeding events during the study.

Dr. Slaby's site screened 69 subjects, and enrolled 66 subjects; a total of 63 subjects completed the study. Three subjects were screen failures, and three subjects died during the study. The field investigators reviewed records for fifteen subjects. These subjects were chosen for review because of having experienced a primary efficacy endpoint event during the study.

The following items were reviewed: informed consent documents; inclusion and exclusion criteria; ECGs; laboratory reports; INR values; concomitant medications; source records matching data listings for treatment assignment, primary efficacy

endpoint, adverse events, serious adverse events, and deaths. As per the assignment, the inspection made sure that primary and secondary efficacy endpoint events were submitted to the Clinical Events Committee (CEC). Bleeding events were reviewed to ensure appropriate reporting.

- b. **General observations/commentary:** Dr. Slaby was significantly involved during the conduct of the study, as evidenced by extensive documentation in source documentation and CRFs.

During review of records, no instances were observed of a patient having a bleeding event or stroke without documentation of the event in the e-CRF. Data listings corroborated well with source documents. The AEs and SAEs were appropriately reported. The inspection did not observe under-reporting of AEs, SAEs, or Events of Special Interest. The primary efficacy endpoint was verifiable, although this was not easily done, as the information was in Czech language, and had to be translated. No significant discrepancies were observed while comparing source data to the data listings.

Monitoring was done by the sponsor and done often throughout the study. No issues were identified with respect to monitoring.

At the conclusion of the inspection, a one observational Form FDA 483 was issued for:

1. An investigation not conducted in accordance with the signed statement of investigator and investigational plan. Specifically, the protocol required that SAEs and endpoint events be reported within 24 hours. For subject records reviewed, the inspection noted several instances where adverse events were reported late. For example:
 - a) Subject 046 experienced a bleeding event of epistaxis on January 22, 2011. This event was reported to the sponsor on May 25, 2011 – approximately four months later. For this same subject, medical notes documented paroxysmal atrial fibrillation (AF) on [REDACTED] (b) (6). This event was reported to the sponsor on [REDACTED] (b) (6) five days later.
 - b) Medical records documented Subject 037 had a bleeding event of hematuria June 17 through June 22, 2010. The CRF audit trail documented the event was reported to the sponsor on August 12, 2010, approximately 40 days later.
 - c) According to medical records, Subject 008 was hospitalized with salmonella infection between [REDACTED] (b) (6) and [REDACTED] (b) (6). The e-CRF audit trail documented that this was reported to the sponsor on [REDACTED] (b) (6) 3 days later. During hospitalization, the subject experienced a bleeding event “cutaneous hematoma” as a result of the intravenous treatment. The start date for the event was [REDACTED] (b) (6).

(b) (6) and the stop date was (b) (6). This event was reported to the sponsor (b) (6), twenty days later.

The issue of late reporting of SAEs, endpoint events and events of special interest was repeatedly discussed during monitoring visits, according to the Clinical Tracking log. In his July 25, 2014 response letter, Dr. Slaby stated that patients were never in jeopardy and the delay was due to lack of having a study coordinator who could help with administrative functions.

In addition, inadequate documentation was noted concerning Subject 022. Specifically, Subject 022 was hospitalized with myocardial infarction between (b) (6) and (b) (6). Although Dr. Slaby signed the hospital medical report there was no date associated with the review. The eCRF audit trail indicates the ischemic event MI was reported to the sponsor on (b) (6) approximately two months later. Three sets of medical notes subsequent to the MI (dated September 2, 2011, October 3, 2011, and October 26, 2011) document that Subject 022 had several visits with Dr. Slaby prior to reporting the MI event to the sponsor, and there was no documentation within the subject's medical records of whether Subject 022's medical condition had resolved or stabilized. However, medical notes did indicate that there was no new SAE, or AE, or endpoint event since the MI event of (b) (6).

One instance was observed in source records of an ischemic attack that occurred with Subject 037, which was not reported to the FDA, and thus did not appear in the data listings. Hospital records dated (b) (6) documented Subject 037 was admitted to the hospital due to recurring disorder of consciousness. A fax was submitted to the Clinical Event Committee with identifier STR01 for suspected cerebrovascular event. An e-CRF audit trailed showed queries from the CEC requesting information about Subject 037 outcome and source documents. There was no cerebrovascular event or stroke for Subject 037 reported in the sponsor's data listings.

- c. **Assessment of data integrity:** Although the above deficiencies were observed concerning late reporting of AEs and SAEs, they are unlikely to significantly impact the integrity of the data submitted. There was one instance of suspected cerebrovascular event that occurred to Subject 037 that was documented in source records, but did not appear in the data listings. The Review Division may wish to include the unreported cerebrovascular event in Subject 037 in the efficacy analysis.. Otherwise, the study appears to have been conducted adequately, and the data generated by this site may be used in support of the respective indication.

Note: The final EIR for Dr. Slaby was not available at the time this clinical inspection summary was written. The observations noted are based on preliminary EIRs or email communications with the field investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the EIRs.

5. Jindrich Spinar (Site 1930)
FN Brno - Bohunice,
Jihlavska 20
Brno, N/A 625 00
CZE Eastern Europe

- a. **What was inspected:** This inspection was conducted according to Compliance Program 7348.811. Dr. Spinar has five INDs in CDER's COMIS database and no prior inspections. This site was chosen to inspect because of high enrollment, high favorable treatment effect size, low number of discontinued subjects, low number of deaths, and low number of reported bleeding events.

Dr. Spinar's site screened 156 subjects, and enrolled 152 subjects. The inspection reviewed the following: source document files for 31 subjects that included corroboration of data listings with source data for inclusion and exclusion criteria, primary and secondary efficacy endpoint events, adverse events, subject disposition (deaths, discontinuations, drop-outs), general adherence to the visit schedule, protocol deviations, concomitant medications; financial disclosure statements for all clinical investigators listed on the Form 1572; and informed consent documents. The records were primarily type written in Czech - a sponsor representative read documents aloud during the inspection.

- b. **General observations/commentary:** The source document records for each study subject's visit and each endpoint event was well-documented. There was no evidence of under-reporting of adverse events. Aside from a few minor discussion items, no deficiencies were observed, and no Form FDA-483 was issued.
- c. **Assessment of data integrity:** The study was conducted well at this site, and OSI recommends that the data is acceptable in support of the claimed indication.

Note: The final EIR for Dr. Spinar was not available at the time this clinical inspection summary was written. The observations noted are based on preliminary EIRs or email communications with the field investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the EIRs.

6. Daiichi Sankyo Pharma Development
399 Thornall Street
Edison, NJ 08837

- a. **What was inspected:** The current inspection was conducted between August 4 and September 9, 2014, and focused on the following five clinical investigator sites:

- Site #7017, Tom Maxwell (Great Britain, 99 subjects enrolled)
- Site #3805, Pedro Monteiro (Portugal, 137 subjects)
- Site #1928, Josef Slaby (Czech Republic, 66 subjects)

- Site #1930, Jindrich Spinar (Czech Republic, 151 subjects)
- Site # 1007, Vivek Awasty (United States, 72 subjects)

The following items were covered during the inspection: review of records for five clinical investigator sites; training and job qualifications of monitors and site personnel; selection and monitoring of clinical investigators; contractual agreements with Contract Research Organizations (CROs); written Standard Operating Procedures (SOPs); monitoring procedures and visit reports; Quality Assurance procedures; Clinical Events Committee and Data Monitoring Committee procedures; nine investigator sites which were closed by the sponsor for non-compliance issues; Informed Consent Documents; adverse event reporting; data verification of primary efficacy endpoints; FDA-1572's and Investigator Agreements; data collection and handling; financial disclosure agreements; electronic records and signatures, and Investigational Product integrity and accountability.

- b. **General observations/commentary:** At the close of this inspection a 3-item FDA 483 was issued for the following:

- I. Failure to ensure the study is conducted in accordance with the protocol and investigational plan.

- a) Specifically, the sponsor failed to follow the Clinical Events Committee (CEC) Charter, Data Monitoring Committee (DMC) Charter, and Academic Contract Research Organization (ACRO) agreement during the adjudication process.

The CEC Charter and other sponsor agreements required that the primary and secondary efficacy endpoints and major safety events be adjudicated by two independent reviewers. The FDA field investigator observed the following: during the adjudication process, each reviewer would individually complete an adjudication form. They would then meet, and during that meeting, a single form would be signed and dated by both adjudicators indicating final agreement. Once the adjudication process was complete and a final decision made, ACRO CEC (TIMI study group) would discard one of the two paper adjudication forms. The Sponsor failed to have copies of paper adjudication forms from both independent adjudicators. The Protocol and CEC Charter states "TIMI will return the original study files to the Sponsor within 30 days of services being completed."

This issue was discussed with members of the Review Division, and considered to be non-significant, as contained in an August 20, 2014 email. It was likely that both adjudicators agreed on the occurrence of the event - since a person either had a stroke, or did not have one. In their response letter dated September 30, 2014, Daiichi Sankyo stated they would revise their procedures in the future so that to ensure proper retention practices.

- b) The Sponsor failed to ensure the CEC organizational meeting was held, as required by the protocol and CEC Charter.

The purpose of the organizational meeting was to train CEC members on the protocol, use of the adjudication forms, and provide information on the endpoint events to be reviewed.

In the September 30, 2014 response letter, the Sponsor indicates that for Study 301, the CEC Chair held an organizational training meeting for CEC members on August 14, 2009, and that no minutes were recorded.

- c) . The Sponsor failed to ensure all CEC members updated their financial disclosure agreements annually, as required.

In the September 30, 2014 response letter, the sponsor indicates this was an oversight, and that forms were available for all years except 2010.

- II. Failure to notify FDA of the termination, for-cause of an investigator's participation in an investigation.

Specifically, the Sponsor failed to notify the FDA regarding the early termination of the investigators' study participation due to non-compliance issues. On February 10, 2012, the Sponsor notified Site #2018 (Gurcharan Syan) of early termination due to serious GCP non-compliance issues. The Sponsor did not notify FDA regarding the site's early termination until the inspection starting August 21, 2014.

In the September 30, 2014 response letter, the sponsor promised corrective action would be implemented. All other site closures during this study appeared to be appropriately reported to FDA.

- III. Lack of records covering receipt, shipment to investigators, and disposition of investigational drug.

Specifically, in the review of shipment records from three clinical sites in the ENGAGE study, the FDA field investigator found the records failed to include the accurate quantity of Investigational Product (IP) returned from the site to the IP depot (b) (4)

In the September 30, 2014 response letter, the Sponsor provided corrective action to be implemented, which included updating language in Scope of Work templates concerning the management of IP.

- c. **Assessment of data integrity:** Although the inspection of the Sponsor found sporadic instances in which the sponsor failed to ensure the study was conducted according to the investigational plan, to notify FDA of termination of an investigator site due to GCP non-compliance, and to maintain accurate records for return of IP, the issues are minor, and unlikely to impact data integrity. Data from this site appear acceptable.

III. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Four foreign and one domestic clinical investigator inspections, and a Sponsor inspection were conducted in support of NDA 206316, for audit of Protocol DU176b-C-U301. No regulatory violations were found during the inspections of Drs. Awasty (U.S. site), Maxwell (Great Britain), Dr. Monteiro (Portugal), and Dr. Spinar (Czech Republic). These inspections were classified as NAI. Minor regulatory violations were found during the inspections of Dr. Slaby (Czech Republic), with a one observational FDA 483 issued for failure to follow the investigational plan. The sponsor site inspection yielded a 3-observational FDA 483 for failure to ensure the study was conducted according to the investigational plan, to notify FDA of termination of an investigator site due to GCP non-compliance, and to maintain accurate records for return of IP. These issues are unlikely to significantly impact the quality or the integrity of the data submitted in support of this NDA. OSI recommends the data be accepted.

Note: The final EIRs for Drs. Monteiro, Maxwell, Slaby and Spinar were not available at the time this clinical inspection summary was written. The observations noted are based on preliminary EIRs or email communications with the field investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the EIRs.

{See appended electronic signature page}

Sharon Gershon, Pharm.D.
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

CONCURRENCE:

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Team Leader
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Acting Branch Chief
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Office 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/

SHARON K GERSHON
10/28/2014

SUSAN D THOMPSON
10/28/2014

KASSA AYALEW
10/28/2014

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review: October 15, 2014

Requesting Office or Division: Division of Cardiovascular and Renal Products (DCRP) and
Division of Hematology Products (DHP)

Application Type and Number: NDA 206316

Product Name and Strength: Savaysa (edoxaban) tablets, 15 mg, 30 mg, 60 mg

Product Type: Single ingredient

Rx or OTC: Rx

Applicant/Sponsor Name: Daiichi-Sankyo

Submission Date: January 8, 2014 and May 21, 2014

OSE RCM #: 2014-64

DMEPA Primary Reviewer: Denise V. Baugh, PharmD, BCPS

DMEPA Acting Team Leader: Tingting Gao, PharmD

1 REASON FOR REVIEW

The Division of Medication Error Prevention and Analysis (DMEPA) has been requested by the Divisions of Cardiovascular and Renal Products (DCRP) and Division of Hematology Products (DHP) to evaluate the container label, carton and insert labeling for Savaysa (Edoxaban) Tablets, NDA 206316 for vulnerabilities to medication errors.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
FDA Adverse Event Reporting System (FAERS)	B - N/A
Previous DMEPA Reviews	C
Human Factors Study	D - N/A
ISMP Newsletters	E - N/A
Other	F -N/A
Container Labels and Carton Labeling	G
Insert Labeling	H

N/A=not applicable for this review

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

For the container label and carton labeling, we note that more adequate differentiation between the strengths is needed to minimize the risk of wrong strength errors. The color schemes that are currently used for the different strengths are not prominent enough and the (b) (4) font color is used (b) (4). Additionally, drug-identifying information such as the established name and dosage form should have more prominence on the container label and carton labeling. We note that improvements can be made to the prescribing information (PI) to make important dosing and administration information more clear and to reduce redundancy. See our recommendations in 4.1 and 4.2.

4 CONCLUSION & RECOMMENDATIONS

We conclude that the proposed container label, carton labeling, and PI can be improved to better differentiate between the strengths and to increase the prominence of important drug-identifying information on the label and labeling in order to promote the safe use of the product. Additionally, improvements can be made to the PI to clarify important dosing and administration information.

4.1 RECOMMENDATIONS FOR THE APPLICANT/SPONSOR

A. Container Labels for 30 count, 90 count, and 500 count bottles for 15 mg, 30 mg, and 60 mg tablets);

Blister Card Labeling for 100 count blister cards – 15 mg, 30 mg, and 60 mg;

Blister Card Labeling for 50 count blister cards – 15 mg, 30 mg, and 60 mg;

Professional Sample Container Label for 7 count bottle – 15 mg, 30 mg, and 60 mg;

Professional Sample Blister Card Label (7 count) – 15 mg, 30 mg, and 60 mg

1. As proposed, the labels lack adequate color differentiation and may contribute to wrong strength errors. Specifically, the proprietary name and the graphic appearing to the top right of the name are presented in the exact same font size, color, and location on the label. Similarly the strength statements are presented in the exact same font size, color, and location on the label. These similarities overwhelm the subtle (pastel) background colors ('grey' for 15 mg, 'rose' for 30 mg, and 'orange' for 60 mg) which are likely intended to provide strength differentiation. To improve on the color differentiation between the strengths and to de-clutter the label/labeling, we recommend reducing the size of or deleting the circular graphic which appears above the latter part of the proprietary name (e.g., above the letter string 'ysa' in the name, Savaysa). Additionally, we recommend using different font colors for the proprietary name and for the strength statement to provide adequate differentiation between these strengths.¹
2. Relocate the manufacturer's name and its associated logo from the top of the principal display panel to the bottom portion of the label and labeling so that it does not have more prominence than drug-identifying information.
3. Ensure the established name (active ingredient and dosage form) is at least half the size of the proprietary name in accordance with 21 CFR 201.10(g)(2).

¹ Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. Food and Drug Administration. 2013. Available from <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf>

B. Professional Sample Carton Labeling for 7 count bottle – 15 mg, 30 mg, and 60 mg

1. Relocate the “Rx Only” statement to appear at the bottom portion of the labeling to give more prominence to drug identifying information, professional sample statement, and to the medication guide statement.
2. See Comment A.1. and A.3.

**C. Carton Labeling for 30 count, 90 count, and 500 count bottles for 15 mg, 30 mg, and 60 mg tablets;
Professional Sample Blister Label and Blister Tray Labeling for 7 count blisters – 15 mg, 30 mg, and 60 mg**

1. See Comment A.1. and A.3.

D. Unit Dose Blister Card Labels (10 count – 15 mg, 30 mg, and 60 mg)

1. Differentiate between the strengths by using different colors, use of color blocking, or by other means to minimize the risk of wrong strength dispensing errors.

4.2 RECOMMENDATIONS TO THE DIVISION

Please consider the following recommendations prior to approval of this NDA:

A. Indication and Usage, Highlights of the PI and Full PI

1. Revise “5-10 days” to read “5 to 10 days” wherever this information appears in the Indication and Usage subsection of the PI to clearly state treatment duration and to minimize the risk that abbreviations (such as the hyphen) are misinterpreted.

B. Section 2.3, Full Prescribing Information

2. Revise (b) (4) to read (b) (4) since (b) (4) are independent of the indication for the drug.
3. Revise (b) (4) to read “CrCL 15 to 50 mL/min” to clearly state the definition of moderate to severe renal impairment.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Savaysa that Daiichi-Sankyo submitted on January 8, 2014.

Table 2. Relevant Product Information for Savaysa	
Active Ingredient	edoxaban
Indication	1) reduction in the risk of stroke and systemic embolism in nonvalvular atrial fibrillation (NVAf); 2) treatment of deep vein thrombosis (DVT); 3) treatment of pulmonary embolism (PE) (b) (4) [REDACTED]
Route of Administration	oral
Dosage Form	tablet
Strength	15 mg, 30 mg, 60 mg
Dose and Frequency	60 mg once daily; 30 mg once daily [REDACTED] (b) (4) [REDACTED] low body weight (≤ 60 kg); or concomitant use of P-glycoprotein inhibitors [REDACTED] (b) (4) To transition from Savaysa 30 mg to warfarin, reduce dose to 15 mg and begin warfarin concomitantly.
How Supplied	bottles of 30 count, 90 count, and 500 count tablets [REDACTED] (b) (4) [REDACTED] blister package containing 100 tablets (10 blister cards containing 10 tablets each)
Storage	20°C to 25°C (68°F to 77°F)

APPENDIX C. PREVIOUS DMEPA REVIEWS

C.1 Methods

We searched our archives (L: drive and AIMS) on February 7, 2014 using the term, "Savaysa" to identify reviews previously performed by DMEPA.

C.2 Results

No previous reviews of the container label, carton labeling, insert labeling or medication guide were retrieved in our search.

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed (and Their Corresponding Images)

Using the principles of human factors and Failure Mode and Effects Analysis,² along with postmarket medication error data, we reviewed the following Savaysa labels and labeling submitted by Daiichi-Sankyo on January 8, 2014 and on May 21, 2014 (50 count unit dose blister labels).

(b) (4)



1 / Page(s) of Draft Labeling have been withheld in full as b4 (CC/TS) immediately following this page

² Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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

/s/

DENISE V BAUGH
10/15/2014

TINGTING N GAO
10/15/2014

MEMORANDUM

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

CLINICAL INSPECTION SUMMARY

DATE: September 30, 2014

TO: Janet G. Higgins, Regulatory Project Manager
Saleh Ayache, M.D., Medical Officer
Kathy Robie-Suh, M.D., Ph.D. Team Leader
Division of Hematology Products (DHP)

FROM: Anthony Orenca, M.D., F.A.C.P.
Medical Officer, GCP Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

THROUGH: Janice Pohlman, M.D., M.P.H.
Team Leader, GCP Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

Kassa Ayalew, M.D., M.P.H.
Branch Chief, GCP Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: 206316

APPLICANT: Daiichi Sankyo Pharma Development

DRUG: edoxaban

NME: Yes

THERAPEUTIC CLASSIFICATION/REVIEW: Standard review

INDICATION: Treatment of adult patients with deep vein thrombosis (DVT) and
pulmonary embolism (PE) (b) (4)
[REDACTED]

CONSULTATION REQUEST DATE (signed): March 18, 2014
INSPECTION SUMMARY GOAL DATE (revised): September 30, 2014
DIVISION ACTION GOAL DATE January 7, 2015
PDUFA DATE: January 8, 2015

I. BACKGROUND:

Oral vitamin K antagonists, inhibitors of factors II, VII, IX, and X synthesis, have been the mainstay as anticoagulation agents to treat deep vein thrombosis (DVT) and pulmonary embolus (PE [venous thromboembolic event (VTE)]). Alternative oral antithrombotic agents are sought such as edoxaban, a selective inhibitor of Factor Xa.

A single adequate and well-controlled trial for DVT and PE treatment, and prevention of recurrent VTE, was submitted [REDACTED] ^{(b) (4)}. Two foreign and two domestic clinical sites were selected for inspection because the sites had large number of enrolled study subjects. Dresden (Germany) was selected because of fewer than expected reported adverse events. Johannesburg (South Africa) and San Antonio, TX were selected because of higher than average reported adverse events. Las Vegas, NV was selected because of higher frequency of reported deaths, and imbalances of deaths between the two treatment arms.

Protocol DU-176b-D-U305

Study DU-176b-D-U305 was a Phase 3, multi-national, multi-center, randomized, double-blind, matching placebo, parallel-group non-inferiority study for efficacy and safety. The maximum possible planned treatment period for any individual subject after randomization was 12 months, with a minimum of three months treatment (consistent with current American College of Chest Physicians (ACCP) Guidelines). The primary objective was to evaluate whether initial treatment with (Low Molecular Weight [LMW]) heparin followed by edoxaban only is non-inferior to initial (LMW) heparin overlapping with warfarin, followed by warfarin only in the treatment of subjects with acute symptomatic VTE for the prevention of symptomatic recurrent VTE during the 12-month study period. A blinded Clinical Events Committee (CEC) was established to objectively verify the adequacy of the presenting index diagnosis, the recurrence of protocol-specified VTE endpoints, major adverse cardiovascular events (MACEs), and to classify bleeding events. The primary efficacy endpoint was symptomatic recurrent VTE (i.e., composite of DVT, non-fatal PE, and fatal PE). The CEC adjudication results were the basis for the final analyses.

II. RESULTS:

Name of CI Location	Protocol/Study Site/Number of Subjects Enrolled (n)	Inspection Date	Classification*
Sebastian Schellong, M.D. Friedrichstr, 41 Dresden, SN 1067 Germany	DU-176b-D-U305/Site1707/ N=144	April 28-May 7, 2014	NAI
Professor Barry Jacobson, MBChB 7 York Road Parktown P.O.Box 1038 Johannesburg, 2000 South Africa	DU-176b-D-U305/Site 4905 N=130	May 12-23, 2014	VAI
Roger Lyons, MD 4411 Medical Drive, Suite 100 San Antonio, TX 78229	DU-176b-D-U305/Site 1002 N=50	May 22-June 6, 2014	Preliminary: NAI
Edwin Kingsley, M.D. Comprehensive Cancer Centers of Nevada 3730 S. Eastern Ave. Las Vegas, NV 89169	DU-176b-D-U305/Site 1039 N=24	July 28-August 7, 2014	Preliminary: VAI
Sponsor: Daiichi Sankyo Pharma Development 399 Thornall St. Edison, NJ 08837	Sponsor monitoring of the clinical trial, Protocol DU-176b-D-U305 [Note: Inspection of Daiichi Sankyo Pharma Development related to Conduct of Protocol DU-176b-C-U301 will be included in a separate CIS for the atrial fibrillation indication]	August 4-September 9, 2014	Preliminary: VAI

*Key to Classifications

NAI = No deviation from regulations. Data acceptable.

VAI-No Response Requested = Deviations(s) from regulations. Data acceptable.

OAI = Significant deviations from regulations. Data unreliable/critical findings may affect data integrity.

Preliminary=The Establishment Inspection Report (EIR) has not been received, findings are based on preliminary communication with the field at the Office of Regulatory Affairs (ORA), or final review of the EIR is pending. Once a final letter is issued by CDER to the inspected entity and the case file is closed, the preliminary designation is converted to a final regulatory classification.

CLINICAL STUDY SITE INVESTIGATOR

1. Sebastian Schellong, M.D./Protocol DU-176b-D-U305/Site #1002

Dresden, Germany

a. What was inspected:

The inspection was conducted in accordance with Compliance Program 7348.811, from April 28 to May 7, 2014. A total of 145 subjects were screened and 144 subjects were enrolled. One hundred forty-three subjects completed the study. An audit of 72 enrolled and randomized subjects' records was conducted.

The inspection evaluated the following documents: source records, screening and enrollment logs, case report forms, study drug accountability logs, study monitoring visits, and correspondence. Informed consent documents and sponsor-generated correspondence were also inspected.

b. General observations/commentary:

Source documents for subjects whose records were reviewed were verified against the case report forms and NDA subject line listings. Source documents for the raw data used to assess the primary study endpoint were verifiable at the study site. The primary efficacy endpoint was determined by a Central Adjudications Committee. No under-reporting of adverse events or serious adverse events was noted. There were no limitations during conduct of the clinical site inspection.

In general, this clinical site appeared to be in compliance with Good Clinical Practices. A Form FDA 483 (List of Inspectional Observations) was not issued at the end of the inspection.

c. Assessment of data integrity:

Data submitted by this clinical site appear acceptable in support of this specific indication.

2. Professor Barry Jacobson, MBChB/Protocol Protocol DU-176b-D-U305/Site #4905

Johannesburg, South Africa

a. What was inspected:

The inspection was conducted in accordance with Compliance Program 7348.811, from May 12 to 23, 2014. A total of 130 subjects were enrolled and randomized. One hundred thirteen subjects completed the study. An audit of 25 subjects' records was conducted.

The inspection evaluated the following documents: source records, screening and enrollment logs, case report forms, study drug accountability logs, study monitoring visits, and correspondence. Informed consent documents and sponsor-generated correspondence were also inspected.

b. General observations/commentary:

Source documents for the subjects whose records were reviewed were verified against the case report forms and NDA subject line listings. Source documents for the raw data used to assess the primary study endpoint were verifiable at the study site. The primary efficacy endpoint was determined by a Central Adjudications Committee. There were no limitations during conduct of the clinical site inspection.

A Form FDA 483 (List of Inspectional Observations) was issued at the end of the inspection for failure to follow the study protocol according to the investigational plan (including informed consent violations) and failure to maintain accurate case histories pertinent to the clinical trial investigation (See selected examples below). The Form FDA 483 was shared and subsequently discussed with CDER DHP. Specifically,

- (i) Informed consent regulatory deficiencies were found. For example:
- a) Subject 7540 did not sign the informed consent form prior to randomization on August 1, 2012. The form was signed by the person explaining consent on July 31, 2012.
 - b) Subject 7655 was not consented with the most current (December 12, 2011) version of the informed consent form. Instead, Subject 7655 signed the November 12, 2010 ICF version on August 13, 2012. Similarly, Subject 5479 was not consented with the most current (December 12, 2011) version of the informed consent form. Instead, Subject 5479 signed the November 12, 2010 ICF version on February 7, 2012.
 - c) Subject 1820 signed the November 12, 2010 ICF version on March 8, 2011, the day of randomization into the study. The person giving consent did not sign the ICF until July 13, 2011.

OSI Reviewer Comment: The examples cited above were considered regulatory deficiencies. Subject 7540's ICF was considered incomplete and not done according to the protocol requirements and consenting process at this clinical study site. However, an ICF was subsequently signed by this subject on September 3, 2012, a copy of which was attached to Dr. Jacobson's June 18, 2014, Form FDA 483 response letter. Following the FDA inspection in May, an updated informed consent SOP was implemented and staff was trained on the process.

- (ii) Subjects did not complete anticoagulation with low molecular weight heparin (LMWH) and warfarin or warfarin placebo for at least five days, according to the protocol. For example:
- a) Subject 0156 received four consecutive days of anticoagulation therapy instead of the required minimum five days.
 - b) Subject 1757's record had no documentation indicating that she received the required minimum five day anticoagulation therapy. According to the Patient Prescription and Administration Chart, for Subject 1757, LMWH (Clexane 80 mg

- s.c. BID) was administered five times after randomization. However, source documentation indicated that Clexane was not dispensed to the subject at the time of discharge.
- c) Subject 0672 missed doses during the required minimum five day anticoagulation therapy with LMWH prior to edoxaban dosing. According to the patient Medicine Administration Sheet, Subject 0672 was prescribed Clexane 80 mg s.c. BID. However, source documentation indicated that only one dose of Clexane on October 13, no doses on October 14, and a last single dose of Clexane on October 15, 2010 were administered.

OSI Reviewer Comment: Although required by protocol, completion of five days of anti-coagulation treatment with LMWH prior to initiating therapy with edoxaban (warfarin placebo) or warfarin (edoxaban placebo) may be difficult to implement. These protocol deviations were thought to be consistent with the practice of clinical medicine. Although, the above findings are regulatory violations, the violation do not appear to affect the overall reliability of safety and efficacy data from this site. DHP concurred.

(iii) The following laboratory assessments were not assessed after the INR value was obtained and before edoxaban or placebo was administered.

- a) Subjects 0156, 3054, and 1757 did not have liver function tests done prior to the administration of edoxaban or placebo.
- b) Subject 3054 did not have a urinalysis test done at the time of randomization.
- c) Subject 2972 did not have serum chemistry test done at Day 30 after randomization.
- d) Subject 0333 did not have pregnancy and urinalysis tests done at the time of randomization.
- e) Subject 0199 did not have a pregnancy test done at the time of randomization.
- f) Subject 5479 did not have a pregnancy test done at the time of randomization.

OSI Reviewer Comment: Although the above findings are regulatory violations, the violation do not appear to be clinically significant, and had no impact on their efficacy or safety assessments. Dr. Jacobson responded in his letter that while the pregnancy tests were not done initially, these were subsequently done at the Day 30 visit and were reported in the study subject source file.

(iv) The following documents appeared to be obliterated. For example:

- a) Subject 0333's concomitant medications log had several obliterations, which appeared to have been "whited-out"/"data filled in".
- b) Subject 0156's LMWH record documentation had overwritten marks. The entry for the Day 2-12 visit was overwritten to change the stop date of Clexane from "12" to "13", making the stop date June 13, 2010, instead of June 12, 2010.

(v) The following examples of study source records listed concomitant medications were not included in the electronic case report forms (eCRFs):

- a) Subject 1261's Clexane (July 12-14, 2011), Proscar (July 12-15, 2011) and Cardura XL (July 12, 2011).
- b) Subject 3054's warfarin (August 25-27, 2011) beclomethasone (Beclato) (August 29, 2011), albuterol (Asthavent) (August 29, 2011), and AB Nebs (August 24-27, 2011).
- c) Subject 561's Decadron (December 27-January 4, 2010), Losec (January 13-16, 2011), piperacillin-tazobactam (Tazocin) (January 13-16, 2011), doxyphene January 10-16, 2011), RBC and fresh frozen plasma (January 10, 2011).

OSI Reviewer Comment:

Although the above findings are regulatory violations, the violation do not appear to be clinically significant as the medications are believed to have minimal contribution towards the Application's safety and efficacy evaluation.

(vi) The following adverse events were not reported in the eCRF:

- a) Subject 0333's lump in the back on January 2011, and mild intermittent shortness of breath (January 31, 2011)
- b) Subject 3054's vomiting episode on August 23, 2011
- c) Subject 4499's syncope on December 20, 1011
- d) Subject 3009's sore chest (November 1, 2011), and
- e) Subject 0278's superficial graze on the left calf throughout the end of treatment.

OSI Reviewer Comment:

Dr. Jacobson stated that this syncopal event was part of the lower gastrointestinal bleeding event, a reported serious adverse event, that ultimately lead to the patient's demise, despite resuscitation measures, e.g., with packed RBCs. The other isolated adverse event deficiency observations have no significant impact on the safety assessments for this NDA.

The above regulatory deficiencies cited above were communicated to the DHP Medical Team, who did not consider these observations to be critical. Dr. Jacobson responded adequately to the inspectional audit in a letter dated June 18, 2014.

c. Assessment of data integrity:

Despite the above observed regulatory deficiencies, the study appears to have been conducted adequately and the data may be used in support of the application.

3. Roger Lyons, M.D./Protocol DU-176b-D-U305/Site 1002
San Antonio, Tx

a. What was inspected:

The inspection was conducted in accordance with Compliance Program 7348.811, from May 22 to June 6, 2014. A total of 53 subjects were screened and 50 subjects were enrolled. Forty one subjects completed the study. An audit of 25 enrolled subjects was conducted regarding primary study endpoint verification.

The inspection evaluated the following documents: source records, screening and enrollment logs, case report forms, study drug accountability logs, study monitoring visits, and correspondence. Informed consent documents and sponsor-generated correspondence were also inspected.

b. General observations/commentary:

Source documents for the subjects whose records were reviewed were verified against the case report forms and NDA subject line listings. Source documents for the raw data used to assess the primary study endpoint were verifiable at the study site. The primary efficacy endpoint was determined by a Central Adjudications Committee. No under-reporting of adverse events or serious adverse events was noted. There were no limitations during conduct of the clinical site inspection.

In general, this clinical site appeared to be in compliance with Good Clinical Practices. A Form FDA 483 (List of Inspectional Observations) was not issued at the end of the inspection.

c. Assessment of data integrity:

Data submitted by this clinical site appear acceptable in support of this specific indication.

4. Edwin Kinglsey, M.D./Protocol DU-176b-D-U305/Site #1039
Las Vegas, NV

a. What was inspected:

The inspection was conducted in accordance with Compliance Program 7348.811, from July 28 to August 7, 2014. A total of 39 subjects were screened and 24 subjects were enrolled. The number of subjects who completed the study was not obtained during the audit. An audit of 12 screened subjects' records was conducted for patient data listings and source document review regarding concomitant medications, prohibited medications, and adverse events. An audit of 22 enrolled subjects was conducted regarding primary study endpoint verification.

The inspection evaluated the following documents: source records, screening and enrollment logs, case report forms, study drug accountability logs, study monitoring

visits, and correspondence. Informed consent documents and sponsor-generated correspondence were also inspected.

b. General observations/commentary:

Source documents for the subjects whose records were reviewed were verified against the case report forms and NDA subject line listings. Source documents for the raw data used to assess the primary study endpoint were verifiable at the study site. The primary efficacy endpoint was determined by a Central Adjudications Committee. No under-reporting of adverse events or serious adverse events was noted. There were no limitations during conduct of the clinical site inspection.

A Form FDA 483 (List of Inspectional Observations) was issued at the end of the inspection. In general, the study was not conducted in accordance with the investigational plan. Specifically:

- (i) Subject 1039-5440's adjudication package was not submitted for an ultrasound that was ordered to investigate a possible recurrent DVT event.

OSI comment: The reported regulatory deficiency did not appear to be a protocol violation. Subject 1039-5440 was consented and enrolled on February 3, 2012. Although source records (physician progress note 3/21/12) list a diagnosis of a right leg DVT with PE, the central adjudication committee concluded that this subject had presented with PE without DVT. At the visit on 3/21/12, the PI noted some increased swelling in the right leg and obtained an ultrasound of the right lower extremity which was noted to show significant improvement in the DVT in the distal right femoral and popliteal veins. This was the ultrasound study which was not sent to the adjudication committee. Based upon the discrepancy between the clinical site and adjudication committee difference in presenting diagnosis (i.e. central diagnosis of PE without DVT), the 3/21/12 study would likely not have made a difference in outcome since the adjudication committee did not agree with the initial DVT diagnosis and this scan was noted to be improved.

- (ii) Subject 1039-0007's 30 day visit was calculated from the edoxaban start date and not from the date of randomization.

The PI responded adequately to the Form FDA 483 in a letter dated August 25, 2014.

c. Assessment of data integrity:

The above regulator deficiencies at this site are isolated. Data submitted by this clinical site appear acceptable in support of this specific indication.

SPONSOR

5. Daiichi Sankyo Pharma Development

Edison, NJ

a. What was inspected:

The inspection was conducted in accordance with Compliance Program 7348.810, from August 4 to September 9, 2014. The inspection evaluated the following: documents related to study monitoring visits and correspondence, Institutional Review Board (IRB) approvals, completed Form FDA 1572s, monitoring reports, drug accountability, and training of staff and site monitors.

b. General observations/commentary:

The sponsor generally maintained adequate oversight of the clinical trial. For the most part, monitoring of the investigator sites was adequate. There was no evidence of under-reporting of adverse events.

A Form FDA 483 was issued at the end of the sponsor inspection. The following observations were noted:

- I. The sponsor failed to follow the protocol, Clinical Events Committee (CEC) Charter, Data Monitoring Committee (DMC) Charter, or Academic Contract Research Organization agreement for Protocol DU-176b-D-U305. Specifically:
 - a) The sponsor failed to ensure the Clinical Events Committee organizational meeting was held as required by section 4.1 “CEC Organizational Meeting” of the CEC Charter. The purpose of the organizational meeting was to train the CEC members on the protocol, become familiar with the adjudication forms and procedures, provide an opportunity for questions, agree upon the definitions of the endpoints that will be reviewed, and ensure consistency among all CEC members
 - b) The sponsor failed to follow section 4.1.7 “Dissemination of Results” of the DMC Charter. The DMC was responsible for protecting the safety of subjects and providing recommendations regarding the status of the study. For example,
 - i. Eleven of 16 meeting minutes failed to document the DMC’s recommendations (continue the study as planned, modify the protocol, or terminate the study early for safety reasons) after each of these DMC meetings, and
 - ii. The DMC failed to send a letter with their recommendations to the Chairman of the Steering Management and Coordination Committee (SMCC) in 4 of 15 of their meetings. The SMCC was responsible for providing oversight of the study design and study conduct.

OSI Reviewer Comments: While the above observations were considered regulatory deficiencies, the administrative deficiencies by the CEC and DMC did not have an impact on the actual conduct of the clinical trial for Study DU-176b-D-U305.

- II. Failure to monitor non-compliant study sites adequately. Specifically:
- a) The investigator who did not comply with the signed agreement was not terminated. The sponsor failed to terminate the Principal Investigator at Site #3322, who failed to conduct the study according to the study protocol investigational plan.
 - b) The sponsor did not notify the FDA regarding early termination of the Principal Investigator at Site #4429 until August 21, 2014. Site #4429's PI was terminated due to non-verifiable and inaccurate local laboratory data to assess study subjects for enrollment to the study.

OSI Reviewer Comment: Although the above findings are regulatory violations, the violation have minimal contribution towards the Application's safety and efficacy evaluation as they only involve two Clinical Investigators in a large clinical study conducted across 439 study sites. The findings would be unlikely to have significant impact on the outcome of the study.

c. Assessment of data integrity:

Notwithstanding the regulatory deficiencies listed above, the sponsor monitoring of sites appeared to be reliable. Data submitted by this sponsor appear acceptable in support of the requested indication.

III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

For this Phase 3, randomized, double-blind, placebo-controlled, parallel group study submitted in support of this NDA, two domestic (U.S.) clinical sites and two foreign study sites were inspected. The sponsor (Daiichi Sankyo Pharma Development) was also inspected.

The regulatory classification for Dr. Sebastian Schellong is No Action Indicated (NAI). The final regulatory classification for Drs. Barry Jacobson and Edwin Kingsley is Voluntary Action Indicated (VAI). The preliminary regulatory classification for Dr. Roger Lyons is No Action Indicated (NAI). The preliminary regulatory classification for the Daiichi Sankyo Pharma Development audit is Voluntary Action Indicated (VAI). The study data collected from this clinical site appears reliable in support of the requested indication.

Note: The inspectional observations noted above for Dr. Lyons and Daiichi Sankyo Pharma Development are based on preliminary communications with the field investigator and/or preliminary review of the EIR. A clinical inspection summary addendum will be generated, if conclusions on the current inspection report changes

significantly, upon receipt the Establishment Inspection Report (EIR). CDER OSI classification of inspection is finalized when written correspondence is issued to the inspected entity.

{See appended electronic signature page}

Anthony Orenca, M.D.
Medical Officer
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

CONCURRENCE:

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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/

ANTHONY J ORENCIA
09/30/2014

JANICE K POHLMAN
10/01/2014

KASSA AYALEW
10/01/2014

Hepatology Consultation

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

DATE: 25 September 2014

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

TO: Norman Stockbridge, M.D., Director, Division of Cardio-Renal Products (DCRP)
Martin Rose, M.D., Medical Team Leader, DCRP
Melanie Blank, M.D., Medical Efficacy Reviewer, DCRP
Tzu-Yun McDowell, M.D., Medical Safety Reviewer, DCRP
Ann Farrell, M.D. Director, Division of Hematology Products (DHP)
Kathie Robie-Suh, M.D., Medical Team Leader, DHP
Saleh Ayache, M.D., Medical Efficacy/Safety Reviewer, DHP

VIA: Solomon Iyasu, M.D., Director, OPE

SUBJECT: Hepatic effects of edoxaban (SAVAYSA[®] Daiichi Sankyo), NDA 206316
submitted 8 January 2014 for (b) (4) indications: 1) prevention of stroke and systemic
embolization in patients with atrial fibrillation (AFib); 2) (b) (4)
(b) (4) treatment of deep vein thrombosis and
pulmonary embolism (b) (4)

Documents reviewed:

- 1) Consultation request from DCRP dated 6 May 2014 asking for review of findings related to liver toxicity, desired response date 8 August 2014, before the primary clinical reviews are due
- 2) Submitted data on 8,292 subjects undergoing knee or hip replacement treated with heparin-warfarin or enoxaparin-edoxaban in the HOKUSAI study U-305
- 3) Submitted data on 21,097 subjects with chronic atrial fibrillation randomized to oral edoxaban or warfarin in the ENGAGE study U-301 in studies carried out worldwide.
- 4) Selected pertinent medical literature articles on edoxaban, atrial fibrillation, etc.
- 5) Toxicology review by Dr Shwu-Luan Lee, 19 August; DHP safety review by Dr. Saleh Ayache, 8 September; statistical review by Dr. John Lawrence, 22 September 2014.

Following submission of an interim draft consultation on 8 August, several primary reviews have been received (see 5) above. No further comments have been received from reviewers.

The manufacturers of the new orally effective anticoagulants (NOAs) claim that they do not require periodic monitoring of their activity. This argument has been very well received by both prescribers and patients, resulting in a very large new market for these drugs. Warfarin, the drug used for standard comparisons, usually has a narrow range of dosing in an individual. It requires periodic venipunctures for measurement of plasma prothrombin time to adjust the warfarin dose, to avoid bleeding risk if too much, or insufficient anticoagulation if too little, and to keep plasma prothrombin time acceptable or its international normalized ratio (INR) between 2.0 and 3.0. An alternative monitoring by finger-stick devices has been around for a decade but is expensive and somewhat cumbersome, and has not become popular. It is accepted that anticoagulation is the treatment of choice for prevention of strokes and systemic embolization in patients with chronic or recurrent atrial fibrillation (AFib), a common disorder in elderly millions worldwide. It is also important in reducing the incidence of deep vein thrombosis (DVT) and pulmonary emboli (PE) in patients after procedures for knee or hip replacement, or preventing recurrent thromboembolic events on patients who had previous DVT or PE. It is important to evaluate the fraction of time of INR in the target therapeutic range of 2 -3 for controlling subjects on warfarin, in comparing effects of the NOAs (Mearns et al., 2014).

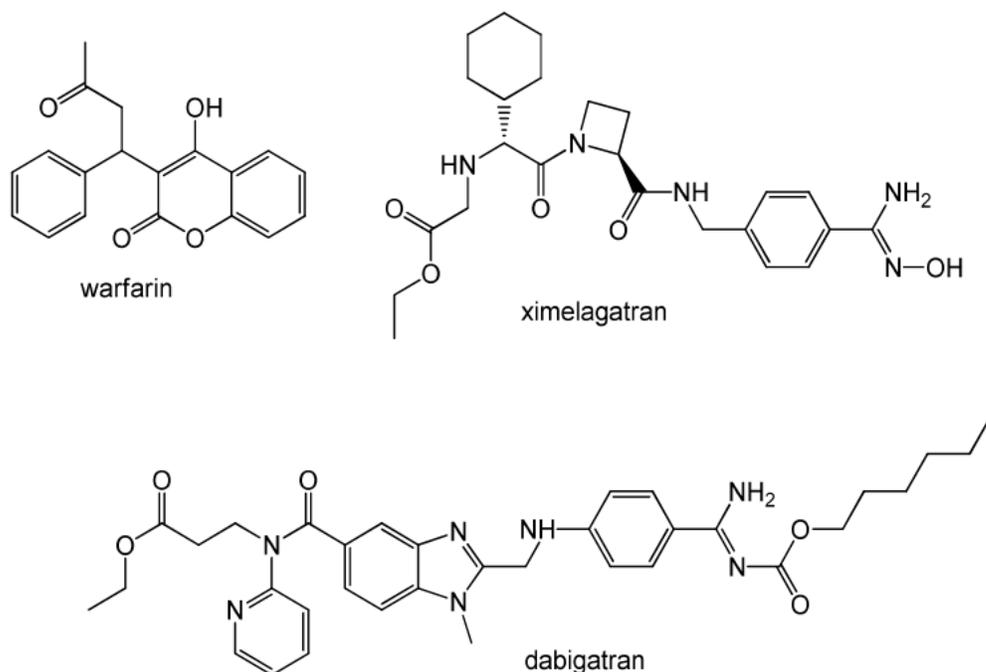
Edoxaban is the fifth candidate novel oral anticoagulant following two direct thrombin inhibitors (ximelagatran and dabigatran) and the two factor Xa inhibitors (rivaroxaban and apixaban). It is pertinent to say a few words about these NOAs.

Ximelagatran, a direct thrombin inhibitor, was the first of the NOAs, developed as EXANTA[®] by AstraZeneca, but its NDA 21-686 was not approved in the United States in October 2004 despite earlier approvals in Europe, because of our concerns about hepatotoxicity. The sponsor contested the disapproval for some years but finally conducted additional studies on samples of subjects included in the clinical trials, comparing some of those who had shown hepatotoxicity with some who had not. They found that incidence of serum alanine aminotransferase (ALT) elevations in patients with AFib treated long-term with ximelagatran was about 15 times higher in northern Europe compared to Asia, triggering genetic studies. On further investigation they found that inheritance of the HLA biomarkers (DRB1*07 and DQA1*02) conveyed greatly an increased susceptibility to ximelagatran-induced sometimes serious liver injury or dysfunction (Kindmark, et al. 2008; Andersson et al., 2009; Keisu et al., 2010). No such differences were found in the warfarin-treated patients, and their incidence of elevations in serum alanine aminotransferase was much lower, as we had found on review of the data submitted for the then-novel eDISH program for the 3922 patients in the large SPORTIF V study. Those differences in ALT were missed by the AstraZeneca statisticians using conventional comparisons of group mean values.

Boehringer Ingelheim proceeded a bit more cautiously (Ezekowitz, 2004) in their development of the next direct thrombin inhibitor, dabigatran (PRADAXA[®]). They amassed a total of 18,113 patients with chronic atrial fibrillation enrolled in the RE-LY clinical trial worldwide (Connolly et al., 2009). No imbalances in either mild ALT elevations or more serious rises with serum bilirubin increases were found in comparisons to warfarin, and NDA 22-512, submitted on 28 July 2008 was approved 19 October 2010. The pivotal clinical trial for the AFib indication was much larger than that for ximalagatran, not only many more patients (18,113 vs. 3,922) but widely dispersed (worldwide for dabigatran vs US & Canada for ximelagatran). It had been planned to study only 3000 patients (1500 per group on ximelagatran at 36 mg b.i.d. and 1500 on

warfarin with dose-adjustment), but the incidence rate of primary events drove an increased estimate of 2000 per group. Even so ximelagatran was not better than warfarin, just not significantly inferior statistically. Such trials need very large numbers of subjects. Subsequent experience with dabigatran has shown no increased incidence of liver toxicity, but many bleeding problems have been reported (a recent lawsuit was settled very recently for \$620 billion).

Structures of warfarin and the two “-gatran” agents are shown below:



Encouraged by the success of dabigatran, development work proceeded rapidly elsewhere to evaluate yet another class of novel oral anticoagulant agents, the “-xaban” series.

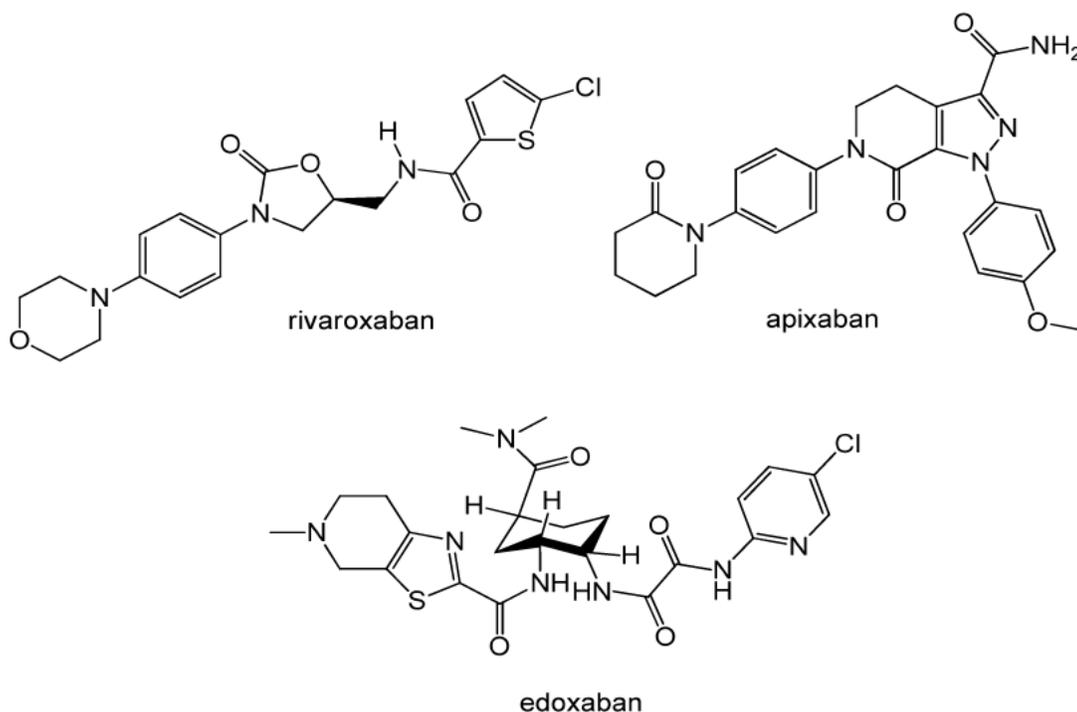
Rivaroxaban was discovered by Bayer Schering Pharma (Roehrig et al. 2005; Misselwitz et al., 2011). It is an oxazolidinone derivative that exerts anticoagulant effects by directly inhibiting factor Xa in the blood coagulation cascade. The product BAY 59-7939 was licensed by Johnson & Johnson for co-development as XARELTO[®] JNJ for possible marketing to prevent DVT and PE, later by Ortho McNeil Janssen Pharmaceuticals, to reduce incidence of ischemic strokes and systemic emboli in patients with non-valvular AFib. The original submission of NDA 22-406 was made on 28 July 2008, but was found to have deficiencies for which a complete response letter was sent 27 May 2009, despite favorable opinion by 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 risks could be avoided by dose reduction. The NDA 22-406 was resubmitted 3 January 2011 as N 022406 for priority review by the Division of Hematology Products (DHP) for prophylaxis of deep vein thrombosis and pulmonary embolism in patients who were undergoing hip or knee replacement surgery.

Another 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 AFib. Rivaroxaban was approved 1 July 2011, after earlier approvals in Europe in 2008, and has been very successful. Despite claimed use in more than (b) (4) patients for over 6 years in Europe and 3 in the United States, no cases of serious hepatotoxicity have been reported, with the exception of a very recent article in the Journal of Hepatology in April 2014 (Sussmann et al.) that initiated a series of angry calls from Dr. Sidney Wolfe. *[I had reviewed the manuscript for that paper for the New England Journal of Medicine in January 2014 and had recommended it not be published, as did the other reviewer, because of falsification of the RUCAM (Roussel-Uclaf Causality Assessment Method) but the same manuscript was submitted to the Journal of Hepatology, and was accepted and published.]* (b) (4)

It was not clear why the authors had selected only rivaroxaban for concern about hepatotoxicity when all of the NOAs showed about the same incidence of mild serum aminotransferase elevations (Caldeira et al., 2014 Apr; and Moore et al., 2014 May;).

Apixaban, ELIQUIS[®] Bristol Myers-Squibb, was the second factor Xa inhibitor submitted as NDA 202155 on 29 September 2009. Because of discrepancies in whether subjects received study drug or warfarin, a Complete Response was issued 22 June 2012, but corrections led to its approval on 28 December 2012 for prevention of embolic stroke and systemic emboli in patients with non-valvular AFib. It had been approved in Europe in May 2011 for preventing thromboses after knee or hip surgery, and in November 2012 for the AFib indication. We were not consulted about the possible hepatotoxicity of apixaban

The structures of the two approved factor Xa inhibitors and the new edoxaban are shown below:



With this background commentary, let us now consider data submitted and available for the new candidate, edoxaban. Some post-marketing experience has already become available in Japan as LIXIANA[®], Daiichi Sankyo, where it was approved in 2011 for prevention of thrombotic events after knee or hip surgery.

The NDA 206316 lists (b) (4) indications for its use as

- 1) Reduce the risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation;
- 2) Treatment of deep vein thrombosis and pulmonary embolism;

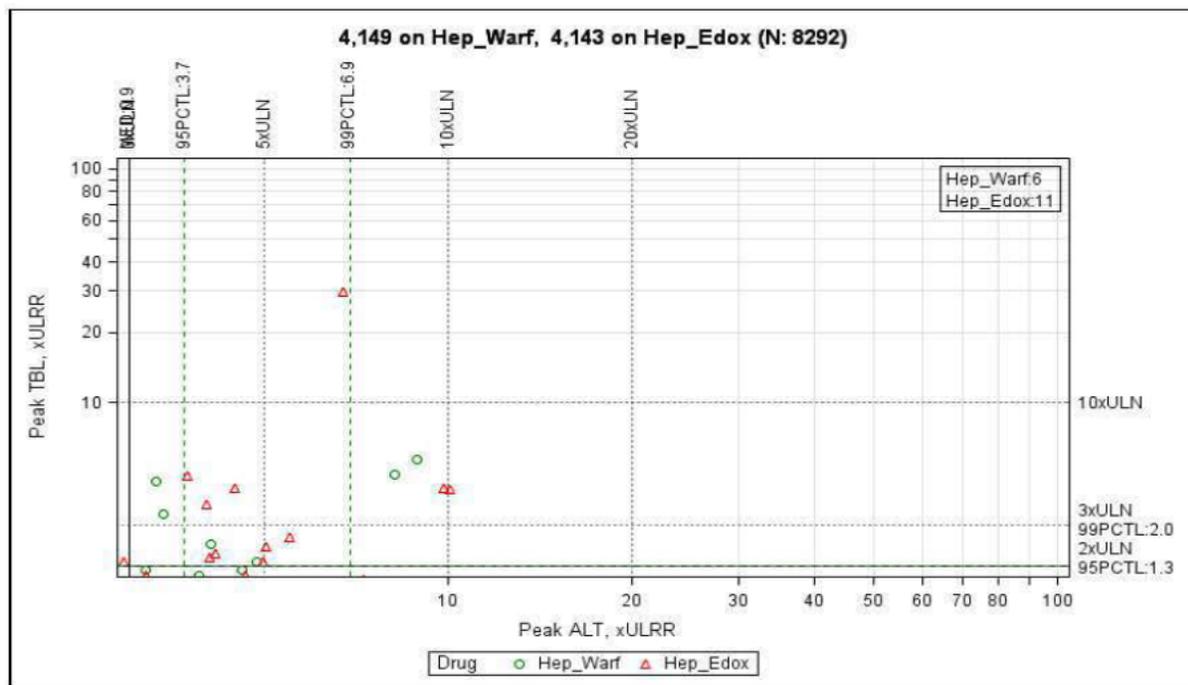
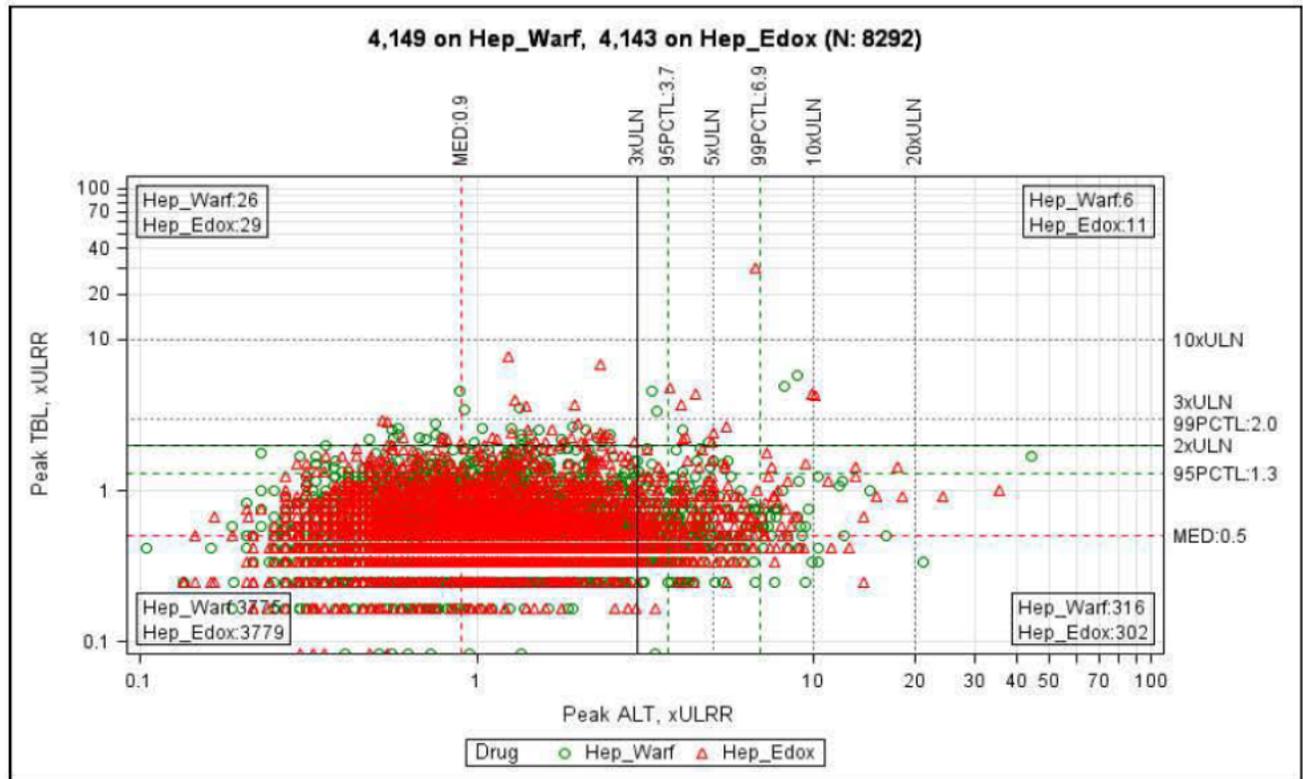
(b) (4)

The request for consultation was sent by Alison Blaus of DCRP on 6 May 2014 to OSE-Liver Team, with desired response by 8 August, for “review of the liver data included in the NDA.” Data for the two major studies for AFib (ENGAGE – Study U301) and the DVT/PE treatment and prevention (Hokusai – Study U305). Mid-cycle review-to-date was planned for 11 June, and final clinical reviews by late August, with no planned advisory committee meeting. Study U-301 involved 21,036 patients with AFib, and Study U305 involved 8292 patients with DVT/PE. These indications and the complexity of the submission resulted in involvement of reviewers from both DCRP and DOHP/DHP, so this consultation will be addressed to all.

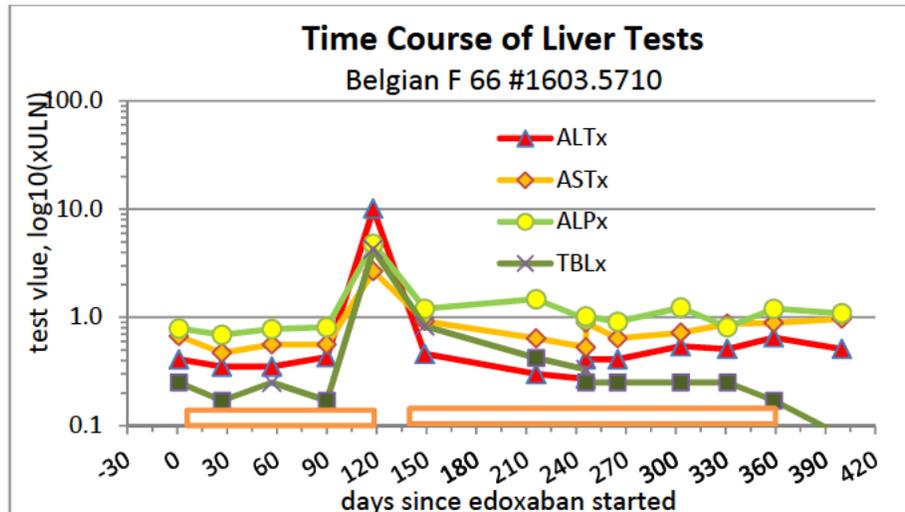
The “smaller” HOKUSAI study of 8292 patients (U305) was carried out from 28 January 2010 to 12 June 2013 at 439 investigative sites in 37 countries. Randomized were 8292 patients, of whom 8240 received study drug for up to a year: 4716 men and 3544 women, mean age 55.8; 4891 (59.7%) with deep vein thromboses, 3349 (40.3 with pulmonary emboli); 4118 to receive edoxaban, 4122 warfarin. The finger-stick INR was in the therapeutic range 2.0 to 3.0 for 63.5% of the time. Although there were fairly frequent serum aminotransferase elevations, there was no notable difference between the incidence on edoxaban and warfarin-treated subjects. Of more concern, the incidence of potentially more serious liver injury with whole-organ dysfunction, as shown by serum bilirubin elevations, was very low: 11/4122 (0.27% or 1/375 for edoxaban, and 6/4118 (0.15% or 1/686). When the cases with both ALT and TBL elevations above 3xULN and 2xULN were evaluated in detail, using the eDISH program to inspect the time course of all liver tests (ALT, TBL, AST, ALP) over their entire periods of observation, plus a narrative describing all pertinent clinical factors observed and recorded, there were no cases found of *probable* Hy’s Law cases of drug-induced hepatocellular jaundice, from either drug treatment.

Shown below is an x-y log-log plot of the peak ALT and TBL values for each of the randomized subjects, one point for each, in four quadrants as separated by ALT 3xULN and TBL 2xULN. The “normal” values were taken as provided by the investigators for local laboratories or the sponsor if a standard laboratory was used. The lower-right or “southeast” quadrant shows those with ALT elevations but normal-range bilirubin concentrations, a little over 300 subjects on each drug for an approximate incidence of 7.5%, while the upper-right or “northeast” quadrant shows only 11 edoxaban and 6 warfarin-treated patients for incidence of about 0.2%. Initial screening was done to find cases of possible interest, not to make diagnosis of either likely cause or clinical severity, which were determined from supplemental medical narrative information. Two

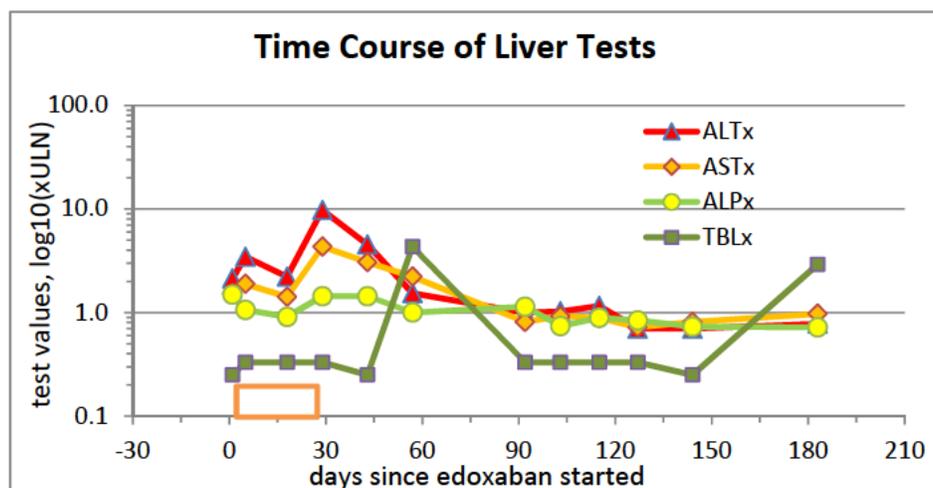
illustrative cases are shown the the time course of all four principal liver tests, and all 17 patients (11 on edoxaban, 6 on warfarin) are summarized in a table on page 8 below..



If we focus on the right-upper quadrant, close inspection shows that there were two patients with ALTs of about 10xULN, subjects #1603-5710 and #5202-1553, who were randomized to edoxaban. By clicking on those symbols it allows eDISH to produce a time course of all the four liver test variables, ALT, TBL, AST, and ALP over the whole time of their observation. We have found this very useful in getting an initial idea of what may have caused the abnormal serum chemistries and when, which is then supplemented by supplemental narrative information to estimate causality and severity. (Note: diagnoses are NOT made on the basis only of the serum chemistry values, but mainly on the narrative information intended to add to what may have been entered into the records).



Comment: This thin Belgian woman received edoxaban for almost 3 months with normal liver tests, but then developed anorexia, nausea, and jaundice on Day 118. She was found to have dilated biliary tree, edoxaban was interrupted on Day 120, and sphincterotomy was done on Day 127. Edoxaban was later restarted and continued for 7 months, without adverse effect (negative rechallenge).



Comment: This Thai woman showed abnormal liver tests immediately on starting edoxaban, was treated

with it on study for 25 days, stopped because of serum AT elevations. She showed recurring high bilirubin and hematuria, pulmonary bleeding. It appeared that here transaminase elevations were a feature of her hemolytic process, dissociated from the intermittent bilirubin rises. Not serious DILI.

U 305 - Prevention of recurrent VTE in patients with DVTs. ± pulmonary emboli (Hokusai study)

8292 subjects randomized 1:1 (4149 to enoxaparin-warfarin, 4132 to enoxaparin-edoxaban)

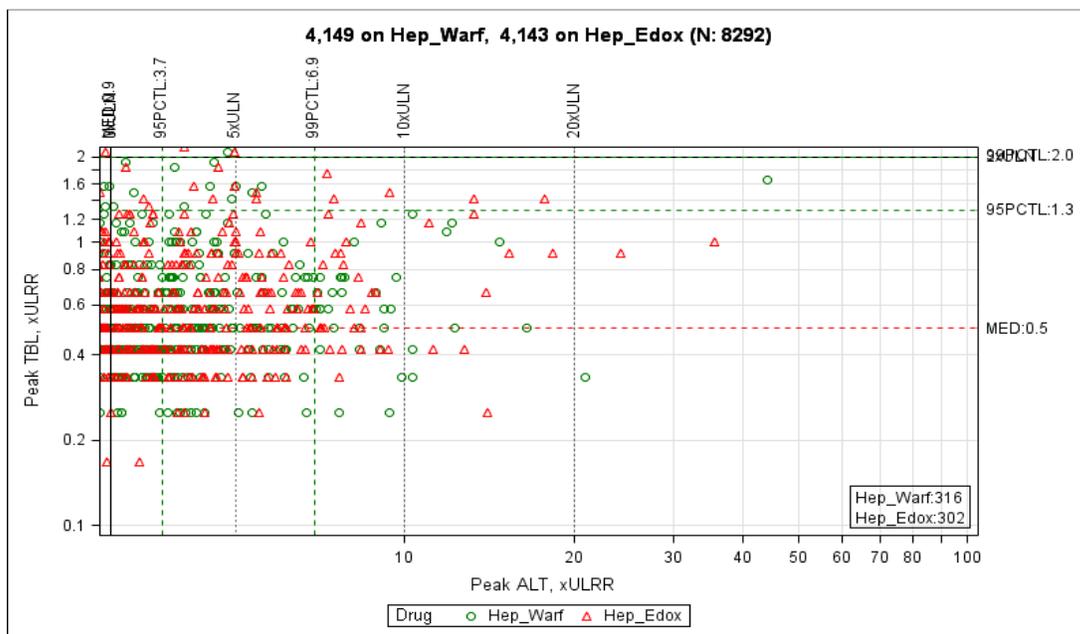
17 patients showing {peak ALT>3xULN & peak TBL>2xULN} - from eDISH upper right quadrant

site.subj	country	sex-age	BMI	pALT xULN	pAST xULN	pALP xULN	pTBL xULN	narrative, explanation
edoxaban								
1603.5710	Belgium	F 66	19.92	10.08	2.67	4.78	4.25	<i>sphincterotomy, biliary stricture</i>
3012.1657	Russia	M 58	28.62	5.50	2.82	0.79	2.67	no narrative; transient AT, Gilbert's
3022.6580	Russia	M 65	22.49	4.06	6.18	0.64	2.17	<i>AST>ALT, ??covert alcoholic?</i>
3022.6827	Russia	M 65	22.24	4.02	14.18	2.63	3.57	<i>AST>ALT, ??covert alcoholic?</i>
3026.2092	Russia	F 56	35.69	6.73	7.03	9.38	29.92	<i>adenoCALiver</i>
4007.1853	Ukraine	M 63	26.12	4.98	1.13	0.72	2.08	<i>transientATsGilbert's</i>
4302.4867	China	M 55	23.84	5.02	3.87	0.92	2.42	no narrative
4802.6039	Philippines	M 25	19.57	4.15	2.69	1.99	2.25	no narrative
5202.1553	Thailand	F 59	25.33	9.81	4.36	1.49	4.33	fatty liver, not explained
5402.1583	Hungary	M 51	20.07	4.46	5.18	1.46	4.33	biliary stricture, pancreatitis
5503.0752	Israel	F 77	25.92	3.73	4.53	18.49	4.83	pancreaticCA
warfarin								
1069.2326	USA	M 62	24.63	3.42	7.60	5.90	3.33	<i>biliary tract disease, renal CA</i>
3900.2469	Sweden	M 38	28.55	4.85	2.51	0.91	2.09	no narrative; transient AT, Gilbert's
4001.8255	Ukraine	F 61	25.52	8.89	7.94	6.02	5.75	<i>endometrial carcinoma, metastases</i>
4402.7986	India	M 42	28.79	4.08	4.62	1.98	2.50	no narrative; unexplained, not DILI
4449.5676	India	M 46	----	8.17	6.87	1.39	4.92	acute hepatitis E
5410.7081	Hungary	M 61	25.61	3.31	1.49	2.70	4.58	pancreaticCA

Commentary: Among these patients there were no clear-cut cases of probably drug-induced serious hepato toxicity. However, no narratives were received for 5 of the 17 patients, and many of those that were received were repetitious and not oriented toward making a diagnosis of the severity and likely cause of the findings, but were simply data-dumps of protocol records. In 3 cases, bilirubin elevations preceded and were independent of aminotransferase rises, suggesting Gilbert syndrome with mild and trivial enzyme increases. Adequate investigation to rule out alternative causes, or to make them, was not done well or at all.

If we look more closely at the *lower* right quadrant of the eDISH plot for study U305, we see many more patients with quite high elevations of serum ALT activities without increases in the bilirubin at any time during their period of observation and serial monitoring. There were 4 of them who showed peak ALT activities greater than 20xULN, which would be assessed as grade 4 using the Common Terminology Criteria for Adverse Events (CTCAE) promulgated by the

National Cancer Institute, which call such abnormal findings “life-threatening.” (It should be noted that this grading was not data based, but was made on consultants’ opinions rendered first in 1982 and carried forward since.). There were 2 patients on edoxaban, and 2 on warfarin, who showed such findings:



The 4 patients who showed peak serum ALT activity levels above 20xULN are described in more detail in the small table below:

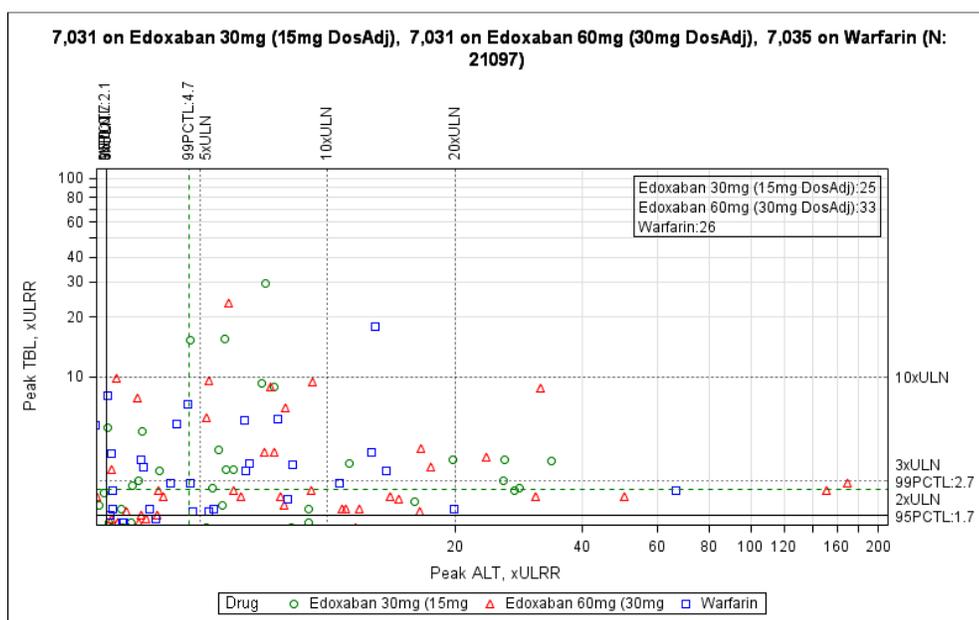
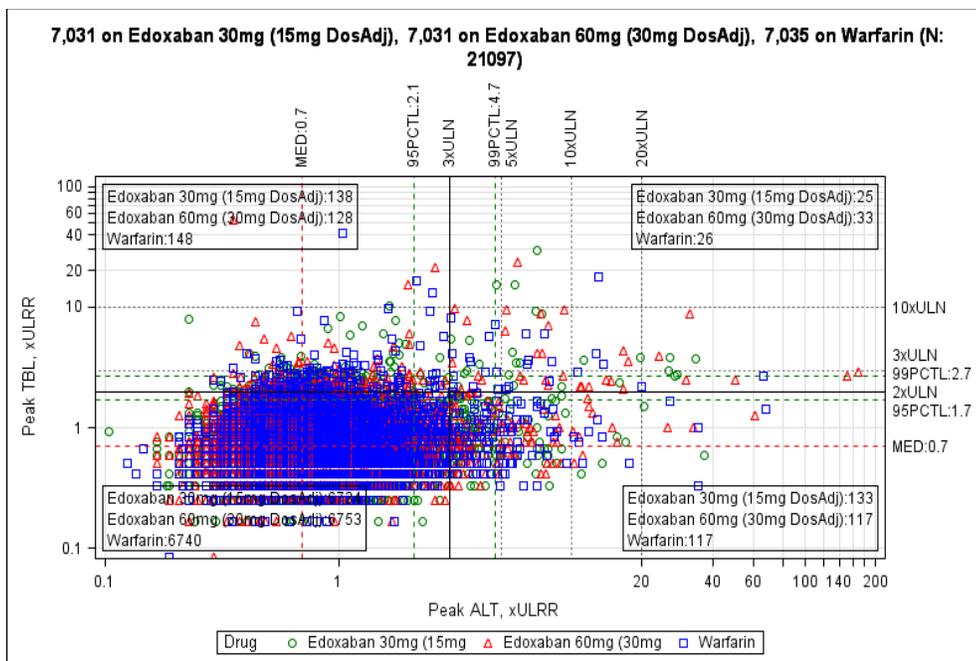
U 305 - Prevention of recurrent VTE in patients with DVTs. ± pulmonary emboli (Hokusai study)
 8292 subjects randomized 1:1 (4149 to enoxaparin-warfarin, 4132 to enoxaparin-edoxaban)
 4 patients showing {peak ALT>20xULN } - from eDISH lower right quadrant

site.subj	country	sex-age	BMI	pALT xULN	pAST xULN	pALP xULN	pTBL xULN	severity	narrative, explanation
edoxaban									
1068.64	USA	M 46	26.03	24.15	7.42	1.59	0.92	mild	alcoholic hepatitis, after edoxaban stopped
4234.234	China	M 52	23.03	35.53	31.56	1.21	1.00	mild	not studied, no symptoms; on edoxaban 1 yr
warfarin									
4315.492	China	F 49	27.43	44.11	42.89	0,68	1.67	fatal	second pulmonary embolus, shock, death
4513.136	Korea	F 50	24.52	20.97	11.08	1,98	0.33	mild	on W only 1 day; metastatic CA from ?

None of these patients showed edoxaban-induced elevations of the ALT, and 3 of 4 were not in acutely severe status and were asymptomatic. The 52 year-old Chinese woman was on edoxaban

for a full year without showing any liver test abnormalities of findings except for unexplained and uninvestigated aminotransferase elevations on study Day 9 and 359.

Turning now to the larger “ENGAGE” study U301 in which 21,105 patients with chronic atrial fibrillation were randomized at 1393 sites around the world, of whom 79 did not receive study drug but 7002 received edoxaban 30 mg, 7012 edoxaban 60 mg, and 7012 warfarin in adjusted doses daily, termed the mITT or safety analysis set. The study ran from 19 November 2008 to 24 May 2013, with a median duration of treatment of 2.5 years plus added follow-up of 0.3 years and median warfarin time in therapeutic range of INR 2.0-3.0 of 68.4% by point-of-care device..



Shown above are eDISH graphs of over 21,000 patients for whom data were provided by the sponsor from the ENGAGE (U301) study, each symbol representing one person, plotting the peak observed serum alanine aminotransferase (ALT) activity on the x-axis, and the peak observed serum total bilirubin (TBL) concentration on the y-axis, both expressed as multiples of the upper limit of the normal (ULN) reference range for the laboratory in which testing was done. The peak values were not necessarily at the same time, for it often takes a few days for TBL to rise after acute hepatocellular injury. Each site set its own schedules for serial liver test monitoring, roughly according to protocol, but there was great variability in the timing and frequency of additional values obtained following reports of abnormalities, dependent on the judgment and practice of the local investigators. When local or hospital laboratories were used to study patients who had abnormalities, the local ULN values were not consistently reported.

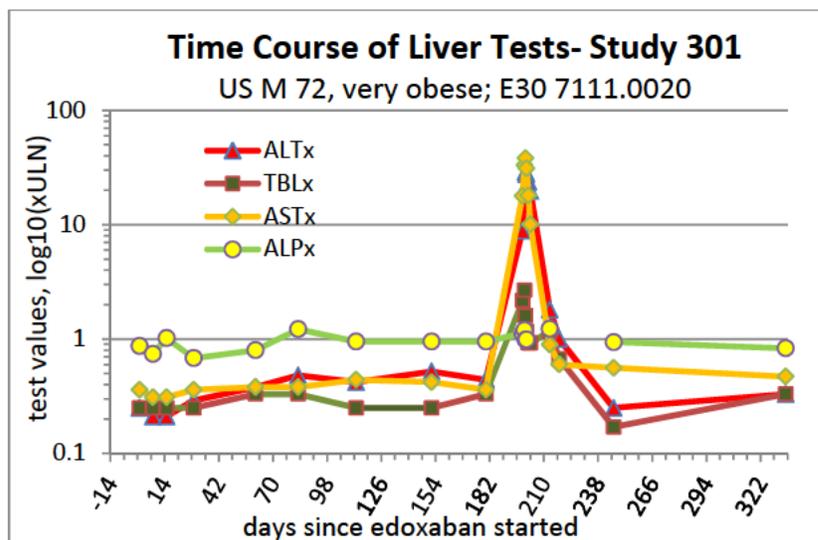
The eDISH (evaluation of Drug-Induced Serious Hepatotoxicity) approach is based on the long experience of Dr. Hyman J. Zimmerman who concluded after many years of observing patients with drug-induced liver injury that “drug-induced hepatocellular jaundice” is a serious lesion, with substantial mortality. This statement captures the essence of the problem, but primary is the idea that the liver disorder must be shown to have been **caused by the drug** in question, and not by some other drug, a viral infection, biliary tract disease, or one of many other possible causes. It also emphasizes succinctly that hepatocellular injury is more threatening than biliary tract injury, and that when enough hepatocytes have been injured that those remaining and functional are unable to clear the plasma of bilirubin so that jaundice becomes apparent. Hepatocellular injury may be mild in some cases, causing no symptoms, so measurement of serum ALT activity increases the sensitivity of detection, and measurement of serum bilirubin concentration is more sensitive than visual appreciation of jaundice, which depends on skin pigmentation, the lighting conditions, and experience of the observer. The two measures have been used together in eDISH to find quickly the few patients who may be a serious risk, but it must be appreciated that it is NOT possible to diagnose a serious case of drug-induced hepatotoxicity by serum chemistries alone. For that reason, steps two and three of the eDISH program involve plotting time courses of all four liver tests on a common time scale by logarithmic transformations of the elevations of test values in ranges for visual comparisons, and the critical third step of medical assessment of supplemental values provided by clinical narratives to enable medical differential diagnoses to the severity of the injury and the most likely cause. Since serum enzyme activities are not valid measure of liver function, but only indicate cellular injury, the bilirubin gives some measure of how much functional disturbance has occurred, and conveys a great deal of specificity to serum ALT measures as representing liver, rather than other organ injury. The time course and narrative contribute additional specificity as to what may have caused the injury. These require evaluation by physicians skilled and experienced in making medical diagnoses of causality, necessary to institute appropriate treatment, an art not learned, practiced, or well understood by other learned professions.

Dr Robert Temple, who coined the term “Hy’s Law” in 1999 after over 20 years of observing that the Zimmerman statement had never been wrong, attempted to define it in the CDER Guidance of 2009, but it is too often misunderstood and incorrectly applied. Our use of eDISH over the past 10 years has also been correct in all cases when it was used, and no drug has been approved since 1997 that later had to be removed from market because of serious hepatotoxicity. We hope to keep it that way.

As emphasized above, the critical task in reviewing cases who showed elevated liver tests or symptoms of liver toxicity lies in determining the probable, or most likely cause. This cannot be done by inspection of serum chemistries alone but requires consideration of the time course of the test abnormalities and clinical information to supplement data in the record. The sponsor has prepared and submitted over 4000 narratives for study subjects who died from any cause, had liver test abnormalities indicating both hepatocellular injury and whole organ dysfunction (in reduced ability to clear bilirubin from plasma, leading to increased serum concentrations), and subjects who discontinued study for various reasons. The quality of those narratives is only fair, and quite variable for making a reasonable medical differential diagnosis of probable cause. It is evident from those narratives that the investigators at many sites really did not know what was going on in their study subjects, and their responses were extremely variable, from extensive work-ups to virtually none. Sometimes they interrupted administration of study drug or stopped it permanently, but often they restarted it (rechallenge) without paying attention to the effects.

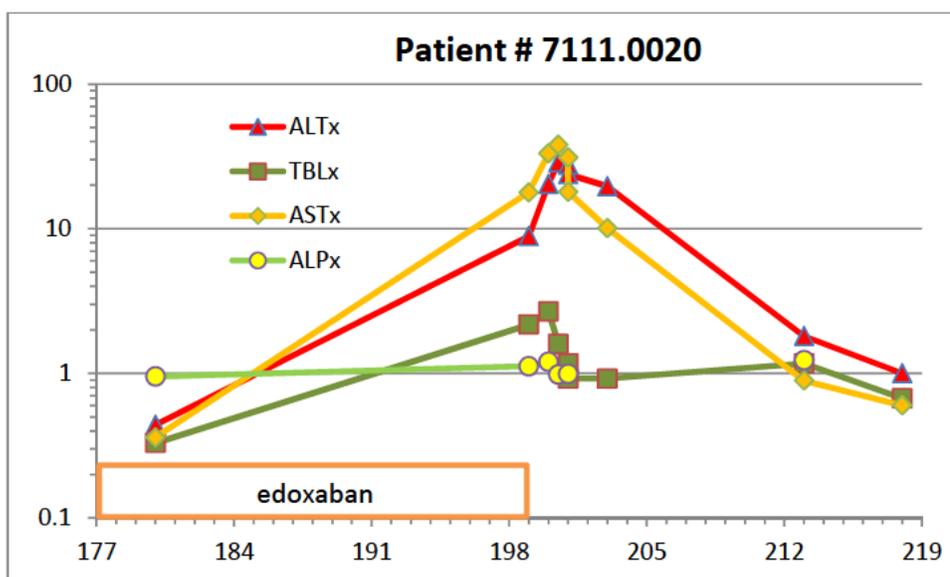
The sponsor's expert hepatologists reviewed many of the questionable cases and concluded that there were none definitely caused by edoxaban (or warfarin), and also claimed that there were none with inadequate data (Table 12.23) in the large study U301 "ENGAGE." However, they used a category of "probably/possible" for 51 cases [25/7012 on E 60, 11/7002 on E 30, and 15/7012 on warfarin. They also called another 435 cases "unlikely/unrelated" for 120/7012 on E 60, 135/7002 on E 30, and 128/7012 on warfarin. Thus, they report attempted adjudication for most likely cause in 486 patients in the mITT safety set of 21,026 subjects. The sponsor reports that there were 3 cases of "Hy's Law" found: #7111.0020 on E30, #4413.0008 and #7035.0002 on E60, and none on warfarin. Let us look more closely at those cases.

Subject **7111.0020** was an extremely obese (body mass index [BMI] 41.54) US male 72 with a history of atrial fibrillation, severely reduced left ventricular function, congestive heart failure, coronary artery disease, hypertension, transient ischemic attack, diabetes, and on more than 20 medications when started on study 8 October 2009, randomized to edoxaban 30 mg.day. He tolerated the study drug for more than 6 months, but on (b) (6) he came to an emergency room with complaints of shortness of breath and orthopnea, and was hospitalized for treatment of cardiomyopathy.



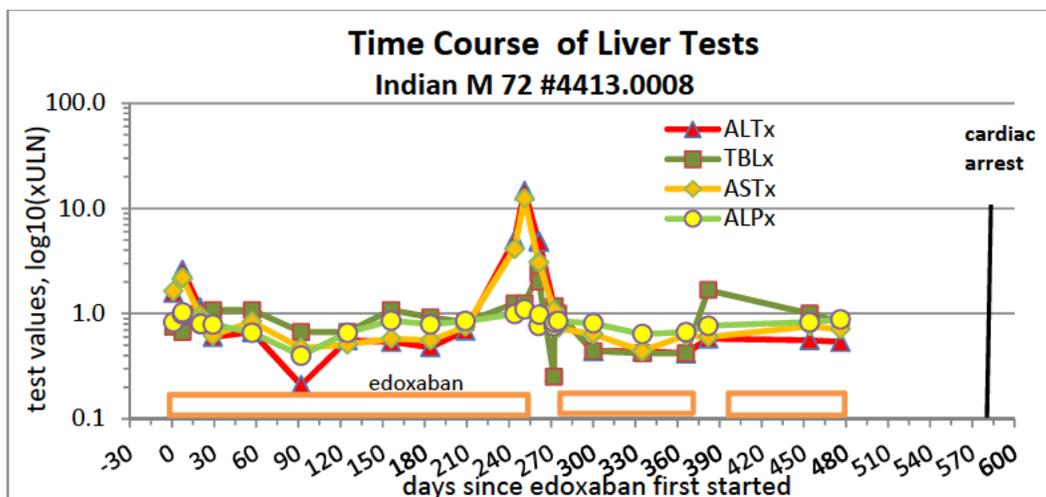
Study drug was stopped permanently, and he was studied for elevated liver tests for which no cause was found. He was treated with furosemide, improved, and was discharged on (b) (6) but was readmitted (b) (6), and a third bout of congestive failure occurred (b) (6). This set of events was adjudicated as “probably/possibly edoxaban-related severe liver injury, Hy’s rule satisfied.”

Comment: It did not seem to occur to the investigator, the expert adjudicators, or the sponsor that this was most uncharacteristic for a drug-induced reaction (if to one or more of the many drugs he was taking) and that he took edoxaban for over 6 months without adverse effect. Yet when he went into a series of congestive heart failure bouts in (b) (6) liver test values became abnormal, and were resolved when his heart failure was treated. Looking more closely at the liver test abnormalities in late (b) (6) it was noted that the serum AST began to increase earlier and faster than the ALT, peaked higher, and then declined more rapidly, along with no change in alkaline phosphatase and only minimal rise in bilirubin. This pattern was seen again and again in the patients of study U301. Let us look more closely:



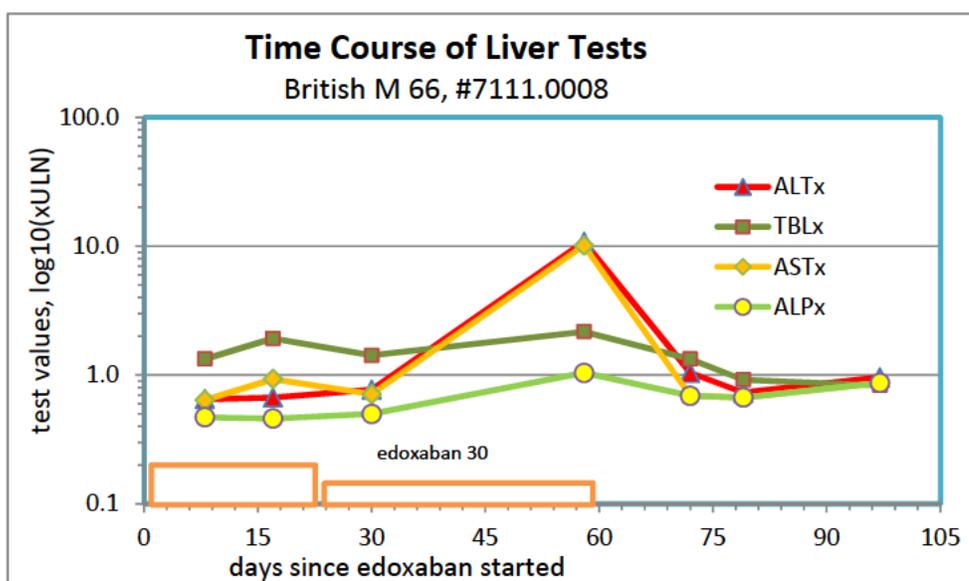
The liver is an oxygen-hungry organ, receiving about a quarter of the cardiac resting output, and is a major consumer at rest of the total oxygen consumption, along with the brain, kidneys, and heart. When blood is backed up in the liver during congestive heart failure, centrilobular zones of the liver become severely hypoxic as hepatocytes continue oxygen consumption. When shock or hypotension occur, reduced delivery of blood from the hepatic artery occurs, further worsening the hepatocellular hypoxia. The serum AST rises more earlier, more rapidly, and higher than does the serum ALT, sometimes to spectacular peak levels, but then quickly subsiding when congestive failure or shock are treated, the AST falling more rapidly than the ALT. Therefore it depends on when the cardiac problem is detected, how often tests are done, if this phenomenon is to be recognized. In study U301, there was great variability in how quickly investigators acted following the onset of heart failure. Some obtained extra information immediately; others did not. This could not be rectified by narratives written later by technicians.

Subject #4413.0008 was an Indian male of 72 who had been randomized to edoxaban 60 mg daily but the dose was reduced to 30 mg because of reduced creatinine clearance. In addition to chronic atrial fibrillation he had a history of hypertension, diabetes, embolic stroke without hemorrhagic conversion. He was not overweight, a non-smoker, used alcohol very sparingly, and was also taking an unspecified digitalis preparation, a renin angiotensin aldosterone inhibitor, gabapentin, glimepiride, and losartan. At randomization and start of edoxaban on 7 April 2010 (Day 1) his serum transaminases were slightly elevated, somewhat more so 6 days later but were lower when rechecked on 26 April (Day 20), without treatment or interruption of edoxaban. No explanation was sought or found for the mild asymptomatic enzyme elevation, and he continued on edoxaban 30 mg daily without further test abnormalities for over six months until recurrent and greater test abnormalities were found on 8 December (Day 246). He was said to be asymptomatic and showed no clinical signs, but edoxaban was interrupted from 16 December (Day 254) until 6 January (Day 275) when the abnormalities subsided. No explanation was found, no treatment given, and study drug was given again for another four months. On (b) (6) he complained of increasing shortness of breath, that led to finding ST depression in leads AVL, V4 and V6, and elevated serum troponin and diagnosis of acute myocardial infarction with heart failure. Edoxaban had again been stopped on (b) (6). He was anemic, and was then found by endoscopy to have esophageal varices, and gastric erosions, and he was thought by abdominal ultrasound to have cirrhosis of undetermined cause and type. No cause for the liver disease was found, and he was restarted on edoxaban again on 6 May 2011 (Day 395). He refused liver biopsy, and studies showed continued decline of renal function, and edoxaban was stopped permanently on 28 July 2011 (Day 474). Following discontinuation of edoxaban, he had another hospitalization for myocardial infarction with ventricular tachycardia in (b) (6) more (b) (6) gastrointestinal bleeding, and sudden death from cardiac arrest at home (b) (6).



Comment: It was evident that the investigator did not know what was going on in this complex case. Concluding that the serum enzyme elevations were edoxaban-related is difficult to accept in view of the long period on drug when nothing happened, and two negative rechallenges. The patient had severe and worsening heart disease, with periods of failure, arrhythmias, infarction, and finally sudden death. It seems more likely that the liver tests abnormalities were secondary to his heart disease. He also diagnosed as "cryptogenic" cirrhosis, and serious renal disease.

Subject #7035.0002 was an obese British male of 66 with atrial fibrillation and a history of a transient ischemic attack, asthma, hypercholesterolemia, and he admitting to consuming 1 or 2 alcoholic drinks daily, and was a former smoker. He was also taking simvastatin, salbutamol, beclomethasone, and terazosin when started on edoxaban 60 mg daily on 3 March 2010. His edoxaban dose was reduced to 30 mg/day on 24 Mar (Day 22) when verapamil was added to control his heart rate. On 29 April (Day 58) his serum aminotransferases were elevated but he was asymptomatic. Study drug was stopped permanently the next day. Physical and abdominal ultrasound examinations were negative on at the next visit 6 May, serum tests for viral hepatitis provided no explanation, but his liver tests abnormalities subsided by 13 May and did not recur over follow-up observations for 22 months while he was on warfarin. The investigator considered the serum enzyme elevations “related to” edoxaban; the sponsor concurred, and the hepatology expert adjudication was “severe liver injury, probably/possibly related, Hy’s Law fulfilled.”



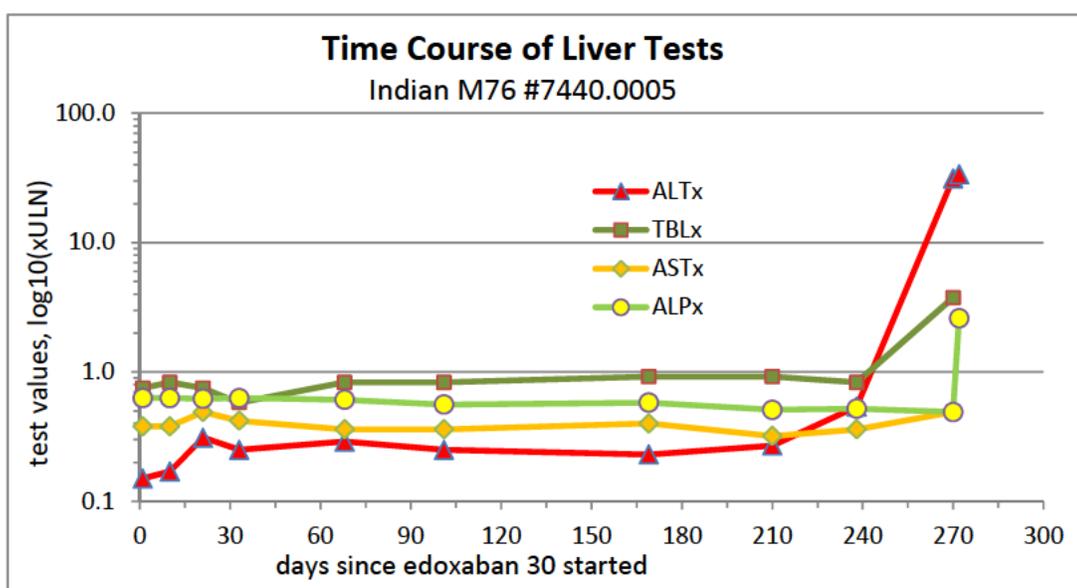
Comment: This investigator was slow to study and quick to stop study drug, and was inadequate in his determining the probable cause of the very mild, asymptomatic rises in transaminases with almost no rise in bilirubin (somewhat high to begin with (Gilbert's syndrome?). This was not a severe, did not fulfill Hy's Law because causality was not determined. It may have been weakly possible that this was an instance of mild (not serious) transient hepatocellular injury due to the reduced dose of edoxaban, but they have not made a convincing case for it. Diagnosis of DILI by exclusion is not made by absence of information.

In addition to the three cases reported by the sponsor as probably/possibly Hy's Law cases, there were three other cases found by our reviewers for which they requested a second opinion from me. They were

DU176b-74400005
DU176b-53040010
DU176b-19050052

...as listed by Dr. McDowell from her preliminary review 16 May.

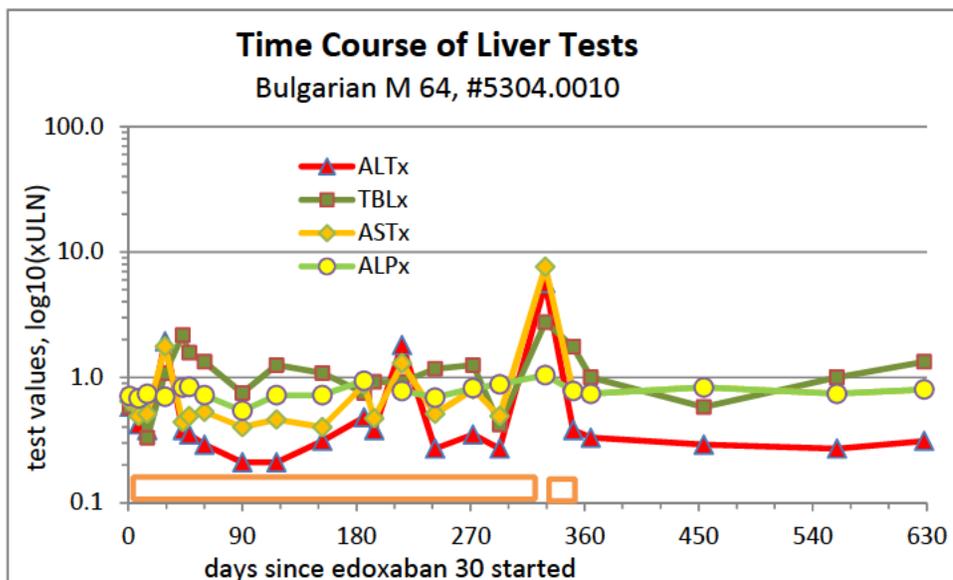
Subject #7440.0005 was an Indian M 76 with atrial fibrillation and history of non-hemorrhagic embolic stroke, transient ischemic attack, aortic and mitral valvular disease but normal ejection fraction, left ventricular hypertrophy, and previous cardiac arrest. He was randomized to reduced dose of edoxaban 30 mg/day because of high creatinine on 29 July 2010 (Day 1). His liver tests remained in the normal range for 8 months on study, but on 18 April 2011 (Day 264) he noted anorexia and fatigue. His digoxin and furosemide were stopped on 20 April, and he was seen on 21 April for his complaint of fatigue, then hospitalized for breathlessness on [REDACTED] (b) (6). On admission he was icteric (serum total bilirubin 4.5 mg/dL, showed blood pressure 90/70 and elevated serum transaminases, and edoxaban was stopped. It was not clear whether the abnormal liver tests were due to study drug or “congestive hepatopathy.” Additional hospital consultations and studies did not reveal primary liver disease, and the consulting gastroenterologist claimed that there were no symptoms or findings of ischemic hepatitis, and diagnosed “acute hepatitis.” On the morning of [REDACTED] (b) (6) he became suddenly unresponsive, and cardiopulmonary resuscitation was unsuccessful. The cause of death appeared to be cardiac arrhythmia, not liver failure. Autopsy was not done, and subsequent test results provided no additional information. The investigator, sponsor, and hepatology adjudicator considered the liver dysfunction unrelated to study drug.



Comment: This was fairly obviously a case of sudden liver injury secondary to congestive heart failure and finally to shock and death. The patient tolerated edoxaban for over 8 months with no adverse liver effect whatsoever, and it is very unlikely that the liver dysfunction was due to the study drug. I concur with the opinions of the sponsor, investigator, and adjudicators.

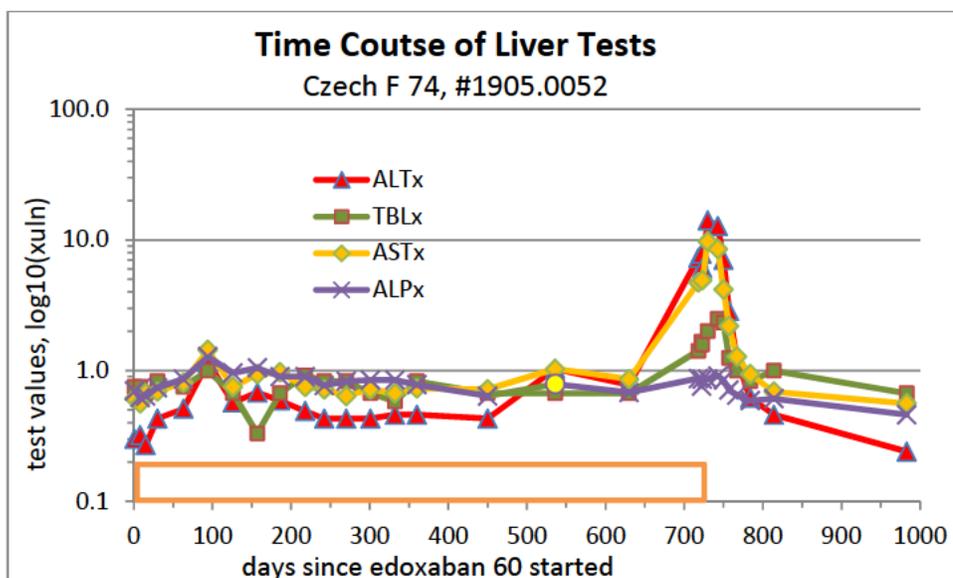
Subject #5304.0010 was a Bulgarian M 64 with chronic atrial fibrillation and a history of renal impairment, transient ischemic attack, congestive failure, mildly reduced ejection fraction, mitral disease, and on a dozen other medications. Because of moderately impaired creatinine clearance his edoxaban dose was reduced to 30 mg/day when started on 28 August 2009 (Day 1). His tests showed moderately elevated serum bilirubin, without jaundice or symptoms, and ultrasound of

the liver was normal. He had epistaxis on [REDACTED] (b) (6) and elevated aminotransferases the next day. Edoxaban was interrupted for 4 days (21-25 July), but was stopped permanently on 13 August (Day 351) because of liver test abnormalities. No explanation was found for the abnormal liver test results, and he continued on acenocoumarol. Sudden rise in liver test values was found on 29 April 2011 (Day 580), and worsening heart failure in [REDACTED] (b) (6) with no liver test changes. The investigator considered the liver abnormalities related to study drug, but adjudicators thought it unlikely.



Comment: This was a case that the investigator clearly did not understand, and he was not helped much by his local consultants. The liver abnormalities were only mild-moderate, not serious, and never well explained. The patient showed fluctuating but modest elevations of his total bilirubin, suggesting Gilbert's syndrome, but the one attempt to clarify that failed in August 2010. He was said to have had an episode of congestive failure in [REDACTED] (b) (6) long after he was off edoxaban, with no recurrent liver test abnormalities. Because he really showed no liver abnormalities other than slight bilirubin increase when off edoxaban, it cannot be excluded that the mild problem possibly may have been edoxaban. The hepatology adjudicator called the case severe and unrelated, with both of which conclusions I disagree.

Subject #1905.0052 was a Czech F 74 with chronic atrial fibrillation and a history of congestive failure, hypertension, mitral disease, but reasonably acceptable ejection fraction. She had been on a beta-blocker, renin angiotensin aldosterone inhibitor (not specified), furosemide, bisoprolol, and spironolactone. She started on edoxaban 60 mg/day on 8 June 2010 (Day 1). She tolerated the high-dose edoxaban for 2 years without evidence of liver injury, but had thrombocytopenia detected on 10 April 2011 (Day 307), attributed to autoimmune thrombocytopenia and treated with prednisone. It was not stated how the diagnosis of autoimmune thrombocytopenia had been made. On 25 May 2012 (Day 718) she was found to have elevated liver tests but no symptoms. The values worsened over the next two weeks, and edoxaban was stopped on 12 June 2012 (Day 736). After stopping edoxaban for a week, her serum transaminases increased, with no adverse symptoms, then subsided over the next two weeks, but no cause was found.

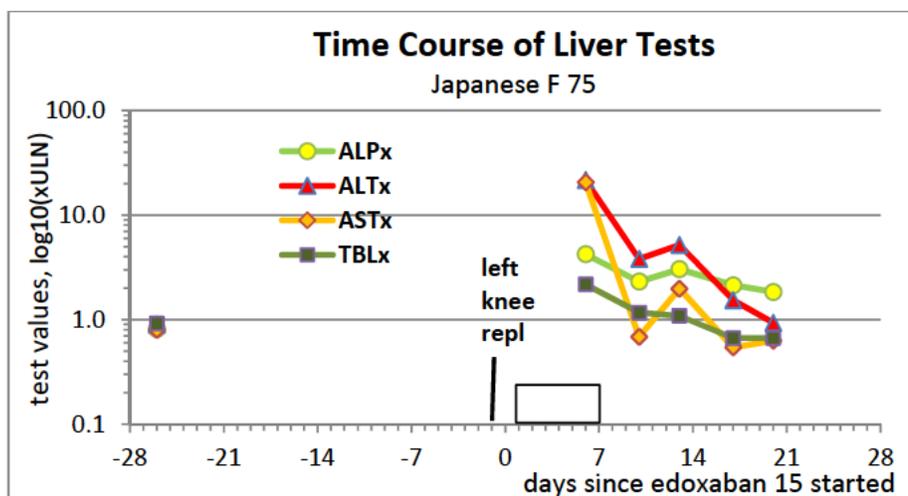


Comment: There were concerns about tumor markers but no definite findings, and the liver abnormalities were not explained. The investigator considered the liver abnormalities unrelated to study drug, and the sponsor also did, but the adjudicators concluded they might possibly/probably be related but mild. Although no other cause was found, despite a rather deultory and fragmented attempt to do so, it seems unlikely that edoxaban could have caused the problem after two years with no effect on the liver. This case, like many reviewed by the expert US hepatologists in the DILIN network, was very difficult to diagnose, and led to conflicting opinions on its causality. My conclusion is probaly not related to or caused by edoxaban, and the real cause was not found.

In addition, the clinical reviewers forwarded postmarketing reports of two cases seen in Japan and reported following approval of edoxaban (LIXIANA®) for prevention of post-operative thromboembolic problem after knee or hip surgery.

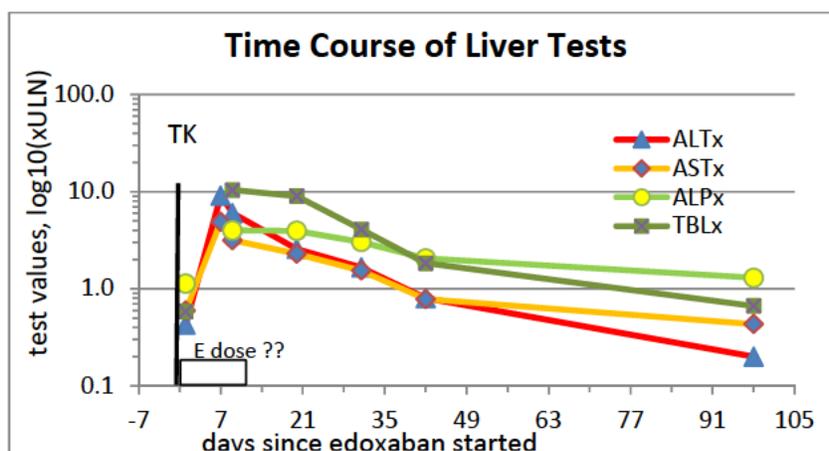
Adverse Reaction Report DSJ-2013-25444 27 February 2014

The first case, JH a Japanese woman 75, was operated upon (b) (6) for left total knee arthroplasty and was started two days later on 15 mg daily of LIXIANA to prevent thromboembolic events. She had had preoperative liver tests done on (b) (6) showing all four measures in the normal range, but when retested postoperatively on (b) (6) she had marked elevations of her serum ALT and AST, and somewhat less of ALP and TBL. The LIXIANA was stopped on 20 January, and subsequent liver testing over the next two weeks showed normalization. She had no clinical symptoms and not disabled but was treated with intravenous Neo-Minophenagen (mixture of glycine, cysteine, monoammonium glycyrrhizinate, and aminoacetic acid) for 10 days. It was “strongly suspected” that Lixiana contributed to the liver abnormalities. It was noted that after her previous right knee replacemnt in (b) (6) (before LIXIANA approved) that she had received “the similar drug” without any liver abnormalities occurring. The report termed this a serious case that had been discussed by (b) (6) at a meeting of Japanese pharmacsts in October 2013 (not in PubMed).



Comment: This simply an association between two events, with no attempt to determine the cause or if they were truly cause-and effect. It was apparently assumed that the liver findings were caused by edoxaban and actually reported by a pharmacist eager for a publication. It should at least have been considered that the trauma of surgery might have played a role. It was mild and not serious, and of questionable causality.

The second case reported, **DSJ-2013-27149**, was that of a Japanese woman 79 who had total knee replacement on [REDACTED] received LIXIANA (dose not stated) from 5 to 12 September. Elevated serum aminotransferases were found on 11 September, and jaundice two days later. No cause was found, and it was simply assumed that edoxaban was the cause. The case was reported to CIOMS 13 December 2013.



Comment: This was another immediate post-operative case assumed but not investigated as to the cause of the liver abnormalities. The prolonged cholestatic features were not studied or considered.

Let us now look at the other cases submitted to Study U301, who had suggestive findings of possibly significant liver injury from edoxaban 60 or 30 mg/day, or from warfarin.

43 Subjects IN both JReview & eDISH												
SS#	USUBJID	AGE	SEX	BMI	country	U301 rand. to	DU176b- pALTx	pASTx	pALPx	pTBLx	severity	most likely cause
	site.subj											
35	1004.0015	70	M	44.82	USA	E 30	11.27	7.60	2.80	3.67	moderate	common duct stone most likely
36	1031.0002	83	M	31.39	USA	E 30	3.65	2.80	3.40	5.33	serious	CA pancreatic head; later fatal
37	1130.0051	85	F	30.58	Argentina	E 30	5.54	2.94	1.60	4.25	fatal	pancreatic CA
1	1143.0042	72	M	28.69	Argentina	warf	7.63	8.47	3.70	6.08	serious	unexplained; cholestasi; warfarin unlikely
14	1167.0011	83	M	26.40	Argentina	E 60	9.17	12.60	2.37	2.67	fatal	myocardial infarction, pulmonary embolus unexplained; negative rechallenge,
15	1726.0001	78	M	24.38	Germany	E 60	11.02	8.56	1.19	2.17	moderate	Gilbert's
2	1905.0024	54	M	33.06	Czech R	warf	4.40	2.44	2.34	5.75	moderate	unexplained; negative rechallenge
16	1905.0052	74	F	32.87	Czech R	E 60	14.07	9.77	1.28	2.50	serious	no cause found; edoxaban 2 yrs. unlikely
38	1913.0028	70	M	34.72	Czech R	E 30	3.02	1.71	1.15	5.50	mild	common duct sludge, stone
17	2908.0071	74	M	24.84	Brazil	E 60	9.21	6.49	1.52	9.42	serious	common duct stone after 2 yrs edoxaban
18	3013.0002	58	M	25.16	Russia	E 60	3.33	2.52	0.59	2.02	mild	heart failure; Gilbert's syndrome
19	3018.0014	54	M	25.42	Russia	E 60	7.31	7.22	2.07	8.83	serious	gallbladder stones; cholecystectomy
3	3022.0040	54	F	41.58	Russia	warf	3.62	8.56	1.33	3.83	serious	congestive heart failre
4	3061.0013	66	F	34.97	Russia	warf	10.65	4.39	5.95	2.92	mild	possile amiodarone-hepatitis
5	3108.0013	66	M	26.51	Columbia	warf	13.73	10.04	0.88	3.33	serious	heart failure; Gilbert's syndrome
20	3506.0006	65	M	29.83	Italy	E 60	5.23	8.04	8.29	9.58	serious	bile duct CA; died later
21	4005.0015	54	M	34.09	Ukraine	E 60	7.88	14.53	0.83	2.25	moderate	alcoholic hepatitis; negative rechallenge
6	4012.0038	34	M	28.62	Ukraine	warf	5.23	4.09	0.53	2.08	moderate	occult alcoholic hepatitis; not warfarin
22	4039.0006	63	M	22.98	Ukraine	E 60	3.98	4.91	0.58	2.67	moderate	uncertain; autoimmune hepatitis
23	4042.0013	68	M	26.18	Ukraine	E 60	4.08	3.54	1.72	2.50	fatal	heart failure, after 2 yrs on edoxaban
7	4335.0015	76	M	26.99	China	warf	8.25	2.51	1.40	3.58	serious	pneumonia, heart failre; no warfarin
24	4402.0012	46	M	31.35	India	E 60	23.73	25.11	1.57	3.92	serious	acute viral hepatitis E
8	4411.0004	70	M	20.20	India	warf	19.90	5.51	1.11	2.17	fatal	sepsis, heart failure, shock
25	4411.0050	40	M	20.31	India	E 60	50.21	83.78	2.82	2.50	fatal	pneumonia, heart failure, shock
39	5003.0007	75	M	27.99	Poland	E 30	28.35	59.91	0.82	2.75	life-threatening	heart failure, shock - recovered
40	5031.0093	80	F	26.03	Poland	E 30	18.08	22.03	2.28	2.33	serious	probable heart failure
26	5032.0034	76	F	29.62	Poland	E 60	16.59	16.14	2.01	4.33	moderate	uncertain; negative rechallenge 3 yrs.
27	5033.0057	80	F	27.82	Poland	E 60	3.18	3.56	2.48	9.75	serious	pancreatic CA; later died
28	5056.0039	77	M	26.90	Poland	E 60	16.54	11.24	1.17	2.08	serious	common duct stone; not edoxaban
41	5304.0010	64	M	24.45	Bulgaria	E 30	5.63	7.62	1.04	2.25	mild	Gilbert syndrome; mild heart failure
42	5404.0010	64	M	30.46	Hungary	E 30	19.77	22.13	2.49	3.83	serious	worse heart failure; Gilbert's syndrome
43	5409.0010	64	M	38.40	Hungary	E 30	9.00	7.11	1.39	2.17	moderate	alcoholic hepatitis
9	5513.0004	79	M	33.50	Israel	warf	6.54	5.96	1.26	3.67	serious	gallbladder stones;later fatal sepsis
29	5609.0006	80	M	23.70	Romania	E 60	17.46	25.04	1.21	3.50	moderate	increased alcohol + acute viral hepatitis E
30	5622.0012	63	F	25.64	Romania	E 60	11.86	18.92	1.05	2.17	mild	uncertain; ?CHF; negative E rechallenge
	6117.0011	76	M	27.11	Japan	E 60	7.06	7.93	1.72	4.17	serious	common duct stone

Edoxaban				NDA 206316				21				
SS#	USUBJID	AGE	SEX	BMI	country	warf	pALTx	pASTx	pALPx	pTBLx	severity	likely cause
31												
10	6186.0002	77	M	22.14	Japan	warf	4.67	2.84	16.23	7.25	serious	pancreatic CA; lost to follow-up
32	7003.0011	77	F	29.84	UK	E 60	3.54	2.92	3.73	7.75	serious	pancreatic CA; later fatal
33	7035.0002	66	M	32.20	UK	E 60	10.81	10.11	1.04	2.17	mild	uncertain; possible E-DILI;
34	7101.0002	43	M	31.24	USA	E 60	7.73	6.38	1.37	2.56	moderate	possible amiodarone; E rechallange neg
11	7155.0004	82	F	19.18	USA	warf	4.24	3.56	2.42	2.92	mild	uti, poss nitrofur tox; E rechallange neg
12	7306.0006	84	M	21.48	USA	warf	3.10	0.25	0.43	2.67	mild	uncertain; unlikely W; Gilbert's syndrome
13	7406.0039	68	F	32.44	India	warf	12.97	29.17	1.32	17.83	moderate	acute viral hepatitis B
	age range	34 - 85	M 32			warf 13						
	median	70	F 11			E 30 9						
	mean	68.2				E 60 21						

In addition to the 43 subjects listed above that were found by JReview, the eDISH program showed 41 more:

41 Subjects NOT in JReview				U301	DU176b-						severity	likely cause
SS#	USUBJID	AGE	SEX	BMI	country	rand	pALTx	pASTx	pALPx	pTBLx	severity	likely cause
	site.subj											
1	1014.0005	78	M	31.63	USA	E 60	5.17	3.76	0.47	6.25	serious	not edoxaban; probable CA pancreas
2	1016.0010	83	F	26.90	USA	E 60	5.84	5.31	6.35	23.58	serious	CA head of pancreas
3	1022.0030	73	M	25.10	USA	Warf	66.56	109.04	0.72	2.67	fatal	acute heart failure, sepsis
4	1041.0011	78	F	35.94	USA	E 60	7.46	16.47	3.56	4.17	serious	very unlikely E; probable autoimmune hepatitis
5	1041.0035	73	M	38.35	USA	E 30	5.77	9.13	1.32	3.42	serious	probable heart failure; Klebsiella pneumonia
6	1095.0007	52	F	26.71	USA	Warf	12.70	8.72	1.37	4.17	serious	not warfarin, probable common duct stones
7	1127.0008	66	M	27.92	Argentina	E 60	6.23	8.67	0.93	2.50	fatal	heart failure, ischemic hepatopathy
8	1129.0045	73	M	24.50	Argentina	E 30	7.13	9.27	2.83	29.50	fatal	heart failure, ischemic hepatopathy
9	1408.0008	70	M	34.60	Peru	E 60	7.96	8.71	2.94	7.00	serious	not edoxaban; probable common duct stones
10	1627.0005	82	M	23.09	Canada	E 30	6.00	7.78	1.24	3.42	serious	common duct stones,
11	1908.0062	68	M	30.07	Czech R	E 30	3.25	1.62	0.65	2.17	mild	Gilbert syndrome; gallbladder stones
12	2035.0027	53	F	39.79	Canada	E 30	6.97	3.22	5.31	9.33	mild	very unlikely edoxaan; possible viral hepatitis
13	2045.0004	63	F	33.63	Canada	E 60	168.78	284.28	0.87	2.93	life-threatening	acute heart failure, shock
14	3100.0010	61	M	16.25	Columbia	Warf	2.92	1.36	0.69	8.08	life-threatening	not edoxaban; acute heart failure
15	3508.0003	72	M	30.85	Italy	E 30	3.46	4.04	2.83	2.83	serious	common duct stonies, biliary colic
16	3805.0009	73	M	30.46	Portugal	E 60	31.81	29.80	0.92	8.75	moderate	uncertain: possible E-DILI, probable hepatitis A
17	3807.0004	72	F	33.41	Portugal	E 30	4.00	3.47	0.78	3.33	serious	gallstone pancreatitis; cholecystectomy
18	3920.0050	77	M	28.61	Sweden	E 30	4.73	1.42	1.14	15.25	serious	gall bladder, biliary sludge
19	4004.0019	57	M	33.13	Ukraine	Warf	4.81	3.56	0.74	2.08	serious	heart failure,
20	4203.0006	73	M	27.38	Australia	Warf	6.42	2.18	3.02	3.33	serious	acute cholecystitis
21	4413.0008	72	M	23.37	India	E 60	14.69	12.40	1.10	2.42	moderate	probable hert failure; later died cardiac arrest

Edoxaban				NDA 206316				22				
22	4901.0012	55	M	26.93	S. Africa	E 60	3.06	3.69	0.91	3.42	moderate	alcoholic hepatitis; later hepatitis E
23	5040.0018	77	F	26.53	Poland	Warf	6.38	12.89	1.36	6.00	serious	acute heart failure; later gallstone pancreatitis
24	5123.0010	73	M	27.43	Taiwan	E 30	5.35	4.11	1.74	2.75	serious	gallbladder stones
25	5503.0001	71	F	31.48	Israel	E 30	7.49	3.72	10.11	8.83	moderate	possible thiazazole-nduced liver injury
26	55170017	80	M	23.12	Israel	E 60	150.83	86.98	0.43	2.67	life threatening	V tach; shock liver; later died cardiac arrest
27	5620.0009	59	M	29.63	Romania	E 60	5.98	4.27	0.68	2.67	serious	alcoholic hepatitis
28	6110.0001	82	M	21.60	Japan	Warf	8.02	16.22	0.66	2.42	serious	probable CD stone, cholangitis
29	6111.0015	74	M	26.49	Japan	Warf	3.87	6.29	0.78	3.50	serious	acute heart failure
30	6118.0014	76	F	27.35	Japan	E 60	30.92	72.64	14.85	2.40	serious	acute cholecystitis, pancreatitis
31	6196.0012	66	M	29.78	Japan	Warf	3.10	1.58	0.70	2.17	mild	unexplained; not edoxabban
32	6200.0001	77	M	23.37	Japan	E 30	3.56	5.91	0.57	3.00	serious	common duct stone
33	7111.0020	72	M	41.54	USA	E 30	27.67	33.20	1.22	2.67	serious	acute heart failure
34	7280.0026	74	M	50.30	USA	Warf	3.08	5.09	0.74	4.08	serious	acute cholecystitis
35	7312.0031	89	F	25.01	USA	E 30	5.70	4.89	3.38	15.50	fatal	pancreatic CA, shock,
36	7408.0003	69	F	27.64	India	Warf	3.78	3.75	0.77	2.17	fatal	sepsis, shock
37	7408.0010	66	F	21.33	India	E 30	25.97	108.08	4.34	3.00	fatal	cardiogenic shock
38	7408.0015	82	M	28.57	India	Warf	6.38	3.93	0.53	2.17	serious	congestive heart failure, off edoxaban
39	-411.0010	64	M	26.36	India	E 30	26.27	85.73	0.92	3.83	life threatening	acute heart failure
40	7433.0005	60	M	21.48	India	Warf	4.75	5.07	2.95	2.93	mild	unexplained; continued without toxicity
41	7440.0005	76	M	24.03	India	E 30	33.75	n.d.	2.61	3.75	fatal	cardiac arrest

age range	52 - 89	M 29	Warf 13
median	73	F 12	E 30 16
mean	71.01		E 60 12

This listing of 84 patients found by eDISH analyses is broken into two sections, because concurrent review of the data submitted to NDA 206316 as analyzed by JReview disclosed only 43 patients. The reason for the discrepancy between the two programs appeared to be a difference in data provided for analyses, and not a programming error. The eDISH data were requested specially from the sponsor, in a specified format, and to include ALL laboratory tests done and reported, whether on or off study drug, whether in the central laboratories or local or hospital laboratories. Inclusion of the latter liver test data was obviously expected to disclose some of the more serious cases. It may be noted from the **bolded** values in the two tables above that there were many more with serum ALT or AST greater than 20 xULN, in the range the NCI calls “life-threatening” or grade 4. Although serum enzyme levels themselves may not be life-threatening, whatever may have *caused* them to be so high needs to be considered. In this study of elderly patients with chronic atrial fibrillation, there were many patients who drifted in and out of mild to moderate heart failure, sometimes with few symptoms, and more danger of really severe, catastrophic heart failure, shock, and death.

Comment: It was not anticipated that a major difference might be encountered from eDISH review and that being taught to reviewers using JReview. The latter is a proprietary program that has been sanctioned by FDA/CDER by contract to a private software vendor (Integrated Clinical Systems, Inc., Stockton NJ) that advertises on its website facilitating modernization of the regulatory review process, including a “JReview standard analysis – Hy’s Law Plot.” The plot shown by the vendor bears some resemblance to the eDISH program devised and developed by Drs. Guo and Senior at FDA, in 1983-4, and used by them for scores of consultations in the 10 years since. They were not contacted by Integrated Systems in their copying of eDISH graphics, and have apparently not fully understood the underlying concepts. When we met with a representative of Integrated Systems, (b) (4) in mid-July, we agreed that the two programs might be working on different data sets. The problem of standardizing required data sets will have to be addressed by both the Office of Computational Sciences and the Office of New Drugs. It will not be sufficient to just make JReview look more like eDISH, but the basic question of what data should be reviewed is fundamental to the FDA mission.

In considering the impact of this on the current review of NDA 206316, it is reassuring that neither program has discovered a “smoking gun” case of edoxaban-induced serious and probably drug-caused hepatocellular jaundice. However, it is unsettling that two of the three cases thought by the sponsor, Daiichi Sankyo, were missed by JReview but captured by eDISH (Cases #4413.0008 and #7111.0020) described above. Also missed by JReview was one of the three cases listed by Dr. McDowell asking for another opinion (case #7440.0005). Also missed was the very serious, life-threatening case #2045.0004 summarized briefly below on page 24.

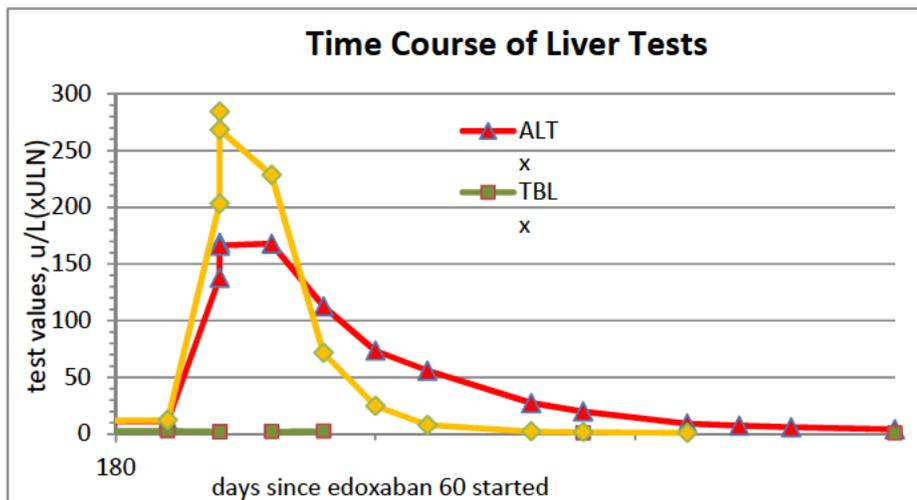
CONCLUSIONS AND RECOMMENDATIONS

It has been a long and tedious task to sift through the almost 30,000 subjects of Daiichi Sankyo’s two pivotal phase III clinical studies U301 and U305 comparing edoxaban to warfarin, looking for cases of serious, probably edoxaban-induced hepatotoxicity. As was found with dabigatran, rivaroxaban, and apixaban, there was no significant difference between warfarin and those drugs with respect to incidence of liver injury with dysfunction. In all four reviews, there was noted to be a fairly high incidence of liver test abnormalities, higher than seen with most drugs and more than seen in studies of those same drugs for other indications than preventing embolic strokes in patients with chronic atrial fibrillation, such as preventing thromboembolic complications after knee or hip surgery, or prevention of recurrence after deep vein thrombosis. Why should this be so? One obvious difference was the older mean age and many multisystem medical problems of patients with chronic AFib in the Study U301, and similar groups in studies of the three drugs already approved --- dabigatran, rivaroxaban, and apixaban. In all the large studies of all these drugs, the similarity of responses by patients with chronic atrial fibrillation is striking, and not different between new study drug and the old work-horse warfarin. The exception was ximelagatran, not approved in 2004 because of marked discrepancy between effects in patients on warfarin and those on ximelagatran, bitterly contested for several years until it was found that European and Asian patients differed strikingly in their responses based on inheritance of the HLA biomarkers (DRB1*07 and DQA1*02) the showed increased susceptibility to ximelagatran-induced serious liver injury and dysfunction. The principle being teased out of all this is that it may not be the **drug** that’s responsible for the hepatotoxicity but the increased **susceptibility** of the patients in a select but still fairly common group with chronic heart disease.

Cardiac Hepatopathy

It has been known for a very long time that chronic heart failure causes a type of cirrhosis called “nutmeg liver” (Kiernan, 1833; Legg and Payne, 1875), because of its appearance at autopsy of deep red-brown spots in the centrilobular areas of the liver. Mallory (1901, 1911) showed that these were due to centrilobular necroses. The importance of vascular shock in causing these lesions (Ellenberg and Osserman, 1951; Sherlock, 1951) became clear, and led to use of other terms: “ischemic hepatitis” (Bynum et al., 1979), “hypoxic hepatitis” (Henrion et al., 1990), “hypoxic hepatopathy” (Birrer et al., 2007). For such a well-known clinical problem that has been around for so long, it is surprising that so many of the investigators in this recent study did not seem to think of its possibility, and attributed elevations of ALT and AST to liver disease rather than to cardiac disease with hepatic effects and complications. We all know that renal and brain function may fail secondary to liver dysfunction, and hepatorenal syndrome and hepatic encephalopathy are used to determine when liver transplantation should be done for primary liver disease. It is also evident that liver function is highly dependent on its blood supply, which is often a problem in cardiac disease, in varying degrees of severity, and as frequently seen in patients with chronic AFib who were being treated in these studies. I lumped those terms as “cardiac hepatopathy” for analyses of causality. The diagnosis was too often missed in these edoxaban studies, especially in U 301, not only by the investigators (many of whom were cardiologists), but also by the sponsor and their consulting hepatologists. The distinction is important, for heart failure can be treated, after which the liver dysfunction very rapidly improves, when treatment of heart failure would be the correct treatment.

An example of the effect of acute heart failure and shock on liver test may be seen in the case of an obese (BMI 33.63) Canadian F 63 who tolerated edoxaban 60 mg/day for six months, with no changes in her normal liver test values, then developed a rapid irregular tachycardia, acute heart failure, cardiac arrest and shock, was twice resuscitated and miraculously survived.



Comment: This is a classic picture of cardiac hepatopathy showing an extremely sharp rise in serum aminotransferases, AST earlier, faster, and higher than ALT, and very rapid decline of AST, and ALT more slowly, with little change in bilirubin and none in ALP. This is not DILI, and correctly diagnosed by both the investigator and the hepatology consultants.

Despite the fairly careful search for evidence of serious liver injury and dysfunction attributable to edoxaban in this gigantic study of more than 21,000 subjects, there were no cases of clear-cut DILI found, either by the sponsor or by our review. This is consistent with findings for the two previously approved drugs in the class, rivaroxaban and apixaban, and for dabigatran (but not for ximelagatran). The medical art of differential diagnosis of most likely cause remains just that; not yet a science, and where experts often disagree, as has been the eight-year experience of the Drug-Induced Liver Injury Network (DILIN) of the NIH. Some of these cases were indeed very difficult to assess and diagnose. It has been a humbling experience. We need to teach sponsors and investigators how best to investigate potential cases of “DISH” – **drug-induced serious hepatotoxicity**, and will keep working to improve the eDISH program even if JReview thinks it has all the answers.

A more serious problem, about which we were not asked to comment, was bleeding. This also been a problem with all of the other novel oral anticoagulants, and appears to be a consequence of inability to measure their effect on coagulation, the assumption that one dose is appropriate for most patients, and the trade-off of convenience for safety. Obviously the patients like not having to have periodic venipunctures or even finger-sticks to measure prothrombin time and adjust the warfarin dose as needed. Physicians also find it easier to prescribe, with no burden of monitoring anticoagulation effect and employing a nurse or assistant to keep track of the drug effects. We see now the consequence of that in the lawsuits have been lodged and are coming.

Iconcur with the DCRP opinion that edoxaan is approvable, and recommend that the labeling include warning about the fairly frequent elevation of liver tests and suggest that some form of serum transaminase monitoring be instituted in patients with AFib being started on this drug, which may be of clinical value not only in detecting liver injury but also early evidence of heart failure that may be asymptomatic but treatable. Test abnormalities should be followed closely and repeatedly until it is clear what is going on in the patient and why, which is simply good medical practice.

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“Cardiac Hepatopathy”

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/s/

JOHN R SENIOR
09/25/2014

DGCPC/OSI CONSULT: Request for Clinical Inspections

Date: 9 April 2014

To: Ni Khin, Acting Division Director, DGCPC
Kassa Ayalew, M.D., Acting Branch Chief, GCPAB
Janice Pohlman, M.D., M.P.H., Team Leader GCPAB
CDEROCDSIPMOs@fda.hhs.gov
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Office of Scientific Investigations
Office of Compliance/CDER

Through: Division of Cardiovascular & Renal Products (DCRP):
Melanie Blank, M.D., Medical Officer (efficacy)
Tzu-Yun McDowell, Ph.D, Clinical Reviewer (safety)
Martin Rose, M.D., Ph.D., CDTL
Norman Stockbridge, M.D., Ph.D., Director

From: Alison Blaus, RAC, Regulatory Health Project Manager, DCRP

Subject: **Request for Clinical Site Inspections**

I. General Information

Application#: NDA 206316 / ORIG-1

IND#: 77254

Applicant: Daiichi Sankyo

Applicant contact information:

Doreen Morgan, Pharm.D., M.S.
Executive Director, Regulatory Affairs
399 Thornall St.
Edison, NJ 08837
(732) 590-5198
Email: dmorgan@dsus.com

Drug Proprietary Name: SAVAYSA

Generic Drug Name: edoxaban tosylate

NME or Original BLA (Yes/No/Not Applicable*): Yes (NME)

Review Priority (Standard or Priority or Not Applicable*): Standard

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

Is this for Pediatric Exclusivity (Yes/No/Not Applicable*): No

DGCPC/OSI Consult
version: 09/28/2011

Proposed New Indication:

Reduction in the Risk of Stroke and Systemic Embolism in Nonvalvular Atrial Fibrillation

SAVAYSA is indicated to reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation (NVAf).

PDUFA: 8 January 2015

Action Goal Date: 8 January 2015

Inspection Summary Goal Date: **8 November 2014**

II. Protocol/Site Identification

(Name,Address, Phone number, email, fax#)	Site #	Protocol ID	Number of Subjects	Indication
Awasty, Vivek R & R Research, 980 South Prospect St Marion, OH 43302 USA United States phone:1 740 3758140 fax:1 740 3758133 email:vivek.awasty@awastyresearch.com	1007	DU176b-C-U301	72	A Phase 3,randomized, double-blind, double-dummy, parallel group, multicenter, multinational study for evaluation of efficacy and safety of DU-176b versus warfarin in subjects with atrial fibrillation
Maxwell, Tom Little Common Surgery, 82 Cooden Sea Road Bexhill on Sea, E.SUSX TN39 4SP GBR Western Europe phone:44 1424 847556 fax:44 1424 848225 email:tgmax@btopenworld.com	7017	DU176b-C-U301	99	A Phase 3,randomized, double-blind, double-dummy, parallel group, multicenter, multinational study for evaluation of efficacy and safety of DU-176b versus warfarin in subjects with atrial fibrillation

(Name,Address, Phone number, email, fax#)	Site #	Protocol ID	Number of Subjects	Indication
Monteiro, Pedro Hospitais da Universidade de Coimbra, Avenida Bissaya Barreto 52 Coimbra, N/A 3000-075 PRT Western Europe phone:351 239 400400 fax:351 239 823097 email:pedromonte@gmail.com	3805	DU176b-C-U301	137	A Phase 3,randomized, double-blind, double-dummy, parallel group, multicenter, multinational study for evaluation of efficacy and safety of DU-176b versus warfarin in subjects with atrial fibrillation
Slaby, Josef Oblastni nemocnice Kolin, Zizkova 146 Kolin, N/A 280 02 CZE Eastern Europe phone:420 321 756207 fax:420 321 756124 email:slaby.josef@post.cz	1928	DU176b-C-U301	66	A Phase 3,randomized, double-blind, double-dummy, parallel group, multicenter, multinational study for evaluation of efficacy and safety of DU-176b versus warfarin in subjects with atrial fibrillation
Spinar, Jindrich FN Brno - Bohunice, Jihlavska 20 Brno, N/A 625 00 CZE Eastern Europe phone:420 532 232601 fax:420 532 232611 email:jspinar@fnbrno.cz	1930	DU176b-C-U301	151	A Phase 3,randomized, double-blind, double-dummy, parallel group, multicenter, multinational study for evaluation of efficacy and safety of DU-176b versus warfarin in subjects with atrial fibrillation

III. Site Selection/Rationale

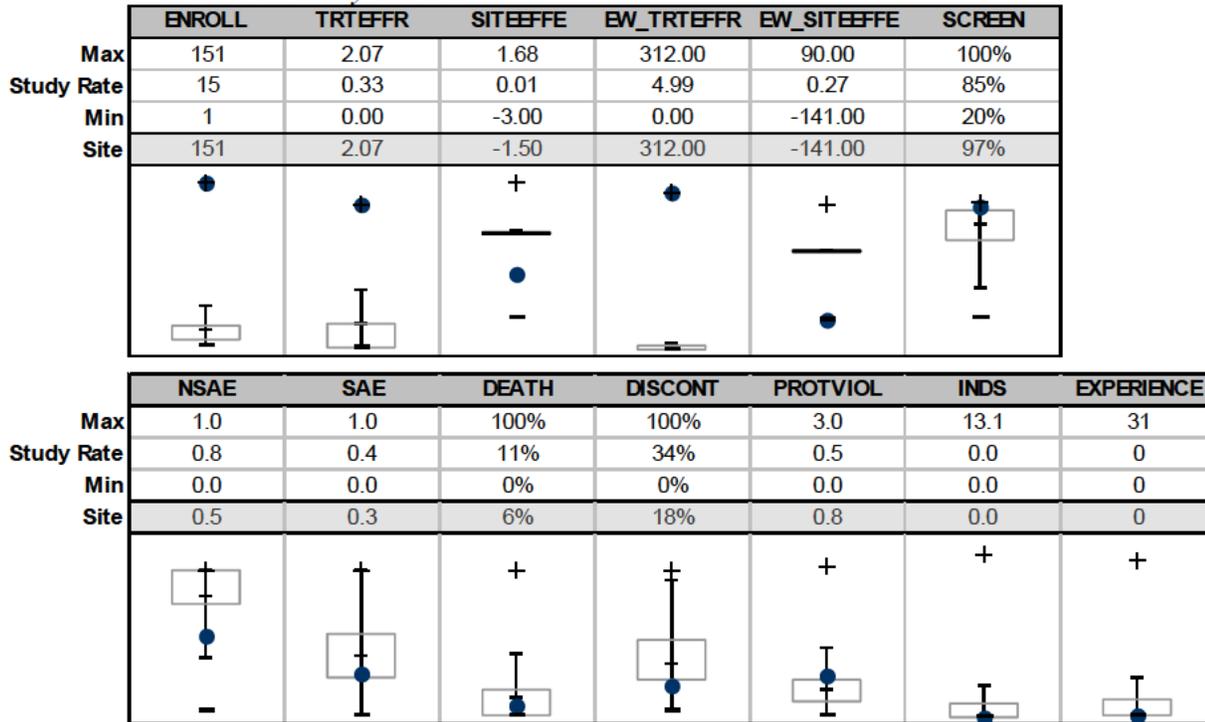
Site Information

STUDY:	DU176b-C-U301	SITEID:	1930
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NAME	Spinar, Jindrich		
LOCATION	FN Brno - Bohunice, Jihlavská 20 Brno, N/A, CZE 625 00		
PHONE/FAX	420 532 232601 / 420 532 232611		
EMAIL	spinar@fnbrno.cz		

RANK	2	FINLISC	0	COMPLAINT	0
SITE RISK	23.3	OAI	0	TSLI	3

Site Values vs. Overall Study Results



Site Memo

Jindrich Spinar - Eastern Europe; high enrollment (151); high site efficacy effect; very low death and discontinuation, low bleeding (under-reporting)

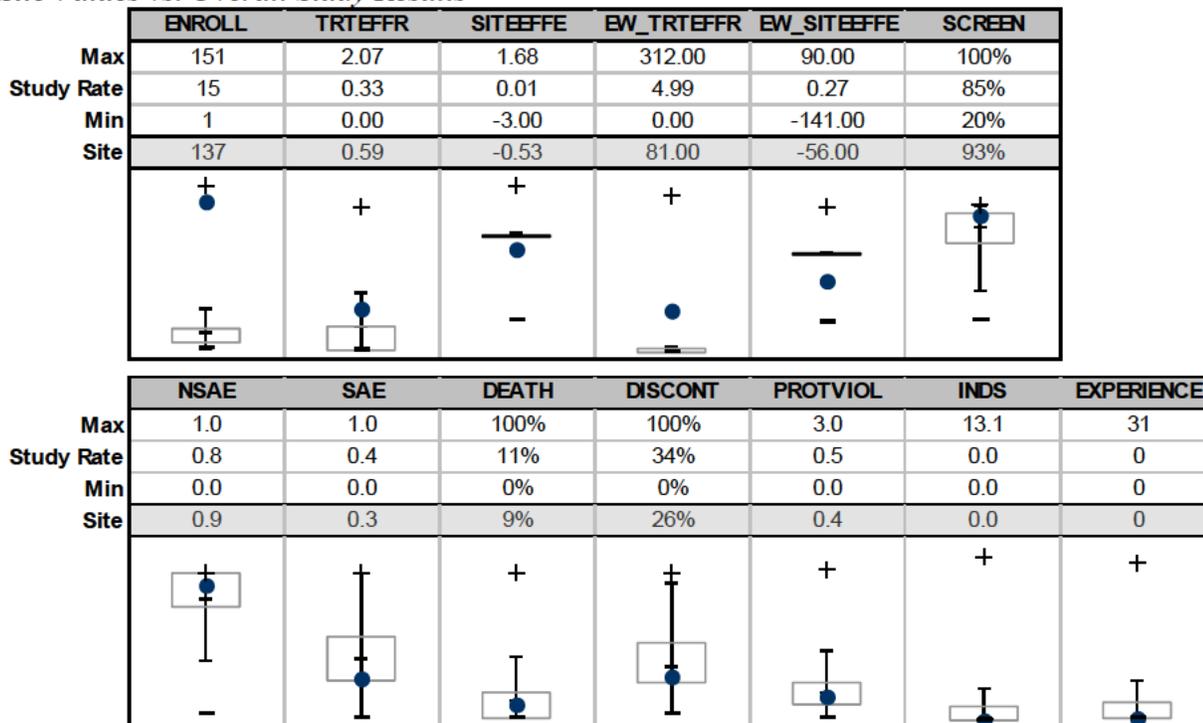
Site Information

STUDY:	DU176b-C-U301	SITEID:	3805
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NAME	Monteiro, Pedro
LOCATION	Hospitais da Universidade de Coimbra, Avenida Bissaya Barreto 52 Coimbra, N/A, PRT 3000-075
PHONE/FAX	351 239 400400 / 351 239 823097
EMAIL	pedromonte@gmail.com

RANK	3	FINLISC	0	COMPLAINT	0
SITE RISK	22.2	OAI	0	TSLI	3

Site Values vs. Overall Study Results



Site Memo

Pedro Monteiro - Western Europe; high enrollment (137); high site efficacy; high ratio of NSAE to SAE; high NSAE

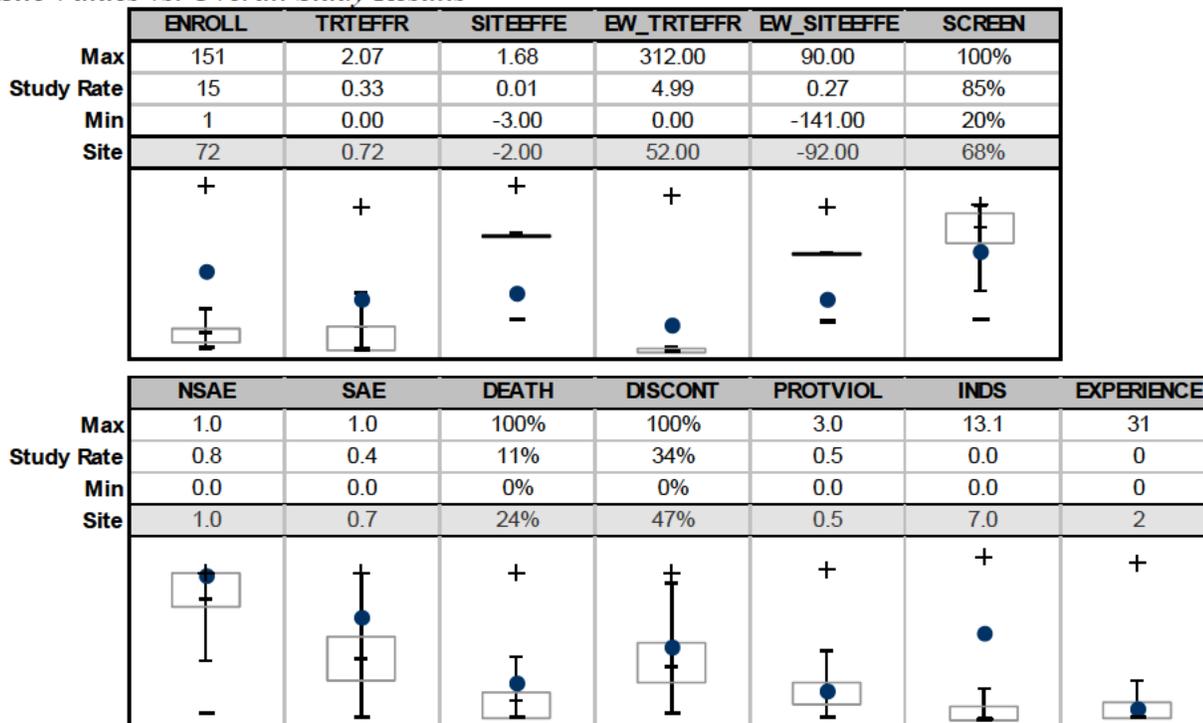
Site Information

STUDY:	DU176b-C-U301	SITEID:	1007
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NAME	Awasty, Vivek
LOCATION	R & R Research, 980 South Prospect St Marion, OH, USA 43302
PHONE/FAX	1 740 3758140 / 1 740 3758133
EMAIL	vivek.awasty@awastyresearch.com

RANK	7	FINLDISC	0	COMPLAINT	0
SITE RISK	15.2	OAI	0	TSLI	3

Site Values vs. Overall Study Results



Site Memo

Vivek Awasty - United States; relatively high enrollment (72); high site efficacy, high deaths and discontinuation

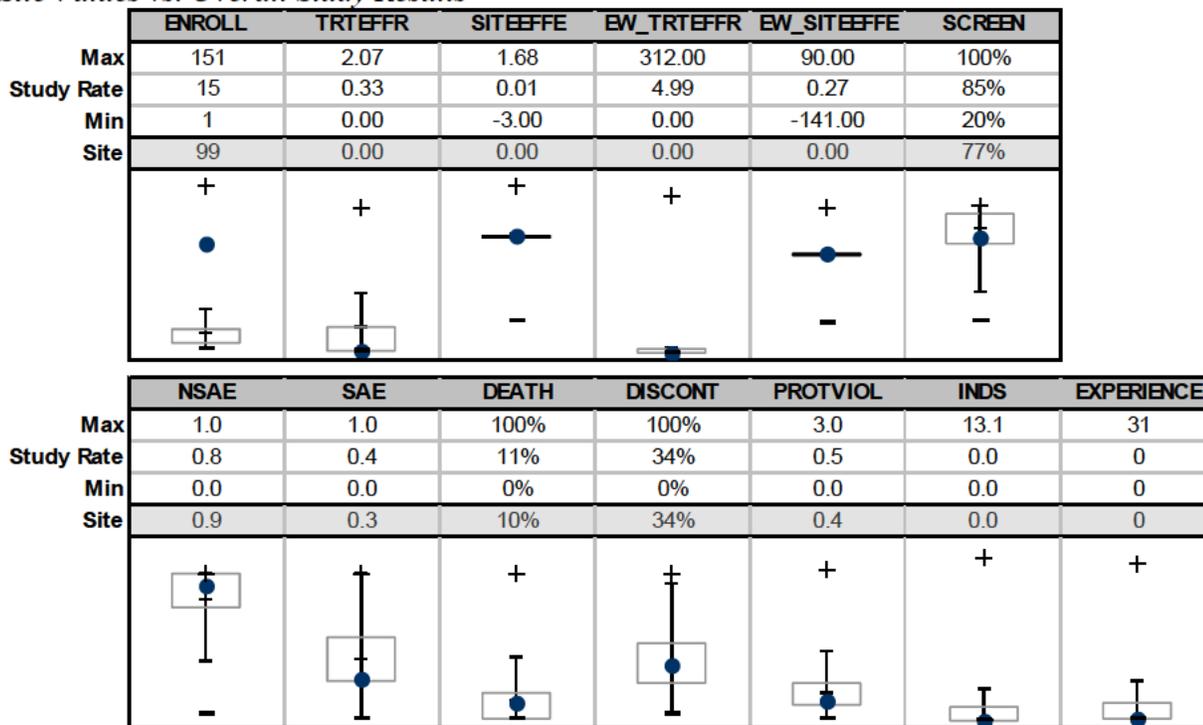
Site Information

STUDY:	DU176b-C-U301	SITEID:	7017
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NAME	Maxwell, Tom
LOCATION	Little Common Surgery, 82 Cooden Sea Road Bexhill on Sea, E.SUSX, GBR TN39 4SP
PHONE/FAX	44 1424 847556 / 44 1424 848225
EMAIL	tgmax@btopenworld.com

RANK	6	FINLDISC	0	COMPLAINT	0
SITE RISK	16.8	OAI	0	TSLI	3

Site Values vs. Overall Study Results



Site Memo

Tom Maxwell - No events for high enrollment; low death rate; high ratio of NSAE to SAE; high discontinuation

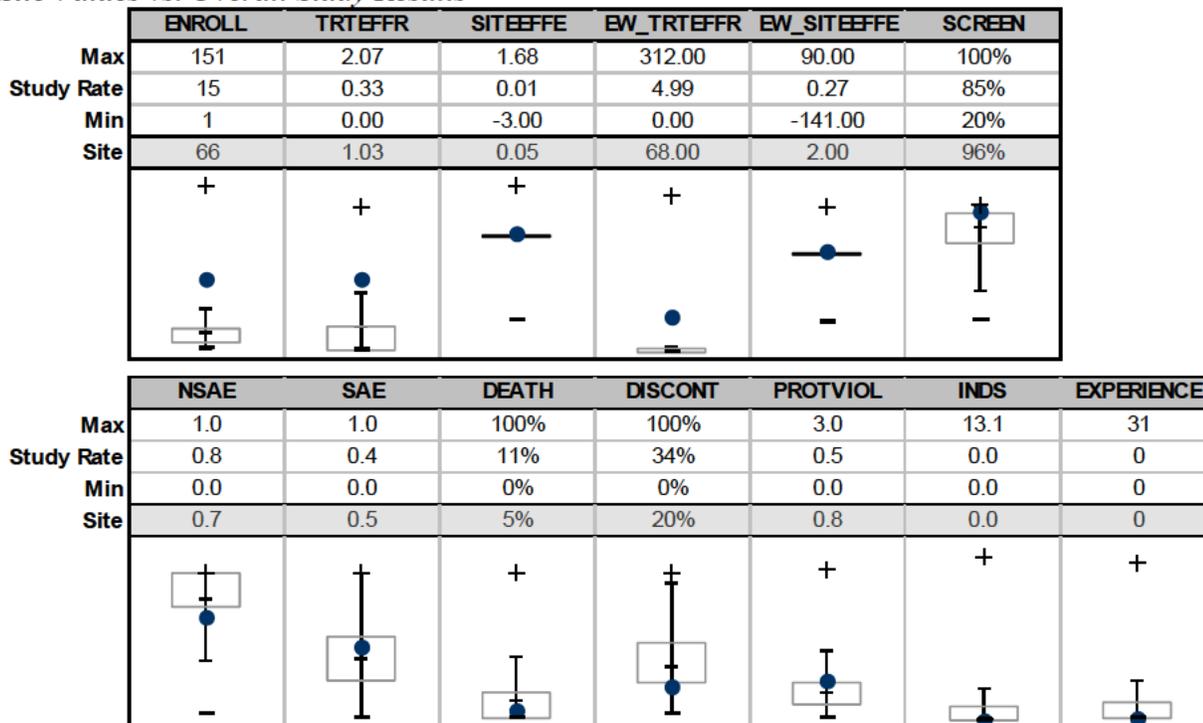
Site Information

STUDY:	DU176b-C-U301	SITEID:	1928
---------------	---------------	----------------	------

NAME	Slaby, Josef
LOCATION	Oblastni nemocnice Kolin, Zizkova 146 Kolin, N/A, CZE 280 02
PHONE/FAX	420 321 756207 / 420 321 756124
EMAIL	slaby.josef@post.cz

RANK	28	FINLISC	0	COMPLAINT	0
SITE RISK	11.0	OAI	0	TSLI	3

Site Values vs. Overall Study Results



Site Memo

Josef Slaby - No major bleeds

Domestic Inspections:

Reasons for inspections (please check all that apply):

- Enrollment of large numbers of study subjects
- High treatment responders (specify): No endpoint events (strokes or systemic embolic events in investigational treatment arms and 2 strokes/SEEs in active comparator (warfarin)
- Significant primary efficacy results pertinent to decision-making
- There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, significant human subject protection violations or adverse event profiles.
- Other (specify): high deaths and discontinuations

International Inspections:

Reasons for inspections (please check all that apply):

- There are insufficient domestic data
- Only foreign data are submitted to support an application
- Domestic and foreign data show conflicting results pertinent to decision-making
- There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, or significant human subject protection violations.
- Other [Enrollment of large numbers of study subjects, high site efficacy, low SAE/AE ratios (possibility of under reporting), low death and discontinuation, low or no major bleeding (possibility of under-reporting, low numbers of endpoint events for size of site)]

Five or More Inspection Sites:

Please see rationale noted above in Section III

IV. Tables of Specific Data to be Verified

Please check back with the Division close to the inspection date to confirm whether there is specific information to verify at the site/sponsor. It is too early in the review to pinpoint specific data.

Should you require any additional information, please contact Alison Blaus (Regulatory Project Manager) at 301-796-1138, Melanie Blank (Primary Clinical Reviewer) at 301-796-1330, or Martin Rose (Cross-Discipline Team Leader) at 301-796-0223.

Concurrence:

- Medical Team Leader
- Medical Reviewer
- Division Director

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/s/

ALISON L BLAUS
04/09/2014

TZU-YUN C MCDOWELL
04/09/2014

MELANIE J BLANK
04/09/2014

MARTIN ROSE
04/09/2014

NORMAN L STOCKBRIDGE
04/10/2014

REGULATORY PROJECT MANAGER PHYSICIAN'S LABELING RULE (PLR) FORMAT REVIEW OF THE PRESCRIBING INFORMATION

Complete for all new NDAs, BLAs, Efficacy Supplements, and PLR Conversion Labeling Supplements

Application: NDA 206316
Application Type: New NME NDA
Name of Drug/Dosage Form: SAVAYSA (edoxaban tosylate) Tablets, 15, 30, and 60 mg
Applicant: Daiichi-Sankyo Inc.
Receipt Date: January 8, 2014
Goal Date: January 8, 2015

1. Regulatory History and Applicant's Main Proposals

Savaysa is an antithrombotic agent and is a member of the anti-factor Xa class of compounds. This drug product was initially submitted to the FDA under two INDs, IND 77254 with the Division of Cardiovascular and Renal Products (DCRP) for Atrial Fibrillation (AF) on May 14, 2007 and IND 63266 with Division of Hematology Products (DHP) for Deep Vein Thrombosis (VTE) on May 27, 2004. This NDA was submitted on January 8, 2014 with (b) (4) proposed indications:

ORIG-1: Reduction in the Risk of Stroke and Systemic Embolism in Nonvalvular Atrial Fibrillation

ORIG-2: Treatment of Deep Vein Thrombosis & Pulmonary Embolism (PE)

(b) (4)

This NDA was administratively split into (b) (4) original applications as indicated above and is undergoing a joint review with DCRP (ORIG-1) and DHP (ORIG-2 (b) (4)).

2. Review of the Prescribing Information

This review is based on the applicant's submitted Word format of the prescribing information (PI). The applicant's proposed PI was reviewed in accordance with the labeling format requirements listed in the "Selected Requirements for Prescribing Information (SRPI)" checklist (see the Appendix).

3. Conclusions/Recommendations

SRPI format deficiencies were identified in the review of this PI. For a list of these deficiencies see the Appendix.

All SRPI format deficiencies of the PI will be conveyed to the applicant in the 74-day letter. The applicant will be asked to correct these deficiencies and resubmit the PI in Word format by [April 14, 2014](#). The resubmitted PI will be used for further labeling review.

Selected Requirements of Prescribing Information

Highlights

See Appendix A for a sample tool illustrating the format for the Highlights.

HIGHLIGHTS GENERAL FORMAT and HORIZONTAL LINES IN THE PI

- YES** 1. Highlights (HL) must be in a minimum of 8-point font and should be in two-column format, with ½ inch margins on all sides and between columns.

Comment:

- YES** 2. The length of HL must be one-half page or less (the HL Boxed Warning does not count against the one-half page requirement) unless a waiver has been granted in a previous submission (e.g., the application being reviewed is an efficacy supplement).

Instructions to complete this item: If the length of the HL is one-half page or less, then select “YES” in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page:

➤ **For the Filing Period:**

- *For efficacy supplements:* If a waiver was previously granted, select “YES” in the drop-down menu because this item meets the requirement.
- *For NDAs/BLAs and PLR conversions:* Select “NO” because this item does not meet the requirement (deficiency). The RPM notifies the Cross-Discipline Team Leader (CDTL) of the excessive HL length and the CDTL determines if this deficiency is included in the 74-day or advice letter to the applicant.

➤ **For the End-of-Cycle Period:**

- Select “YES” in the drop down menu if a waiver has been previously (or will be) granted by the review division in the approval letter and document that waiver was (or will be) granted.

Comment:

- YES** 3. A horizontal line must separate HL from the Table of Contents (TOC). A horizontal line must separate the TOC from the FPI.

Comment:

- YES** 4. All headings in HL must be **bolded** and presented in the center of a horizontal line (each horizontal line should extend over the entire width of the column as shown in Appendix A). The headings should be in UPPER CASE letters.

Comment:

- YES** 5. White space should be present before each major heading in HL. There must be no white space between the HL Heading and HL Limitation Statement. There must be no white space between the product title and Initial U.S. Approval. See Appendix A for a sample tool illustrating white space in HL.

Comment:

- YES** 6. Each summarized statement or topic in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contain more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each summarized statement or topic.

Selected Requirements of Prescribing Information

Comment:

- YES** 7. Section headings must be presented in the following order in HL:

Section	Required/Optional
• Highlights Heading	Required
• Highlights Limitation Statement	Required
• Product Title	Required
• Initial U.S. Approval	Required
• Boxed Warning	Required if a BOXED WARNING is in the FPI
• Recent Major Changes	Required for only certain changes to PI*
• Indications and Usage	Required
• Dosage and Administration	Required
• Dosage Forms and Strengths	Required
• Contraindications	Required (if no contraindications must state "None.")
• Warnings and Precautions	Not required by regulation, but should be present
• Adverse Reactions	Required
• Drug Interactions	Optional
• Use in Specific Populations	Optional
• Patient Counseling Information Statement	Required
• Revision Date	Required

* RMC only applies to the BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS sections.

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

- YES** 8. At the beginning of HL, the following heading must be **bolded** and should appear in all UPPER CASE letters: "**HIGHLIGHTS OF PRESCRIBING INFORMATION**".

Comment:

Highlights Limitation Statement

- YES** 9. The **bolded** HL Limitation Statement must include the following verbatim statement: "**These highlights do not include all the information needed to use (insert name of drug product) safely and effectively. See full prescribing information for (insert name of drug product).**" The name of drug product should appear in UPPER CASE letters.

Comment:

Product Title in Highlights

- YES** 10. Product title must be **bolded**.

Comment:

Initial U.S. Approval in Highlights

- YES** 11. Initial U.S. Approval in HL must be **bolded**, and include the verbatim statement "**Initial U.S. Approval:**" followed by the **4-digit year**.

Comment:

Boxed Warning (BW) in Highlights

Selected Requirements of Prescribing Information

- N/A** 12. All text in the BW must be **bolded**.
Comment:
- N/A** 13. The BW must have a heading in UPPER CASE, containing the word “**WARNING**” (even if more than one warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the warning (e.g., “**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**”). The BW heading should be centered.
Comment:
- N/A** 14. The BW must always have the verbatim statement “*See full prescribing information for complete boxed warning.*” This statement should be centered immediately beneath the heading and appear in *italics*.
Comment:
- N/A** 15. The BW must be limited in length to 20 lines (this includes white space but does not include the BW heading and the statement “*See full prescribing information for complete boxed warning.*”).
Comment:

Recent Major Changes (RMC) in Highlights

- N/A** 16. RMC pertains to only the following five sections of the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS. RMC must be listed in the same order in HL as the modified text appears in FPI.
Comment:
- N/A** 17. The RMC must include the section heading(s) and, if appropriate, subsection heading(s) affected by the recent major change, together with each section’s identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, “Warnings and Precautions, Acute Liver Failure (5.1) --- 9/2013”.
Comment:
- N/A** 18. The RMC must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).
Comment:

Indications and Usage in Highlights

- YES** 19. If a product belongs to an established pharmacologic class, the following statement is required under the Indications and Usage heading in HL: “(Product) is a (name of established pharmacologic class) indicated for (indication)”.
Comment:

Dosage Forms and Strengths in Highlights

- YES** 20. For a product that has several dosage forms (e.g., capsules, tablets, and injection), bulleted subheadings or tabular presentations of information should be used under the Dosage Forms and Strengths heading.
Comment:

Selected Requirements of Prescribing Information

Contraindications in Highlights

- YES** 21. All contraindications listed in the FPI must also be listed in HL or must include the statement “None” if no contraindications are known. Each contraindication should be bulleted when there is more than one contraindication.

Comment:

Adverse Reactions in Highlights

- NO** 22. For drug products other than vaccines, the verbatim **bolded** statement must be present: “**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**”.

Comment: *The sponsor has left in the following phrases: <<Insert manufacturer>> at <<Insert phone No. and Web address>>. The sponsor should insert the correct information into the label.*

Patient Counseling Information Statement in Highlights

- YES** 23. The Patient Counseling Information statement must include one of the following three **bolded** verbatim statements that is most applicable:

If a product **does not** have FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION**”

If a product **has** FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling**”
- “**See 17 for PATIENT COUNSELING INFORMATION and Medication Guide**”

Comment:

Revision Date in Highlights

- NO** 24. The revision date must be at the end of HL, and should be **bolded** and right justified (e.g., “**Revised: 9/2013**”).

Comment: *The revision date is not listed in the following format: "Revised: 1/2014" but rather is listed as: "Revised: Mon 20XX"*

Selected Requirements of Prescribing Information

Contents: Table of Contents (TOC)

See Appendix A for a sample tool illustrating the format for the Table of Contents.

- YES** 25. The TOC should be in a two-column format.
Comment:
- YES** 26. The following heading must appear at the beginning of the TOC: “**FULL PRESCRIBING INFORMATION: CONTENTS**”. This heading should be in all UPPER CASE letters and **bolded**.
Comment:
- N/A** 27. The same heading for the BW that appears in HL and the FPI must also appear at the beginning of the TOC in UPPER CASE letters and **bolded**.
Comment:
- YES** 28. In the TOC, all section headings must be **bolded** and should be in UPPER CASE.
Comment:
- YES** 29. In the TOC, all subsection headings must be indented and not bolded. The headings should be in title case [first letter of all words are capitalized except first letter of prepositions (through), articles (a, an, and the), or conjunctions (for, and)].
Comment:
- YES** 30. The section and subsection headings in the TOC must match the section and subsection headings in the FPI.
Comment:
- YES** 31. In the TOC, when a section or subsection is omitted, the numbering must not change. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading “FULL PRESCRIBING INFORMATION: CONTENTS” must be followed by an asterisk and the following statement must appear at the end of TOC: “*Sections or subsections omitted from the full prescribing information are not listed.”
Comment:

Selected Requirements of Prescribing Information

Full Prescribing Information (FPI)

FULL PRESCRIBING INFORMATION: GENERAL FORMAT

- YES** 32. The **bolded** section and subsection headings in the FPI must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below (section and subsection headings should be in UPPER CASE and title case, respectively). If a section/subsection required by regulation is omitted, the numbering must not change. Additional subsection headings (i.e., those not named by regulation) must also be **bolded** and numbered.

BOXED WARNING
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Labor and Delivery
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment:

- YES** 33. The preferred presentation for cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. The entire cross-reference should be in *italics* and enclosed within brackets. For example, “[*see Warnings and Precautions (5.2)*]” or “[*see Warnings and Precautions (5.2)*]”.

Comment:

Selected Requirements of Prescribing Information

- N/A** 34. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

FPI Heading

- YES** 35. The following heading must be **bolded** and appear at the beginning of the FPI: “**FULL PRESCRIBING INFORMATION**”. This heading should be in UPPER CASE.

Comment:

BOXED WARNING Section in the FPI

- N/A** 36. In the BW, all text should be **bolded**.

Comment:

- N/A** 37. The BW must have a heading in UPPER CASE, containing the word “**WARNING**” (even if more than one Warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the Warning (e.g., “**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**”).

Comment:

CONTRAINDICATIONS Section in the FPI

- N/A** 38. If no Contraindications are known, this section must state “None.”

Comment:

ADVERSE REACTIONS Section in the FPI

- YES** 39. When clinical trials adverse reactions data are included (typically in the “Clinical Trials Experience” subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.”

Comment:

- N/A** 40. When postmarketing adverse reaction data are included (typically in the “Postmarketing Experience” subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.”

Comment:

PATIENT COUNSELING INFORMATION Section in the FPI

- YES** 41. Must reference any FDA-approved patient labeling in Section 17 (PATIENT COUNSELING INFORMATION section). The reference should appear at the beginning of Section 17 and

Selected Requirements of Prescribing Information

include the type(s) of FDA-approved patient labeling (e.g., Patient Information, Medication Guide, Instructions for Use).

Comment:

- YES** 42. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under section 17 (PATIENT COUNSELING INFORMATION). All FDA-approved patient labeling must appear at the end of the PI upon approval.

Comment:

Selected Requirements of Prescribing Information

Appendix A: Format of the Highlights and Table of Contents

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use [DRUG NAME] safely and effectively. See full prescribing information for [DRUG NAME].

[DRUG NAME (nonproprietary name) dosage form, route of administration, controlled substance symbol]
Initial U.S. Approval: [year]

WARNING: [SUBJECT OF WARNING]

See full prescribing information for complete boxed warning.

- [text]
- [text]

RECENT MAJOR CHANGES

[section (X.X)] [m/year]
[section (X.X)] [m/year]

INDICATIONS AND USAGE

[DRUG NAME] is a [name of pharmacologic class] indicated for:

- [text]
- [text]

DOSAGE AND ADMINISTRATION

- [text]
- [text]

DOSAGE FORMS AND STRENGTHS

- [text]

CONTRAINDICATIONS

- [text]
- [text]

WARNINGS AND PRECAUTIONS

- [text]
- [text]

ADVERSE REACTIONS

Most common adverse reactions (incidence > x%) are [text].

To report SUSPECTED ADVERSE REACTIONS, contact [name of manufacturer] at [phone #] or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- [text]
- [text]

USE IN SPECIFIC POPULATIONS

- [text]
- [text]

See 17 for PATIENT COUNSELING INFORMATION [and FDA-approved patient labeling OR and Medication Guide].

Revised: [m/year]

FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING: [SUBJECT OF WARNING]

1 INDICATIONS AND USAGE

- 1.1 [text]
- 1.2 [text]

2 DOSAGE AND ADMINISTRATION

- 2.1 [text]
- 2.2 [text]

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS

- 5.1 [text]
- 5.2 [text]

6 ADVERSE REACTIONS

- 6.1 [text]
- 6.2 [text]

7 DRUG INTERACTIONS

- 7.1 [text]
- 7.2 [text]

8 USE IN SPECIFIC POPULATIONS

- 8.1 Pregnancy
- 8.2 Labor and Delivery
- 8.3 Nursing Mothers
- 8.4 Pediatric Use
- 8.5 Geriatric Use

9 DRUG ABUSE AND DEPENDENCE

- 9.1 Controlled Substance
- 9.2 Abuse
- 9.3 Dependence

10 OVERDOSAGE

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

- 12.1 Mechanism of Action
- 12.2 Pharmacodynamics
- 12.3 Pharmacokinetics
- 12.4 Microbiology
- 12.5 Pharmacogenomics

13 NONCLINICAL TOXICOLOGY

- 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
- 13.2 Animal Toxicology and/or Pharmacology

14 CLINICAL STUDIES

- 14.1 [text]
- 14.2 [text]

15 REFERENCES

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

*Sections or subsections omitted from the full prescribing information are not listed.

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/s/

JANET G HIGGINS
03/19/2014

MONSURAT O AKINSANYA
03/19/2014

OSI/DGCPC CONSULT: Request for Clinical Inspections

Date: February 10, 2014

To: Ann Meeker-O'Connell, Acting Division Director, DGCPC
Constance Lewin, M.D., M.P.H, Branch Chief, GCPEB*
Susan Thompson, M.D., Acting Branch Chief, GCPAB
Janice Pohlman, M.D., M.P.H., Team Leader GCPAB
Susan Leibenhaut, M.D. Acting Team Leader, GCPAB
CDER OSI PM Track
Anthony Orenca, M.D.
Division of Good Clinical Practice Compliance
Office of Scientific Investigations
Office of Compliance/CDER

Through: Saleh Ayache, M.D., Clinical Reviewer
Division of Hematology Products
and
Kathy Robie Suh, MD, PhD, Clinical Team Leader

From: Janet Higgins, Division of Hematology Products

Subject: **Request for Clinical Site Inspections**

I. General Information

Application#: NDA 206316

IND#: 63266

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

Doreen Morgan, Pharm.D., M.S.

Executive Director, Regulatory Affairs

Daiichi Sankyo Incorporated (DSI)

399 Thornall Street

Edison, NJ 46285

Work: 732-590-5198

Cell: 973-652-0820

E-mail address: dmorgan@dsi.com

Drug Proprietary Name: Savaysa TM

Generic Drug Name: edoxaban

NME or Original BLA: Yes

Review Priority (Standard or Priority): Standard

OSI/DGCPC Consult

version: 09/12/2013

Page 2-Request for Clinical Inspections

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

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

Proposed New Indication: For the treatment of venous thromboembolism (VTE) including deep vein thrombosis (DVT) and pulmonary embolism (PE) (b) (4)

PDUFA: **January 8, 2015**

Action Goal Date: **January 7, 2015**

Inspection Summary Goal Date: August 7, 2014

II. Protocol/Site Identification

DUI176b-D-U305 (Hokusai VTE): A Phase 3, Randomized, Double-Blind, Double-Dummy, Parallel-Group, Multi-Center, Multi-National Study for the Evaluation of Efficacy and Safety of (LMW) Heparin/Edoxaban Versus (LMW) Heparin/Warfarin in Subjects With Symptomatic Deep-Vein Thrombosis and/or Pulmonary Embolism.

Site # (Name,Address, Phone number, email, fax#)	Protocol ID	Number of Subjects	Indication/Primary endpoint and other endpoints for verification
Schellong, Sebastian Friedrichstr. 41 Dresden, SN 1067 DEU Western Europe phone:49 351 4804555 fax:49 351 4804559	1707	144	Treatment of VTE (DVT or PE) ^{(b) (4)} [REDACTED]
Jacobson, Barry 7 York rd, Parktown Johannesburg, 2000 ZAF Africa phone:27 11 4898414 fax:27 11 4898513 email:neroshalaher@gmail.com	4905	130	Treatment of VTE (DVT or PE) ^{(b) (4)} [REDACTED]
Lyons, Roger 4411 Medical Drive, Suite 100 San Antonio, TX 78229 USA United States phone:1 210 5955300 fax:1 210 6151988	1002	50	Treatment of VTE (DVT or PE) ^{(b) (4)} [REDACTED]
Kingsley, Edwin Comprehensive Cancer Centers of Nevada 3730 S. Eastern Avenue Las Vegas NV 89169	1039	24	Treatment of VTE (DVT or PE) ^{(b) (4)} [REDACTED]

III. Site Selection/Rationale

Site selection was based on the numbers of patient enrollment (sites # 1707 and # 4905), the high incidence of death and imbalances of deaths between the two arms (site # 1039), and among highest U.S. enrolling sites (site # 1002). The number of patients enrolled in USA was approximately 10%

of the total number of patients enrolled in the trial. Note there is only a single large study in the application for the indication being sought.

Domestic Inspections:

Reasons for inspections (please check all that apply):

- Enrollment of large numbers of study subjects
- High treatment responders (specify):
- Significant primary efficacy results pertinent to decision-making
- There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, significant human subject protection violations or adverse event profiles.
- Other (specify): imbalances of deaths between the two arms.

International Inspections:

Reasons for inspections (please check all that apply):

- There are insufficient domestic data
- Only foreign data are submitted to support an application
- Domestic and foreign data show conflicting results pertinent to decision-making
- There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, or significant human subject protection violations.
- Other (specify) (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).

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

None.

Should you require any additional information, please contact Janet Higgins *or* Saleh Ayache, M.D. at 301-796-4867.

DHP requesting that FDA ORA independently inspect the following US or foreign clinical sites listed in this consult regardless if they recently inspected or not. Please inspect the Applicant's sites(S) concurrently with the requested clinical sites.

Concurrence: (as needed)

_____ Saleh Ayache, M.D., Medical Reviewer
_____ Kathy Robie Suh, M.D, PhD, Medical Team Leader
_____ Ann Farrell, MD, Division Director (for foreign inspection requests or requests for 5 or more sites only)

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/s/

SALEH AYACHE
03/17/2014

KATHY M ROBIE SUH
03/17/2014

ANN T FARRELL
03/18/2014

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data)]

Application Information		
NDA # 206316	NDA Supplement #:S-	Efficacy Supplement Type SE-
Proprietary Name: SAVAYSA Established/Proper Name: edoxaban tosylate Dosage Form: Tablets Strengths: 15, 30, and 60 mg		
Applicant: Daiichi-Sankyo Inc. Agent for Applicant (if applicable): n/a		
Date of Application: 8 January 2014 Date of Receipt: 8 January 2014 Date clock started after UN: n/a		
PDUFA Goal Date: 8 January 2015	Action Goal Date (if different):	
Filing Date: 9 March 2014	Date of Filing Meeting: 14 February 2014	
Chemical Classification: (1,2,3 etc.) (original NDAs only) 1 (NME)		
Proposed indication(s)/Proposed change(s): <ul style="list-style-type: none"> • NDA 206316 ORIG-2: Treatment of deep vein thrombosis and pulmonary embolism (DHP) • (b) (4) 		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:	<input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)	
<i>If 505(b)(2): Draft the "505(b)(2) Assessment" review found at:</i> http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499		
Type of BLA <i>If 351(k), notify the OND Therapeutic Biologics and Biosimilars Team</i>	<input type="checkbox"/> 351(a) <input type="checkbox"/> 351(k)	
Review Classification: <i>If the application includes a complete response to pediatric WR, review classification is Priority.</i> <i>If a tropical disease priority review voucher or pediatric rare disease priority review voucher was submitted, review classification is Priority.</i>	<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority <input type="checkbox"/> Tropical Disease Priority Review Voucher submitted <input type="checkbox"/> Pediatric Rare Disease Priority Review Voucher submitted	
Resubmission after withdrawal? <input type="checkbox"/>	Resubmission after refuse to file? <input type="checkbox"/>	
Part 3 Combination Product? <input type="checkbox"/> <i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i>	<input type="checkbox"/> Convenience kit/Co-package <input type="checkbox"/> Pre-filled drug delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Pre-filled biologic delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Device coated/impregnated/combined with drug <input type="checkbox"/> Device coated/impregnated/combined with biologic <input type="checkbox"/> Separate products requiring cross-labeling <input type="checkbox"/> Drug/Biologic	

		<input type="checkbox"/> Possible combination based on cross-labeling of separate products <input type="checkbox"/> Other (drug/device/biological product)		
<input type="checkbox"/> Fast Track Designation <input type="checkbox"/> Breakthrough Therapy Designation <input type="checkbox"/> Rolling Review <input type="checkbox"/> Orphan Designation <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC Other:		<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)		
Collaborative Review Division (<i>if OTC product</i>): n/a				
<ul style="list-style-type: none"> List referenced IND Number(s): 77254 (DCRP) and 63266 (DHP) 				
Goal Dates/Product Names/Classification Properties	YES	NO	NA	Comment
PDUFA and Action Goal dates correct in tracking system? <i>If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		“Priority” changed to “Standard NME-PDUFA”
Are the proprietary, established/proper, and applicant names correct in tracking system? <i>If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug)? <i>For NDAs/NDA supplements, check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at: http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm</i> <i>If no, ask the document room staff to make the appropriate entries.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	“Priority” changed to “Standard NME-PDUFA”
Application Integrity Policy	YES	NO	NA	Comment
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at: http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
<i>If yes, explain in comment column.</i>				
<i>If affected by AIP, has OC/OMPQ been notified of the submission? If yes, date notified:</i>	<input type="checkbox"/>	<input type="checkbox"/>		
User Fees	YES	NO	NA	Comment
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		

<p><u>User Fee Status</u></p> <p><i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.</i></p>	<p>Payment for this application:</p> <p><input checked="" type="checkbox"/> Paid <input type="checkbox"/> Exempt (orphan, government) <input type="checkbox"/> Waived (e.g., small business, public health) <input type="checkbox"/> Not required</p>																			
<p><i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.</i></p>	<p>Payment of other user fees:</p> <p><input checked="" type="checkbox"/> Not in arrears <input type="checkbox"/> In arrears</p>																			
<p>505(b)(2) (NDAs/NDA Efficacy Supplements only)</p>	<p>YES</p>	<p>NO</p>	<p>NA</p>	<p>Comment</p>																
<p>Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?</p>	<p><input type="checkbox"/></p>	<p><input type="checkbox"/></p>	<p><input checked="" type="checkbox"/></p>																	
<p>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 is less than that of the reference listed drug (RLD)? [see 21 CFR 314.54(b)(1)].</p>	<p><input type="checkbox"/></p>	<p><input type="checkbox"/></p>	<p><input checked="" type="checkbox"/></p>																	
<p>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)]?</p> <p><i>If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs</i></p>	<p><input type="checkbox"/></p>	<p><input type="checkbox"/></p>	<p><input checked="" type="checkbox"/></p>																	
<p>Is there unexpired exclusivity on any drug product containing the active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)?</p> <p><i>Check the Electronic Orange Book at: http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm</i></p> <p>If yes, please list below:</p> <table border="1" data-bbox="203 1482 1349 1619"> <thead> <tr> <th>Application No.</th> <th>Drug Name</th> <th>Exclusivity Code</th> <th>Exclusivity Expiration</th> </tr> </thead> <tbody> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> </tbody> </table>	Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration													<p><input type="checkbox"/></p>	<p><input type="checkbox"/></p>	<p><input checked="" type="checkbox"/></p>	
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration																	
<p><i>If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 314.108(b)(2). Unexpired, 3-year exclusivity may block the approval but not the submission of a 505(b)(2) application.</i></p>																				
<p>Exclusivity</p>	<p>YES</p>	<p>NO</p>	<p>NA</p>	<p>Comment</p>																
<p>Does another product (same active moiety) have orphan exclusivity for the same indication? <i>Check the Orphan Drug</i></p>	<p><input type="checkbox"/></p>	<p><input checked="" type="checkbox"/></p>																		

Designations and Approvals list at: http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm				
If another product has orphan exclusivity , is the product considered to be the same product according to the orphan drug definition of sameness [see 21 CFR 316.3(b)(13)]? <i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? (<i>NDAs/NDA efficacy supplements only</i>) If yes, # years requested: 5 years <i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (<i>NDAs only</i>)?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
If yes , did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? <i>If yes, contact the Orange Book Staff (CDER-Orange Book Staff).</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
For BLAs: Has the applicant requested 12-year exclusivity under section 351(k)(7) of the PHS Act? <i>If yes, notify Marlene Schultz-DePalo, OBP Biosimilars RPM</i> <i>Note: Exclusivity requests may be made for an original BLA submitted under Section 351(a) of the PHS Act (i.e., a biological reference product). A request may be located in Module 1.3.5.3 and/or other sections of the BLA and may be included in a supplement (or other correspondence) if exclusivity has not been previously requested in the original 351(a) BLA. An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	

Format and Content	
<i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i>	<input type="checkbox"/> All paper (except for COL) <input checked="" type="checkbox"/> All electronic <input type="checkbox"/> Mixed (paper/electronic) <input checked="" type="checkbox"/> CTD <input type="checkbox"/> Non-CTD <input type="checkbox"/> Mixed (CTD/non-CTD)
If mixed (paper/electronic) submission , which parts of the application are submitted in electronic format?	

Overall Format/Content	YES	NO	NA	Comment
If electronic submission, does it follow the eCTD guidance? ¹ If not, explain (e.g., waiver granted).	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Index: Does the submission contain an accurate comprehensive index?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
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: <input checked="" type="checkbox"/> legible <input checked="" type="checkbox"/> English (or translated into English) <input checked="" type="checkbox"/> pagination <input checked="" type="checkbox"/> navigable hyperlinks (electronic submissions only) If no, explain.	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
BLAs only: Companion application received if a shared or divided manufacturing arrangement? If yes, BLA #	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
Forms and Certifications				
<i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, paper forms and certifications with hand-written signatures must be included. Forms include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i>				
Application Form	YES	NO	NA	Comment
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)? <i>If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Are all establishments and their registration numbers listed on the form/attached to the form?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Patent Information (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Financial Disclosure	YES	NO	NA	Comment
Are financial disclosure forms FDA 3454 and/or 3455	<input checked="" type="checkbox"/>	<input type="checkbox"/>		

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

<p>included with authorized signature per 21 CFR 54.4(a)(1) and (3)?</p> <p><i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</i></p> <p><i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i></p>				
Clinical Trials Database	YES	NO	NA	Comment
<p>Is form FDA 3674 included with authorized signature?</p> <p><i>If yes, ensure that the application is also coded with the supporting document category, "Form 3674."</i></p> <p><i>If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</i></p>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Debarment Certification	YES	NO	NA	Comment
<p>Is a correctly worded Debarment Certification included with authorized signature?</p> <p><i>Certification is not required for supplements if submitted in the original application; If foreign applicant, <u>both</u> the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].</i></p> <p><i>Note: Debarment Certification should use wording in FD&C Act Section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge..."</i></p>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Field Copy Certification (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
<p>For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included?</p> <p><i>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)</i></p> <p><i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i></p>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
Controlled Substance/Product with Abuse Potential	YES	NO	NA	Comment
<p><u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)?</p> <p><i>If yes, date consult sent to the Controlled Substance Staff:</i></p> <p><u>For non-NMEs:</u> <i>Date of consult sent to Controlled Substance Staff:</i></p>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	

Pediatrics	YES	NO	NA	Comment
PREA Does the application trigger PREA? <i>If yes, notify PeRC RPM (PeRC meeting is required)²</i> <i>Note: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		Agreed upon iPSP issued 10/31/13 for IND 63266
If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
If studies or full waiver not included, is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included? <i>If no, request in 74-day letter</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
If a request for full waiver/partial waiver/deferral is included, does the application contain the certification(s) required by FDCA Section 505B(a)(3) and (4)? <i>If no, request in 74-day letter</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Request for deferral is included.
BPCA (NDAs/NDA efficacy supplements only): Is this submission a complete response to a pediatric Written Request? <i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)³</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
Proprietary Name	YES	NO	NA	Comment
Is a proposed proprietary name submitted? <i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Sponsor submitted SAVAYSA in SD3 on 21Jan14
REMS	YES	NO	NA	Comment
Is a REMS submitted? <i>If yes, send consult to OSE/DRISK and notify OC/OSI/DSC/PMSB via the CDER OSI RMP mailbox</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
Prescription Labeling	<input type="checkbox"/> Not applicable			
Check all types of labeling submitted.	<input checked="" type="checkbox"/> Package Insert (PI) <input type="checkbox"/> Patient Package Insert (PPI) <input type="checkbox"/> Instructions for Use (IFU) <input checked="" type="checkbox"/> Medication Guide (MedGuide)			

² <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829.htm>

³ <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027837.htm>

	<input checked="" type="checkbox"/> Carton labels <input checked="" type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is Electronic Content of Labeling (COL) submitted in SPL format? <i>If no, request applicant to submit SPL before the filing date.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Is the PI submitted in PLR format? ⁴	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
If PI not submitted in PLR format , was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted , what is the status of the request? <i>If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Submitted by DCRP on 1/23/2014 Emily Baker/Zarna Patel (joint consult sent)
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (send WORD version if available)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	No consult needed. OSE reviewer is a primary reviewer under "The Program"
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Submitted by DCRP 1/23/2014
OTC Labeling	<input checked="" type="checkbox"/> Not Applicable			
Check all types of labeling submitted.	<input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is electronic content of labeling (COL) submitted? <i>If no, request in 74-day letter.</i>	<input type="checkbox"/>	<input type="checkbox"/>		
Are annotated specifications submitted for all stock keeping units (SKUs)? <i>If no, request in 74-day letter.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	

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<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm>

If representative labeling is submitted, are all represented SKUs defined? <i>If no, request in 74-day letter.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Other Consults	YES	NO	NA	Comment
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) <i>If yes, specify consult(s) and date(s) sent:</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Carcinogenicity stats consult put in DARRTS on 22Jan14. OSI (clinical) will be consulted once the site-selection has been identified by the clinical team.
Meeting Minutes/SPAs	YES	NO	NA	Comment
End-of Phase 2 meeting(s)? Date(s): End Of Phase 2/Pre-Phase 3 MM dated 11/25/2008 End Of Phase 2/Pre-Phase 3 MM dated 05/28/2009 End Of Phase 2 CMC Only MM dated 07/01/2010 End Of Phase 2/Pre-Phase 3 MM dated 05/27/2011 <i>If yes, distribute minutes before filing meeting</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? Date(s): 24 Sept 2013 (DHP); 28 Feb 2012 <i>If yes, distribute minutes before filing meeting</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Any Special Protocol Assessments (SPAs)? Date(s): SPA-1: Carcinogenicity -- Denied 11/17/2006 SPA-2: Carcinogenicity -- Pending 11/22/2006 SPA-3: Carcinogenicity -- Pending 11/24/2006 SPA-4: Carcinogenicity -- No Agreement 08/01/2007 SPA-5: Carcinogenicity -- No Agreement 08/01/2007 SPA-6: Clinical -- No Agreement 08/04/2009 <i>If yes, distribute letter and/or relevant minutes before filing meeting</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		

ATTACHMENT

MEMO OF FILING MEETING

DATE: February 14, 2014

NDA #: 206316

PROPRIETARY NAME: SAVAYSA

ESTABLISHED/PROPER NAME: edoxaban tosylate

DOSAGE FORM/STRENGTH: Tablets, 15, 30, and 60 mg

APPLICANT: Daiichi Sankyo

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

ORIG-2: Treatment of Deep Vein Thrombosis & Pulmonary Embolism

(b) (4)

BACKGROUND: This NME NDA was submitted on January 8, 2014 under the PDUFA V “program” with (b) (4) proposed indications:

- ORIG-1: Reduction in the Risk of Stroke and Systemic Embolism in Nonvalvular Atrial Fibrillation (managed by the Division of Cardio-Renal Products - DCRP);
- ORIG-2: Treatment of Deep Vein Thrombosis & Pulmonary Embolism:

(b) (4)

Each ORIG portion of the application (ORIG-1 in DCRP and ORIG-2 (b) (4) in DHP) will have separate actions.

REVIEW TEAM: (Below are only the reviewers for ORIG-2 (b) (4). ORIG-1 is captured in a separate review).

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Janet G. Higgins	Y
	CPMS/TL:	Lara Akinsanya/ Ebla Ali Ibrahim	Y
Cross-Discipline Team Leader (CDTL)	Kathy Robie Suh		Y
Clinical	Reviewer:	Saleh Ayache	Y
	TL:	Kathy Robie Suh	Y
Clinical Microbiology (for antimicrobial products)	Reviewer:	n/a	n/a
	TL:	n/a	n/a

Pharmacometrics	Reviewer:	Justin Earp and Jiang Liu	Y
	TL:		
Pharmacogenomics	Reviewer:	Robert Schuck	Y
	TL:		
Clinical Pharmacology	Reviewer:	Divya Menon-Andersen Young Jin Moon	Y Y
	TL:	Raj Madabushi Julie Bullock	Y Y
Biostatistics	Reviewer:	Yun Wang	
	TL:	Lei Nie	
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Baichun Yang Shwu-Luan Lee	Y Y
	TL:	Thomas Papoian Haleh Saber	Y Y
Statistics (carcinogenicity)	Reviewer:	TBD	N
	TL:	Karl Lin	N
Product Quality (CMC)	Reviewer:	Dabasis Ghosh (DS) Akm Khairuzzaman (DP) Sandra Suarez (Biopharm)	N N Y
	TL:	Kasturi Srinivasachar Janice Brown Angelica Dorantes	Y Y N
Quality Microbiology	Reviewer:	Steven Donald	N
	TL:	n/a	N
CMC Labeling Review	Reviewer:	n/a	n/a
	TL:	n/a	n/a
Facility Review/Inspection	Reviewer:	n/a	n/a
	TL:	n/a	n/a
OSE/DMEPA (proprietary name)	Reviewer:	Denise Baugh	Y
	TL:	Lisa Khosla	N
OSE/DRISK (REMS)	Reviewer:	Cathy Miller	Y
	TL:	Kim Lehrfeld	N
OC/OSI/DSC/PMSB (REMS)	Reviewer:	n/a	n/a

	TL:	n/a	n/a
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Bioresearch Monitoring (OSI)	Reviewer:	Sharon Gershon	Y
	TL:	Susan Leibenhaut	N
Controlled Substance Staff (CSS)	Reviewer:	n/a	n/a
	TL:	n/a	n/a
Other reviewers	OSE (DPV) – Susan Lu (TL), Anne Tobenkin (the reviewer):		N, N
Other attendees			

FILING MEETING DISCUSSION:

GENERAL	
<ul style="list-style-type: none"> • 505(b)(2) filing issues: <ul style="list-style-type: none"> ○ Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? ○ Did the applicant provide a scientific “bridge” demonstrating the relationship between the proposed product and the referenced product(s)/published literature? <p>Describe the scientific bridge (e.g., BA/BE studies):</p> 	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • Per reviewers, are all parts in English or English translation? <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • Electronic Submission comments <p>List comments:</p>	<input checked="" type="checkbox"/> Not Applicable
<p>CLINICAL</p> <p>Comments: This determination is just for the indications reviewed by DHP.</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> • Clinical study site(s) inspections(s) needed? <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO

<ul style="list-style-type: none"> Advisory Committee Meeting needed? <p>Comments:</p> <p><i>If no, for an NME NDA or original BLA , include the reason. For example:</i></p> <ul style="list-style-type: none"> <i>this drug/biologic is not the first in its class</i> <i>the clinical study design was acceptable</i> <i>the application did not raise significant safety or efficacy issues</i> <i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i> 	<input type="checkbox"/> YES Date if known: <input type="checkbox"/> NO <input checked="" type="checkbox"/> To be determined Reason: This drug is not the first in its class. There were no issues identified thus far that would warrant discussion at an ADCOM.
<ul style="list-style-type: none"> Abuse Liability/Potential <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> 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? <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p>CLINICAL MICROBIOLOGY</p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>CLINICAL PHARMACOLOGY</p> <p>Comments: Request for data sets was sent by A. Blaus, RPM in DCRP.</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> Clinical pharmacology study site(s) inspections(s) needed? 	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p>BIOSTATISTICS</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE

Comments:	<input type="checkbox"/> Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) Comments:	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
IMMUNOGENICITY (BLAs/BLA efficacy supplements only) Comments:	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
PRODUCT QUALITY (CMC) Comments: IR to be sent. They will be communicated by DCRP.	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<u>Environmental Assessment</u> <ul style="list-style-type: none"> • Categorical exclusion for environmental assessment (EA) requested? <p>If no, was a complete EA submitted?</p> <p>If EA submitted, consulted to EA officer (OPS)?</p> Comments:	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
<u>Quality Microbiology (for sterile products)</u> Comments:	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO

<p><u>Facility Inspection</u></p> <ul style="list-style-type: none"> • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to OMPQ? <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p><u>Facility/Microbiology Review (BLAs only)</u></p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p><u>CMC Labeling Review</u></p> <p>Comments:</p>	<input type="checkbox"/> Review issues for 74-day letter
<p>APPLICATIONS IN THE PROGRAM (PDUFA V) (NME NDAs/Original BLAs)</p> <ul style="list-style-type: none"> • Were there agreements made at the application’s pre-submission meeting (and documented in the minutes) regarding certain late submission components that could be submitted within 30 days after receipt of the original application? • If so, were the late submission components all submitted within 30 days? 	<input type="checkbox"/> N/A <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • What late submission components, if any, arrived after 30 days? 	
<ul style="list-style-type: none"> • Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components? 	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO

<ul style="list-style-type: none"> • Is a comprehensive and readily located list of all clinical sites included or referenced in the application? 	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO - An IR was sent out on 2/14/2014 requesting this data.
<ul style="list-style-type: none"> • Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application? 	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
REGULATORY PROJECT MANAGEMENT	
<p>Signatory Authority: Office Director</p> <p>Date of Mid-Cycle Meeting (for NME NDAs/BLAs in “the Program” PDUFA V): Mid-Cycle Meeting (Joint): 11 June 2014 Mid-Cycle Communication Meeting (DHP): 18 June 2014 Mid-Cycle Communication Meeting w/Applicant: 24 June 2014</p> <p>Comments: Each ORIG portion of the application (ORIG-1 in DCRP and ORIG-2 ^(b)₍₄₎ in DHP will have separate actions.</p>	
REGULATORY CONCLUSIONS/DEFICIENCIES	
<input type="checkbox"/>	The application is unsuitable for filing. Explain why:
<input checked="" type="checkbox"/>	The application, on its face, appears to be suitable for filing. <u>Review Issues:</u> <input checked="" type="checkbox"/> No review issues have been identified for the 74-day letter. <u>Review Classification:</u> <input checked="" type="checkbox"/> Standard Review <input type="checkbox"/> Priority Review
ACTIONS ITEMS	
<input checked="" type="checkbox"/>	Send review issues/no review issues by day 74: Comment: One Day 74 letter will be sent for ORIG 1 ^(b) ₍₄₎ There will be issues included.
<input checked="" type="checkbox"/>	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
<input checked="" type="checkbox"/>	Update the PDUFA V DARRTS page (for NME NDAs in the Program)
<input type="checkbox"/>	

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

/s/

JANET G HIGGINS
03/11/2014

MONSURAT O AKINSANYA
03/11/2014

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data)]

Application Information		
NDA # 206316 BLA# n/a	NDA Supplement #:S- n/a BLA Supplement # n/a	Efficacy Supplement Type SE- n/a
Proprietary Name: SAVAYSA Established/Proper Name: edoxaban Dosage Form: Tablets Strengths: 15, 30, and 60 mg		
Applicant: Daiichi-Sankyo Agent for Applicant (if applicable): n/a		
Date of Application: 8 January 2014 Date of Receipt: 8 January 2014 Date clock started after UN: n/a		
PDUFA Goal Date: 8 January 2015	Action Goal Date (if different): n/a	
Filing Date: 9 March 2014	Date of Filing Meeting: 14 February 2014	
Chemical Classification: 1		
Proposed indication: Reduction in the Risk of Stroke and Systemic Embolism in Nonvalvular Atrial Fibrillation SAVAYSA is indicated to reduce the risk of stroke and systemic embolism in patients with Nonvalvular atrial fibrillation (NVAF).		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:	<input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)	
<i>If 505(b)(2): Draft the "505(b)(2) Assessment" review found at: http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499.</i>		
Type of BLA	<input type="checkbox"/> 351(a) <input type="checkbox"/> 351(k)	
<i>If 351(k), notify the OND Therapeutic Biologics and Biosimilars Team</i>		
Review Classification:	<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority <input type="checkbox"/> Tropical Disease Priority Review Voucher submitted <input type="checkbox"/> Pediatric Rare Disease Priority Review Voucher submitted	
<i>If the application includes a complete response to pediatric WR, review classification is Priority.</i>		
<i>If a tropical disease priority review voucher or pediatric rare disease priority review voucher was submitted, review classification is Priority.</i>		
Resubmission after withdrawal? <input type="checkbox"/>	Resubmission after refuse to file? <input type="checkbox"/>	
Part 3 Combination Product? <input type="checkbox"/>	<input type="checkbox"/> Convenience kit/Co-package <input type="checkbox"/> Pre-filled drug delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Pre-filled biologic delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Device coated/impregnated/combined with drug	
<i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i>		

	<input type="checkbox"/> Device coated/impregnated/combined with biologic <input type="checkbox"/> Separate products requiring cross-labeling <input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Possible combination based on cross-labeling of separate products <input type="checkbox"/> Other (drug/device/biological product)			
<input type="checkbox"/> Fast Track Designation <input type="checkbox"/> Breakthrough Therapy Designation <input type="checkbox"/> Rolling Review <input type="checkbox"/> Orphan Designation <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC Other:	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)			
Collaborative Review Division (if OTC product): n/a				
List referenced IND Number(s): 77254				
Goal Dates/Product Names/Classification Properties	YES	NO	NA	Comment
PDUFA and Action Goal dates correct in tracking system? <i>If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		“Priority” changed to “Standard NME-PDUFA”
Are the proprietary, established/proper, and applicant names correct in tracking system? <i>If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug)? <i>For NDAs/NDA supplements, check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at: http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm</i> <i>If no, ask the document room staff to make the appropriate entries.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	“Priority” changed to “Standard NME-PDUFA”
Application Integrity Policy	YES	NO	NA	Comment
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at: http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</i> <i>If yes, explain in comment column.</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
If affected by AIP, has OC/OMPQ been notified of the submission? If yes, date notified:	<input type="checkbox"/>	<input type="checkbox"/>		

User Fees		YES	NO	NA	Comment
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?		<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<u>User Fee Status</u> <i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.</i>		Payment for this application: <input checked="" type="checkbox"/> Paid <input type="checkbox"/> Exempt (orphan, government) <input type="checkbox"/> Waived (e.g., small business, public health) <input type="checkbox"/> Not required			
<i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.</i>		Payment of other user fees: <input checked="" type="checkbox"/> Not in arrears <input type="checkbox"/> In arrears			
505(b)(2) (NDAs/NDA Efficacy Supplements only)		YES	NO	NA	Comment
Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?		<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
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 is less than that of the reference listed drug (RLD)? [see 21 CFR 314.54(b)(1)].		<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
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)]?		<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
<i>If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs</i>					
Is there unexpired exclusivity on any drug product containing the active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)?		<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
<i>Check the Electronic Orange Book at:</i> http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm					
If yes, please list below:					
Application No.	Drug Name	Exclusivity Code		Exclusivity Expiration	
<i>If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric</i>					

exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 314.108(b)(2). Unexpired, 3-year exclusivity may block the approval but not the submission of a 505(b)(2) application.

Exclusivity	YES	NO	NA	Comment
Does another product (same active moiety) have orphan exclusivity for the same indication? <i>Check the Orphan Drug Designations and Approvals list at: http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
If another product has orphan exclusivity , is the product considered to be the same product according to the orphan drug definition of sameness [see 21 CFR 316.3(b)(13)]? <i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? (<i>NDAs/NDA efficacy supplements only</i>) If yes, # years requested: FIVE <i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (<i>NDAs only</i>)?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
If yes , did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? <i>If yes, contact the Orange Book Staff (CDER-Orange Book Staff).</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
Has the applicant requested 12-year exclusivity under section 351(k)(7) of the PHS Act? (<i>351(a)BLAs only</i>) If yes, notify Marlene Schultz-DePalo, OBP Biosimilars RPM <i>Note: Exclusivity requests may be made for an original BLA submitted under Section 351(a) of the PHS Act (i.e., a biological reference product). A request may be located in Module 1.3.5.3 and/or other sections of the BLA and may be included in a supplement if exclusivity has not yet been granted. An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	

Format and Content	
<i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i>	<input type="checkbox"/> All paper (except for COL) <input checked="" type="checkbox"/> All electronic <input type="checkbox"/> Mixed (paper/electronic) <input checked="" type="checkbox"/> CTD

	<input type="checkbox"/> Non-CTD <input type="checkbox"/> Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission , which parts of the application are submitted in electronic format?				
Overall Format/Content	YES	NO	NA	Comment
If electronic submission , does it follow the eCTD guidance? ¹ If not , explain (e.g., waiver granted).	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Index: Does the submission contain an accurate comprehensive index?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
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: <input checked="" type="checkbox"/> legible <input checked="" type="checkbox"/> English (or translated into English) <input checked="" type="checkbox"/> pagination <input checked="" type="checkbox"/> navigable hyperlinks (electronic submissions only) If no , explain.	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
BLAs only: Companion application received if a shared or divided manufacturing arrangement? If yes , BLA #	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
Forms and Certifications				
<i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, paper forms and certifications with hand-written signatures must be included. Forms include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i>				
Application Form	YES	NO	NA	Comment
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)? <i>If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Are all establishments and their registration numbers listed on the form/attached to the form?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Patent Information (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
Is patent information submitted on form FDA 3542a per 21	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	

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

CFR 314.53(c)?				
Financial Disclosure	YES	NO	NA	Comment
<p>Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)?</p> <p><i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</i></p> <p><i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i></p>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Clinical Trials Database	YES	NO	NA	Comment
<p>Is form FDA 3674 included with authorized signature?</p> <p><i>If yes, ensure that the application is also coded with the supporting document category, "Form 3674."</i></p> <p><i>If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</i></p>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Debarment Certification	YES	NO	NA	Comment
<p>Is a correctly worded Debarment Certification included with authorized signature?</p> <p><i>Certification is not required for supplements if submitted in the original application; If foreign applicant, <u>both</u> the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].</i></p> <p><i>Note: Debarment Certification should use wording in FD&C Act Section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge..."</i></p>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Field Copy Certification (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
<p>For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included?</p> <p><i>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)</i></p> <p><i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i></p>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	

Controlled Substance/Product with Abuse Potential	YES	NO	NA	Comment
<p><u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)?</p> <p><i>If yes, date consult sent to the Controlled Substance Staff:</i></p> <p><u>For non-NMEs:</u> <i>Date of consult sent to Controlled Substance Staff:</i></p>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
Pediatrics	YES	NO	NA	Comment
<p><u>PREA</u></p> <p>Does the application trigger PREA?</p> <p><i>If yes, notify PeRC RPM (PeRC meeting is required)²</i></p> <p><i>Note: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i></p>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		Notified PeRC on 27Jan14. Once standard vs priority has been decided, they will schedule this application for a PeRC meeting. Since ORIG-1 will be RTF, Janet Higgins to contact PeRC to reschedule edoxaban for PeRC for ORIG-2 ^{(b)(4)}
<p>If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?</p>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Agreed-upon PSP (full waiver) included in the submission.
<p>If studies or full waiver not included, is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included?</p> <p><i>If no, request in 74-day letter</i></p>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
<p>If a request for full waiver/partial waiver/deferral is included, does the application contain the certification(s) required by FDCA Section 505B(a)(3) and (4)?</p> <p><i>If no, request in 74-day letter</i></p>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
<p><u>BPCA</u> (NDAs/NDA efficacy supplements only):</p> <p>Is this submission a complete response to a pediatric Written Request?</p> <p><i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)³</i></p>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		

² <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829.htm>

³ <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027837.htm>

Proprietary Name	YES	NO	NA	Comment
Is a proposed proprietary name submitted? <i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Sponsor submitted SAVAYSA in SD3 on 21Jan14
REMS	YES	NO	NA	Comment
Is a REMS submitted? <i>If yes, send consult to OSE/DRISK and notify OC/OSI/DSC/PMSB via the CDER OSI RMP mailbox</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
Prescription Labeling	<input type="checkbox"/> Not applicable			
Check all types of labeling submitted.	<input checked="" type="checkbox"/> Package Insert (PI) <input type="checkbox"/> Patient Package Insert (PPI) <input type="checkbox"/> Instructions for Use (IFU) <input checked="" type="checkbox"/> Medication Guide (MedGuide) <input checked="" type="checkbox"/> Carton labels <input checked="" type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is Electronic Content of Labeling (COL) submitted in SPL format? <i>If no, request applicant to submit SPL before the filing date.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Is the PI submitted in PLR format? ⁴	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
If PI not submitted in PLR format , was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted , what is the status of the request? <i>If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Consult in DARRTS on 23Jan14
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (send WORD version if available)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	No consult needed. OSE reviewer is a primary reviewer under "The Program"
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Consult in DARRTS on 23Jan14
OTC Labeling	<input checked="" type="checkbox"/> Not Applicable			
Check all types of labeling submitted.	<input type="checkbox"/> Outer carton label			

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<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm>

	<input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is electronic content of labeling (COL) submitted? <i>If no, request in 74-day letter.</i>	<input type="checkbox"/>	<input type="checkbox"/>		
Are annotated specifications submitted for all stock keeping units (SKUs)? <i>If no, request in 74-day letter.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
If representative labeling is submitted, are all represented SKUs defined? <i>If no, request in 74-day letter.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Other Consults	YES	NO	NA	Comment
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) <i>If yes, specify consult(s) and date(s) sent:</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Carcinogenicity stats consult put in DARRTS on 22Jan14. OSI-BE Audit consult put in DARRTS on 4Feb14. OSI (clinical) will be consulted once the site-selection tool meeting is held.
Meeting Minutes/SPAs	YES	NO	NA	Comment
End-of Phase 2 meeting? Date(s): 13Aug08 <i>If yes, distribute minutes before filing meeting</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		EoP2 Minutes dated 24Sep08 (clarification letter dated 17Oct08)
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? Date(s): 28Feb12 (preNDA) and 10Sep13 (P3 Topline) <i>If yes, distribute minutes before filing meeting</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		PreNDA Minutes dated 16Mar12; Topline Minutes dated 4Oct13
Any Special Protocol Assessments (SPAs)? Date(s): 15Oct08 <i>If yes, distribute letter and/or relevant minutes before filing meeting</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		The SPA was initially submitted in April 2008 but the request was denied on 28April2008. We denied to review the protocol under a SPA until they first met with the Agency for an EoP2 meeting.

ATTACHMENT

MEMO OF FILING MEETING

DATE: 14 February 2014

NDA #: 206316

PROPRIETARY NAME: SAVAYSA

ESTABLISHED/PROPER NAME: edoxaban tosylate

DOSAGE FORM/STRENGTH: 15, 30, and 60 mg Tablets

APPLICANT: Daiichi Sankyo

PROPOSED INDICATION:

Reduction in the Risk of Stroke and Systemic Embolism in Nonvalvular Atrial Fibrillation - SAVAYSA is indicated to reduce the risk of stroke and systemic embolism in patients with Nonvalvular atrial fibrillation (NVAF).

BACKGROUND:

The trial to support ORIG-1 (NVAF), reviewed under a SPA (agreement letter dated 15Oct08), was DU176b-C-U301/TIMI 48 entitled, "A Phase 3 Randomized, Double-Blind, Double-Dummy, Parallel Group, Multi-Center, Multi-National Study for Evaluation of Efficacy and Safety of DU-176b versus Warfarin in Subjects with Atrial Fibrillation - Effective aNticoaGulation with factor xA next Generation in Atrial Fibrillation (**ENGAGE AF-TIMI 48**)". The Pre-NDA Meeting for this indication, under IND 77254, was 28Feb12 (minutes dated 16Mar12) and the Top Line Meeting was on 10Sep13 (minutes dated 4Oct13).

REVIEW TEAM: (Below are only the reviewers for ORIG-1. ORIG-2^(b)₍₄₎ are captured in a separate RPM review).

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Alison Blaus	Y
	CPMS/TL:	Edward Fromm	N
Cross-Discipline Team Leader (CDTL)	Martin Rose		Y
Clinical	Reviewer:	Melanie Blank Tzu-Yun McDowell	N Y
	TL:	Mary Ross Southworth	N

Social Scientist Review (<i>for OTC products</i>)	Reviewer:	n/a	n/a
	TL:	n/a	n/a
OTC Labeling Review (<i>for OTC products</i>)	Reviewer:	n/a	n/a
	TL:	n/a	n/a
Clinical Microbiology (<i>for antimicrobial products</i>)	Reviewer:	n/a	n/a
	TL:	n/a	n/a
Clinical Pharmacology	Reviewer:	Divya Menon-Andersen Young Jin Moon	Y Y
	TL:	Raj Madabushi Julie Bullock	Y Y
Biostatistics	Reviewer:	John Lawrence	Y
	TL:	Jim Hung	N
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Baichun Yang Shwu-Luan Lee	Y Y
	TL:	Thomas Papoian	Y
Statistics (carcinogenicity)	Reviewer:	TBD	N
	TL:	Karl Lin	N
Immunogenicity (assay/assay validation) (<i>for BLAs/BLA efficacy supplements</i>)	Reviewer:	n/a	n/a
	TL:	n/a	n/a
Product Quality (CMC)	Reviewer:	Dabasis Ghosh (DS) Akm Khairuzzaman (DP) Sandra Suarez (Biopharm)	N N Y
	TL:	Kasturi Srinivasachar Janice Brown Angelica Dorantes	Y Y N
Quality Microbiology (<i>for sterile products</i>)	Reviewer:	Steven Donald	N
	TL:	n/a	N
CMC Labeling Review	Reviewer:	n/a	n/a
	TL:	n/a	n/a
Facility Review/Inspection	Reviewer:	n/a	n/a
	TL:	n/a	n/a

OSE/DMEPA (proprietary name)	Reviewer:	Denise Baugh	Y
	TL:	Lisa Khosla	N
OSE/DRISK (REMS)	Reviewer:	Cathy Miller	Y
	TL:	Kim Lehrfeld	N
OC/OSI/DSC/PMSB (REMS)	Reviewer:	n/a	n/a
	TL:	n/a	n/a
Bioresearch Monitoring (OSI)	Reviewer:	Sharon Gershon	Y
	TL:	Susan Leibenhaut	N
Controlled Substance Staff (CSS)	Reviewer:	n/a	n/a
	TL:	n/a	n/a
Other reviewers	OSE (DPV) – Susan Lu (TL), Anne Tobenkin (the reviewer):		N, N
Other attendees	Norman Stockbridge (DCRP Director), Stephen Grant (DCRP Deputy), Nhi Beasley (Clinical)		

FILING MEETING DISCUSSION:

<p>GENERAL</p> <ul style="list-style-type: none"> • 505(b)(2) filing issues: <ul style="list-style-type: none"> ○ Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? ○ Did the applicant provide a scientific “bridge” demonstrating the relationship between the proposed product and the referenced product(s)/published literature? <p>Describe the scientific bridge (e.g., BA/BE studies):</p> 	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • Per reviewers, are all parts in English or English translation? <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • Electronic Submission comments 	<input checked="" type="checkbox"/> Not Applicable

List comments:	
<p>CLINICAL</p> <p>Comments: The submission was not complete upon submission. A number of missing items or files with errors are noted in the clinical filing review as well as the subsequent "Refuse to File Letter".</p>	<input type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input checked="" type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> • Clinical study site(s) inspections(s) needed? <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • Advisory Committee Meeting needed? <p>Comments: This is the third drug in this class and the fourth for this indication (NVAF). There were no issues identified thus far that would warrant discussion at an ADCOM.</p> <p>If no, for an NME NDA or original BLA , include the reason. For example:</p> <ul style="list-style-type: none"> ○ <i>this drug/biologic is not the first in its class</i> ○ <i>the clinical study design was acceptable</i> ○ <i>the application did not raise significant safety or efficacy issues</i> ○ <i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i> 	<input type="checkbox"/> YES Date if known: <input checked="" type="checkbox"/> NO <input type="checkbox"/> To be determined Reason:
<ul style="list-style-type: none"> • Abuse Liability/Potential <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> • 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? <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO

<p>CLINICAL MICROBIOLOGY</p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>CLINICAL PHARMACOLOGY</p> <p>Comments: One information request already sent for the PG datasets. These data were provided on 27Feb14 (SD 20)</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>• Clinical pharmacology study site(s) inspections(s) needed?</p> <p>Comments: OSI-BE Audit consult put in DARRTS on 4Feb14</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p>BIOSTATISTICS</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>IMMUNOGENICITY (BLAs/BLA efficacy supplements only)</p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>PRODUCT QUALITY (CMC)</p> <p>Comments: QbD. Review issues for 74day letter from biopharm.</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input checked="" type="checkbox"/> Review issues for 74-day letter
<p><u>Environmental Assessment</u></p> <p>• Categorical exclusion for environmental assessment (EA) requested?</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO

<p>If no, was a complete EA submitted?</p> <p>If EA submitted, consulted to EA officer (OPS)?</p> <p>Comments:</p>	<input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
<p><u>Quality Microbiology (for sterile products)</u></p> <ul style="list-style-type: none"> Was the Microbiology Team consulted for validation of sterilization? (NDAs/NDA supplements only) <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p><u>Facility Inspection</u></p> <ul style="list-style-type: none"> Establishment(s) ready for inspection? Establishment Evaluation Request (EER/TBP-EER) submitted to OMPQ? <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p><u>Facility/Microbiology Review (BLAs only)</u></p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p><u>CMC Labeling Review</u></p> <p>Comments:</p>	<input type="checkbox"/> Review issues for 74-day letter
<p>APPLICATIONS IN THE PROGRAM (PDUFA V) (NME NDAs/Original BLAs)</p> <ul style="list-style-type: none"> Were there agreements made at the application's pre-submission meeting (and documented in the minutes) regarding certain late submission components that could be submitted within 30 days after receipt of the original application? If so, were the late submission components all submitted within 30 days? 	<input type="checkbox"/> N/A <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO

<ul style="list-style-type: none"> • What late submission components, if any, arrived after 30 days? 	Over 2k adjudication packages and analyses/datasets that were requested at the 28Feb2012 pre-NDA meeting.
<ul style="list-style-type: none"> • Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components? 	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<ul style="list-style-type: none"> • Is a comprehensive and readily located list of all clinical sites included or referenced in the application? 	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application? 	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO

REGULATORY PROJECT MANAGEMENT

Signatory Authority: Robert Temple, M.D.

Date of Mid-Cycle Meeting (for NME NDAs/BLAs in “the Program” PDUFA V): 11 June 2014

21st Century Review Milestones (see attached) (listing review milestones in this document is optional):

Comments: Each ORIG portion of the application (ORIG-1 in DCRP and ORIG-2^(b)₍₄₎ in DHP will have separate actions.

REGULATORY CONCLUSIONS/DEFICIENCIES

<input type="checkbox"/>	The application is unsuitable for filing. Explain why:
<input checked="" type="checkbox"/>	<p>The application, on its face, appears to be suitable for filing.</p> <p><u>Review Issues:</u></p> <p><input type="checkbox"/> No review issues have been identified for the 74-day letter.</p> <p><input checked="" type="checkbox"/> Review issues have been identified for the 74-day letter.</p> <p><u>Review Classification:</u></p> <p><input checked="" type="checkbox"/> Standard Review</p>

<input type="checkbox"/>	Priority Review
ACTIONS ITEMS	
<input type="checkbox"/>	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug).
<input type="checkbox"/>	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
<input type="checkbox"/>	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
<input type="checkbox"/>	BLA/BLA supplements: If filed, send 60-day filing letter
<input type="checkbox"/>	If priority review: <ul style="list-style-type: none"> • notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices) • notify OMPQ (so facility inspections can be scheduled earlier)
<input checked="" type="checkbox"/>	Send review issues/no review issues by day 74. Comment: One Day 74 letter will be sent for ORIG 1 (b) (4) There will be issues included.
<input checked="" type="checkbox"/>	Conduct a PLR format labeling review and include labeling issues in the 74-day letter Comment: As agreed at the time of acknowledgement, Janet Higgins will conduct a labeling review and will provide comments for the 74-day letter.
<input checked="" type="checkbox"/>	Update the PDUFA V DARRTS page (for NME NDAs in the Program)
<input type="checkbox"/>	BLA/BLA supplements: Send the Product Information Sheet to the product reviewer and the Facility Information Sheet to the facility reviewer for completion. Ensure that the completed forms are forwarded to the CDER RMS-BLA Superuser for data entry into RMS-BLA one month prior to taking an action [These sheets may be found in the CST eRoom at: http://eroom.fda.gov/eRoom/CDER2/CDERStandardLettersCommittee/0_1685f]
<input type="checkbox"/>	Other:

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

/s/

ALISON L BLAUS
03/07/2014

MEMORANDUM

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

DATE: February 10, 2014

TO: Director, Investigation Branch
New Jersey District Office
10 Waterview Blvd.
Third Floor
Waterview Corp. Center
Parsippany, NJ 07054

Director, Investigation Branch
New York District Office
158-15 Liberty Avenue
Jamaica, NY 11433

FROM: Sam H. Haidar, Ph.D., R.Ph.
Chief, Bioequivalence Branch
Division of Bioequivalence and GLP Compliance (DBGLPC)
Office of Scientific Investigations (OSI)

SUBJECT: **FY 2014, CDER High Priority Pre-Approval NDA Data
Validation Inspection**, Bioresearch Monitoring, Human
Drugs, CP 7348.001

RE: NDA 206-316
DRUG: Edoxaban
SPONSOR: Daiichi Sankyo Inc., Edison, NJ

This memo requests that you arrange for inspections of the clinical and analytical portions of the following in vivo bioequivalence (BE) study.

Once you identify an ORA investigator, please contact the DBGLPC point of contact (POC) listed at the end of this assignment memo to schedule the inspection of the analytical site. A DBGLPC scientist will participate in the inspection of the analytical site to provide scientific and technical expertise.

Background materials will be available in ECMS under the ORA folder. **The inspections should be completed prior to November 8, 2014.**

Do not reveal the applicant/sponsor, application number, study to be inspected, drug name, or the study investigators to the sites prior to the start of the inspections. The sites will receive this information during the inspection opening meeting. The inspections will be conducted under Bioresearch Monitoring Compliance Program CP 7348.001, not under CP 7348.811 (Clinical Investigators).

At the completion of the inspection, please send a scanned copy of the completed sections A and B of this memo to the DBGLPC POC.

Study #1: DU176b-A-U142
Study Title: "An open-label, Phase I, randomized, two-treatment, replicated crossover bioequivalence study of the round shape tablet and the current tablet formulation of edoxaban in healthy subjects under fasting conditions."

Clinical Site: Celerion
1930 Heck Avenue, Bldg 2,
Neptune, NJ 07753
TEL: (732)502-8900
FAX: (732)502-9679

Investigator: Frank Lee, MD,

SECTION A - RESERVE SAMPLES

Because the bioequivalence study is subject to 21 CFR 320.38 and 320.63, the site conducting the study (i.e., investigator site) is responsible for randomly selecting and retaining reserve samples from each shipment of drug product provided by the Applicant/sponsor for subject dosing.

The final rule for "Retention of Bioavailability and Bioequivalence Testing Samples" (Federal Register, Vol. 58, No. 80, pp. 25918-25928, April 28, 1993) specifically addresses the requirements for bioequivalence studies
(<http://www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/ucm120265.htm>).

Please refer to CDER's "Guidance for Industry, Handling and Retention of BA and BE Testing Samples" (May 2004), which clarifies the requirements for reserve samples
(<http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126836.pdf>).

During the clinical site inspection, please:

- Verify that the site retained reserve samples according to the regulations. If the site did not retain reserve samples or the samples are not adequate in quantity, notify the DBGLPC POC immediately.
- If the reserve samples were stored at a third party site, collect an affidavit to confirm that the third party is independent from the applicant/sponsor, manufacturer, and packager. Additionally, verify that the site notified the applicant/sponsor, in writing, of the storage location of the reserve samples.
- Obtain written assurance from the clinical investigator or the responsible person at the clinical site that the reserve samples are representative of those used in the specific bioequivalence studies, and that samples were stored under conditions specified in accompanying records. Document the signed and dated assurance [21 CFR 320.38(d, e, g)] on the facility's letterhead, or Form FDA 463a Affidavit.
- Collect and ship samples of the test and reference drug products **in their original containers** to the following address:

John Kauffman, Ph.D.
Center for Drug Evaluation and Research
Division of Pharmaceutical Analysis (DPA)
Center for Drug Analysis (HFH-300)
645 S. Newstead Ave
St. Louis, MO 63110
TEL: 1-314-539-2135

SECTION B - CLINICAL DATA AUDIT

Please remember to collect relevant exhibits for all findings, including discussion items at closeout, as evidence of the findings.

During the clinical site inspection, please:

- Confirm the informed consent forms and study records for 100% of subjects enrolled at the site.

- Compare the study report in the NDA submission to the original documents at the site.
- Check for under-reporting of adverse events (AEs).
- Check for evidence of inaccuracy in the electronic data capture system.
- Check reports for the subjects audited.
 - o Number of subject records reviewed during the inspection:_____
 - o Number of subjects screened at the site:_____
 - o Number of subjects enrolled at the site:_____
 - o Number of subjects completing the study:_____
- Confirm that site personnel conducted clinical assessments in a consistent manner and in accordance with the study protocols.
- Confirm that site personnel followed SOPs during study conduct.
- Examine correspondence files for any applicant or monitor-requested changes to study data or reports.
- Include a brief statement summarizing your findings including IRB approvals, study protocol and SOPs, protocol deviations, AEs, concomitant medications, adequacy of records, inclusion/exclusion criteria, drug accountability documents, and case report forms for dosing of subjects, etc.
- Other comments:

SECTION C - AUDIT OF ANALYTICAL DATA

Study #1: DU176b-A-U142
Study Title: "Quantitative determination of DU-176 and D21-2393 in human plasma samples from Study DU176b-A-U142 using turbo ion spray LC/MS/MS."

Analytical Site: (b) (4)

(b) (4)

Investigator: John R. Perkins, Ph.D

Methodology: LC-MS/MS

During the analytical site inspection, please:

- Examine all pertinent items related to the analytical method used for the measurement of analytes (Edoxaban and its active metabolite D21-2393) concentrations in human plasma.
- Compare the accuracy of the analytical data in the NDA submission against the original documents at the site.
- Determine if the site employed a validated analytical method to analyze the subject samples.
- Compare the assay parameters (such as variability between and within runs, accuracy and precision, etc.) observed during the study sample analysis with those obtained during method validation.
- Confirm that the accuracy and precision in matrix were determined using standards and QCs prepared from separate stock solutions.
- Determine if the subject samples were analyzed within the conditions and times of demonstrated stability.
- Confirm that freshly made calibrators and/or freshly made QCs were used for stability evaluations during method validation.
- Scrutinize the number of repeat assays of the subject plasma samples, the reason for such repetitions, the SOP(s) for repeat assays, and if relevant stability criteria (e.g., number of freeze-thaw cycles) sufficiently covered the stability of reanalyzed subject samples.
- Examine correspondence files between the analytical site and the Applicant for their content.

Additional instructions to the ORA Investigator:

In addition to the compliance program elements, other study specific instructions may be provided by the DBGLPC POC prior to

commencement of the inspection. Therefore, we request that the DBGLPC POC be contacted for any further instructions, inspection related questions or clarifications before the inspection and also regarding any data anomalies or questions noted during review of study records on site.

If you issue Form FDA 483, please forward a copy to the DBGLPC POC. If it appears that the observations may warrant an OAI classification, notify the DBGLPC POC as soon as possible.

Remind the inspected site of the 15 business-day timeframe for submission of a written response to the Form FDA 483. In addition, please forward a copy of the written response as soon as it is received and EIR to the DBGLPC POC.

DBGLPC POC: Hansong Chen, Ph.D., Pharm.D.
Pharmacologist
Office of Scientific Investigations
Tel: (240)-402-4143
FAX: (301)-847-8748
Email: Hansong.Chen@fda.hhs.gov

DARRTS cc:
CDER OSI PM TRACK
OSI/DBGLPC/Taylor/Bonapace/Haidar/Choi/Chen/Dejernett
CDER/OTS/OCP/DCPI/Menon-Andersen
CDER/OND/ODEI/DCRP/Blaus

Email cc:
ORA -DO/ORA BIMO
ORA (b)(4) -DO/ORA (b)(4) BIMO

Draft: HC 02/05/2014
Edit: YMC 02/07/2014; SHH 2/8/14
ECMS: Cabinets/CDER_OC/OSI/Division of Bioequivalence & Good
Laborat tical
Sites/ (b)(4)
ECMS: Cabinets/CDER_OC/OSI/Division of Bioequivalence & Good
Laboratory Practice Compliance/INSPECTIONS/BE Program/ Clinical
Sites/Celerion, Neptune, NJ

OSI file #: BE 6670, bio206316
FACTS: 8748798

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

/s/

HANSONG CHEN
02/10/2014

SAM H HAIDAR
02/10/2014